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Comprehensive Invited Review

Mechanisms of Cell Death in Oxidative Stress

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ABSTRACT

Reactive oxygen or nitrogen species (ROS/RNS) generated endogenously or in response to environmental stress have long been implicated in tissue injury in the context of a variety of disease states. ROS/RNS can cause cell death by nonphysiological (necrotic) or regulated pathways (apoptotic). The mechanisms by which ROS/RNS cause or regulate apoptosis typically include receptor activation, caspase activation, Bcl-2 family proteins, and mitochondrial dysfunction. Various protein kinase activities, including mitogen-activated protein kinases, protein kinases-B/C, inhibitor-of-I-κB kinases, and their corresponding phosphatases modulate the apoptotic program depending on cellular context. Recently, lipid-derived mediators have emerged as potential intermediates in the apoptosis pathway triggered by oxidants. Cell death mechanisms have been studied across a broad spectrum of models of oxidative stress, including H_2O_2, nitric oxide and derivatives, endotoxin-induced inflammation, photodynamic therapy, ultraviolet-A and ionizing radiations, and cigarette smoke. Additionally ROS generated in the lung and other organs as the result of high oxygen therapy or ischemia/reperfusion can stimulate cell death pathways associated with tissue damage. Cells have evolved numerous survival pathways to counter proapoptotic stimuli, which include activation of stress-related protein responses. Among these, the heme oxygenase-1/carbon monoxide system has emerged as a major intracellular antiapoptotic mechanism. *Antioxid. Redox Signal.* 9, 49–89.

I. INTRODUCTION

Aerobic organisms require molecular oxygen (O_2) for vital cellular processes. As the consequence of respiration and enzymatic activities, cells can generate partially reduced forms of O_2 collectively referred to as "reactive oxygen species" (ROS). The gaseous molecule nitric oxide (NO) and its derivatives, also produced intracellularly, define a subclass of ROS termed reactive nitrogen species (RNS) (289). The production of ROS/RNS in excess of an endogenous cellular capacity for their detoxification and/or utilization results in nonhomeostatic states referred to as "oxidative" or "nitrosative" stress, respectively (289). In addition to metabolic production, which is governed in part by O_2 tension, a multiplicity of xenobiotics, drugs, cytokines, and environmental factors (*i.e.*, solar ultraviolet radiation, ionizing radiation, and cigarette smoke) can elevate intracellular ROS production (122). ROS can cause the progressive modification or degradation of cellular biochemicals, including DNA, protein, lipids, and carbohydrates, when produced at elevated nonphysiological concentrations (122). Such cumulative damage induced by ROS can lead to loss of cell function or cell death. Consequently, ROS have been implicated in the aging process (41), in tumorigenesis/carcinogenesis (47), and in the progression of various pathologies, such as cardiovascular diseases, neurodegenerative disorders, rheumatoid arthritis, and inflammatory diseases of the lung (78). In addition to their roles in subcellular damage, an emerging hypothesis states that ROS may exert physiological effector functions in the signaling pathways that regulate cellular

processes, including gene expression, growth, and regulated forms of cell death (*e.g.*, apoptosis) (78). Following an introduction on general mechanisms of cell death (Part I), this review will examine the mechanisms underlying cell death caused by, and/or regulated by ROS and related metabolites *in vitro* and *in vivo*, in diverse model systems of oxidative cellular stress (Part II). The review will continue with a focus on cell death mechanisms in the context of physiologically relevant models with an emphasis on oxidative/inflammatory lung injuries and organ ischemia/reperfusion (I/R) injuries (Part III). Finally, the role of stress protein responses in modulating apoptosis will be discussed, with a concentration on the antiapoptotic properties of the heme oxygenase-1/carbon monoxide (HO-1/CO) system (Part IV).

A. Reactive oxygen species

A free radical is defined as a molecule with one or more unpaired electrons in an outermost valence shell. By this definition, O_2 is a biradical, since it has two unpaired electrons. ROS include O_2-derived free radicals: superoxide anion radical (O_2^-) and the hydroxyl radical (·OH); as well as nonradical derivatives of O_2 such as hydrogen peroxide (H_2O_2) (89, 122). ROS have long been recognized by radiation chemists as products generated by the radiolysis of water (197). However, the endogenous biological production of ROS can occur, with the mitochondria as the principle site of energy generation, representing a major intracellular source. Approximately 2% of the total mitochondrial O_2 consumption results in O_2^- production (14). The electron transport chain of mitochondria terminates with the cytochrome *c* (Cyt-*c*): oxidase-dependent tetravalent reduction of O_2 to form water. O_2^-, a free radical, can arise from univalent electron transfer to O_2, such as from the reaction of O_2 with the ubisemiquinone site of complex III (Fig. 1). While not particularly reactive towards organic molecules, O_2^-, can act as a reductant toward divalent metal ions, and can react with itself by spontaneous or enzymatic (*e.g.,* superoxide dismutase, SOD) dismutation to form hydrogen peroxide (H_2O_2). H_2O_2 is a mild oxidant not particularly reactive toward organic molecules. In the presence of divalent metal catalysts (*e.g.,* iron), the formation and decomposition of H_2O_2 in the metal-catalyzed Haber–Weiss cycle can generate the reactive hydroxyl radical (·OH). ·OH rapidly oxidizes most organic substrates at diffusion controlled rates, by electron abstraction (Fig. 2). In addition to mitochondrial production, ROS can arise as the product of enzymatic reactions. NADPH oxidases, also known as NOX proteins, produce ROS in response to exogenous stimuli (196). NADPH oxidases catalyze the univalent reduction of O_2 to produce O_2^-, which is rapidly converted to H_2O_2 (Fig. 3). Phagocytic cells, such as macrophages, contain a NADPH oxidase complex (NOX-2) that produces ROS as part of the innate immune response to infection. A family of NADPH oxidases (*e.g.,* NOX-1) has now been identified in nonphagocytic cells, including vascular tissue, which produce ROS in a regulated manner at lower levels than in phagocytes, presumably for signaling responses to physiological stimuli (230). ROS can also arise as the indirect by-product of enzyme activities, such as monooxygenases (*e.g.,* cytochrome p-450). Singlet molecular oxygen ($^1O_2$), a highly reactive form of oxygen, typically arises as the product of the light-dependent activation of photosensitizing chromophores (305). Its relevance to biological systems most commonly occurs in the context of ultraviolet-A radiation exposure (Section III-F), or in the use of synthetic photosensitizers for therapeutic applications (Section III-E). $^1O_2$ reacts with organic molecules by

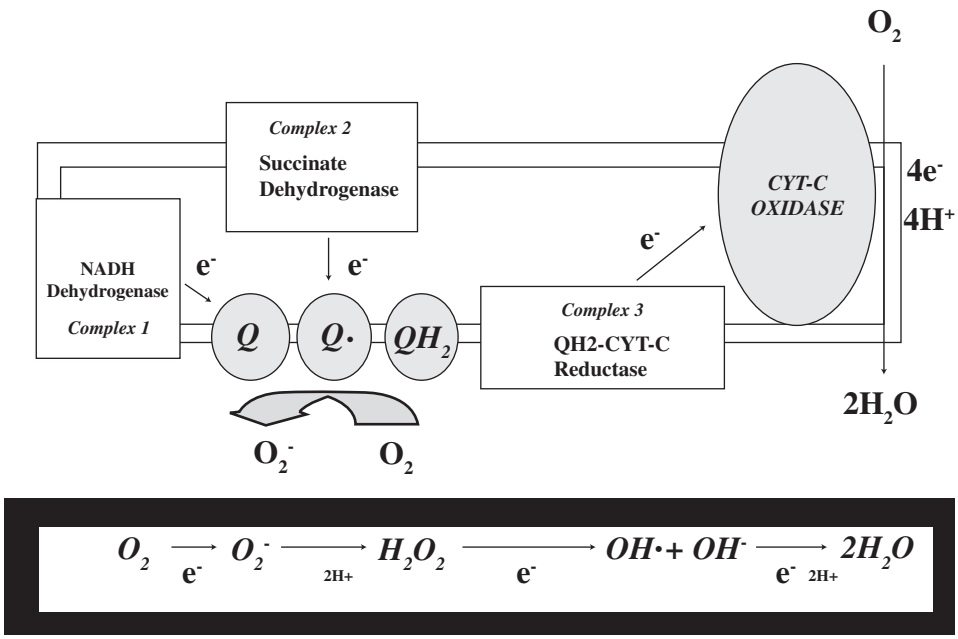

FIG. 1. Generation of ROS during mitochondrial electron transport. The metabolism of oxygen to water depends on a four-electron reduction catalyzed by cytochrome-c oxidase in the inner mitochondrial membrane. The sequential addition of electrons to oxygen generates ROS, including O_2^-, H_2O_2, and ·OH (*lower panel*). O_2^- is generated during ordinary metabolism. Reaction of oxygen at the ubiquinone (Q) site of complex III represents a possible major source of mitochondrial O_2^- production.

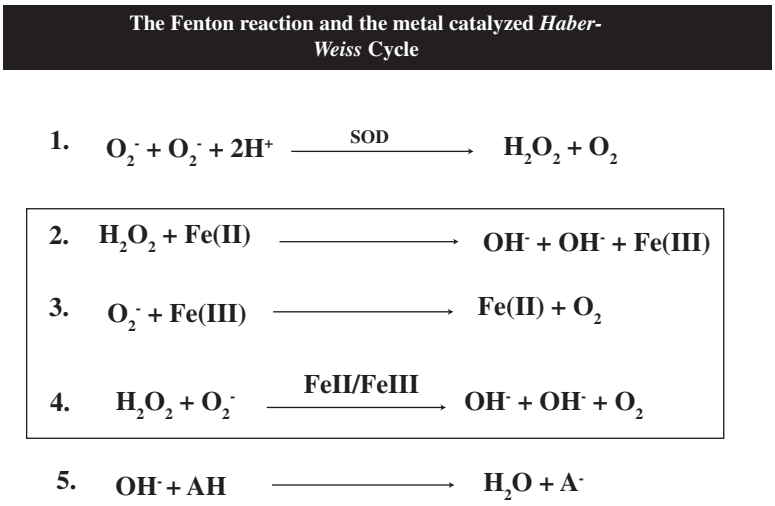

FIG. 2. The Fenton reaction and the metal catalyzed Haber–Weiss cycle. O_2^-, which is formed by enzymatic or electron transfer processes, is converted rapidly to hydrogen peroxide (H_2O_2) by dismutation (*reaction 1*) catalyzed by superoxide dismutase (SOD) enzymes. H_2O_2 reacts with reduced iron (FeII) in the Fenton reaction to generate hydroxyl radical and hydroxyl anion (*reaction 2*). O_2^- may reduce ferric iron to the ferrous form (*reaction 3*). The metal catalyzed Haber–Weiss reaction (*reaction 4*) represents the addition of reactions 2 and 3. Hydroxyl radical reacts with organic substrates (AH) to generate carbon-centered radicals (A·) by electron extraction (*reaction 5*).

a number of reaction mechanisms, typified by addition across unsaturated double bonds (305).

The gaseous molecule NO is synthesized enzymatically by nitric oxide synthase enzymes (NOS; E.C. 1:14:13:39), which occur in both constitutive (eNOS/NOS III, nNOS/NOSI) and inducible (iNOS/NOSII) forms. NO arises from the NOS-dependent oxidation of L-arginine to L-citrulline, in a reaction requiring NADPH, O_2, heme, flavin nucleotides, tetrahydrobiopterin, and Ca^{2+}—calmodulin (constitutive forms) as cofactors (410). NO thus formed can react rapidly with O_2^- to form the oxidant peroxynitrite ($K = 1.9 \times 10^{10}\ M^{-1}s^{-1}$) (181). Other RNS with potential biological reactivity include nitrogen dioxide (NO_2), nitroxyl (HNO), and nitrosonium cation (NO^+) (410).

The peroxidation of lipids represents a primary consequence of cellular oxidative stress. Lipid peroxidation refers to the addition of oxygen to unsaturated fatty acids to form organic hydroperoxides (ROOH). Organic peroxyl (ROO·) radicals arise during the radical-initiated, and O_2-dependent peroxidation of lipids, which can also produce alkoxyl radicals (RO·) in metal-catalyzed reactions (328). The oxidation of membrane phospholipids in the plasma membrane, as well as within internal organelle membranes such as the mitochondria, leads to biophysical changes that disrupt membrane and organelle function. Whereas such a process may stimulate cellular signaling pathways (see section II D), these are generally associated with the promotion of cell death. Lipid peroxidation yields additional reactive species, (*e.g.,* 4-hydroxynonenal, 4-HNE, and malonaldehyde) which may contribute to toxicity and/or cellular signaling (21).

To defend against possible deleterious effects of ROS, cells maintain an endogenous antioxidative capacity consisting of water or lipid-soluble antioxidant compounds, and enzyme systems that remove ROS by metabolic conversion (122). Cells contain millimolar quantities of the reduced thiol glutathione (GSH), which maintains sulfhydryl buffering capacity. The Mn- (mitochondrial), CuZn- (cytoplasmic), and extracellular superoxide dismutases (SOD), catalyze the conversion of O_2^- to H_2O_2, that is in turn converted to water and O_2 by catalase. The selenium-containing glutathione per-

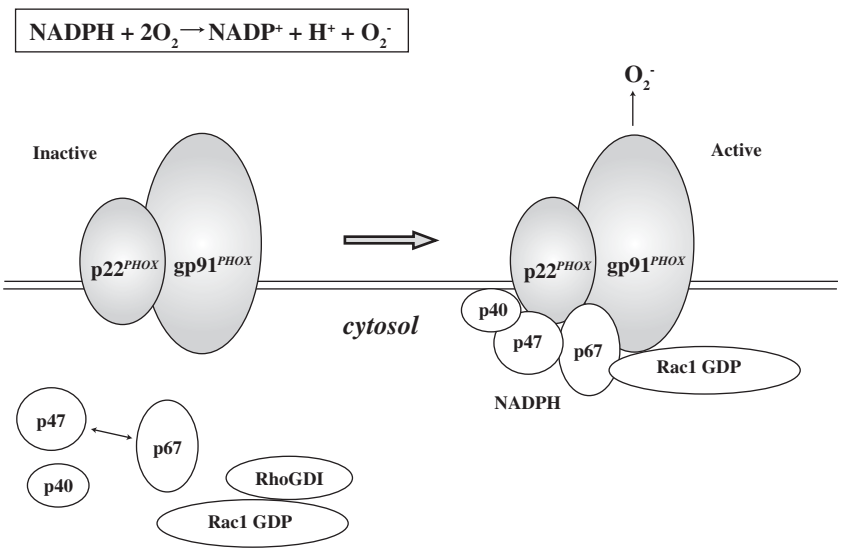

FIG. 3. Generation of superoxide anion by NADPH:oxidase. NADPH oxidase exists as a membrane-bound complex of $gp91^{PHOX}$ and $p22^{PHOX}$, which together constitute the heme and flavin-containing active site (cytochrome b_{558}). In the resting state, the cofactors p40, p47, and p67 exist in the cytoplasm in equilibrium between bound and free forms. Upon cellular stimulation, the p40, p47, p67, $p22^{PHOX}$, and $gp91^{PHOX}$, along with the GTPase Rac1, associate to form a multimeric complex in the membrane. This complex generates superoxide (O_2^-) at the extracellular face of the membrane, at the expense of NADPH (*see insert*).

oxidases (GP_X) degrade organic peroxides at the expense of GSH. The GSH/GSH reductase and thioredoxin (Trx)/thioredoxin reductase systems regenerate cellular GSH or reduced thioredoxin, respectively, at the expense of NADPH (122). A host of plant-derived flavonoid and polyphenolic compounds constitute a dietary souce of antioxidants. Among these include water-soluble (*e.g.,* ascorbate) or lipid-phase antioxidants (*e.g.,* vitamin E) (122). Secondary antioxidant defenses refer to processes that repair, remove, or replace oxidatively-modified molecules (72). These may include protease systems specialized for the removal of oxidatively modified proteins as well as DNA repair or lipid repair enzymes. For example, several enzymes known to directly reduce peroxidized phospholipids include the phospholipid hydroperoxide glutathione peroxidase (GPx4) and peroxiredoxin 6**.** Alternatively, phospholipids may be repaired by the phospholipase A2 (PLA2)-dependent excision of oxidized fatty acids, followed by reacylation (72).

B. Classifications of cell death

Two major distinct types of cell death, apoptosis and necrosis, have been delineated according to cellular, morphological, and biochemical characteristics (227). In necrosis, an extensive cell lysis results from acute, accidental, or non-physiological injury. This type of cell death is associated with gross membrane damage, and leakage of cell constituents into the extracellular space, that may lead to local inflammation and damage to the surrounding tissue. In certain cases, cell swelling or oncosis, may precede the endpoint of necrosis (227). On the other hand, apoptosis represents a regulated form of cell death that requires the action of proteases and nucleases within an intact plasma membrane (184). Mitochondrial dysfunction, respiratory chain inhibition, loss of inner mitochondrial membrane potential ($\Delta\psi_m$), and increased mitochondrial membrane permeability (MMP) represent cardinal biochemical features of apoptosis (184). Morphological characteristics of apoptosis include DNA fragmentation, membrane blebbing, cell shrinkage, and cellular decomposition into membrane-bound apoptotic bodies destined for phagocytosis (184). Apoptosis serves a critical function in the maintenance of tissue homeostasis under physiological conditions, as a component of developmental programs, and may also contribute to disease pathogenesis. At least two temporal windows of apoptosis have been described, an early apoptosis, primarily associated with direct mitochondrial damage, and a late phase, primarily associated with DNA damage. Where DNA damage is involved, stress-induced apoptosis may represent an antimutagenic/carcinogenic defense mechanism to eliminate cells expressing unrepairable DNA damage. Cells can initiate the apoptotic process by two known pathways, an intrinsic (mitochondria-dependent) pathway (Section I-*C.c*) and an extrinsic (receptor-dependent) pathway (Section I-*C.d*) (184), which are regulated by multiple protein factors of the Bcl-2 family (Section I-*C.b*) (Fig. 4).

Apoptosis or necrosis can occur in response to treatment with many injurious stimuli, usually in a dose-dependent fashion. Many agents that cause apoptosis at low to moderate doses may ultimately cause necrosis at relatively higher applied doses. A number of endogenous events can govern the balance between apoptotic and necrotic death. The intracellular ATP concentration may represent such a signal capable of directing cells toward either type of cell death, according to

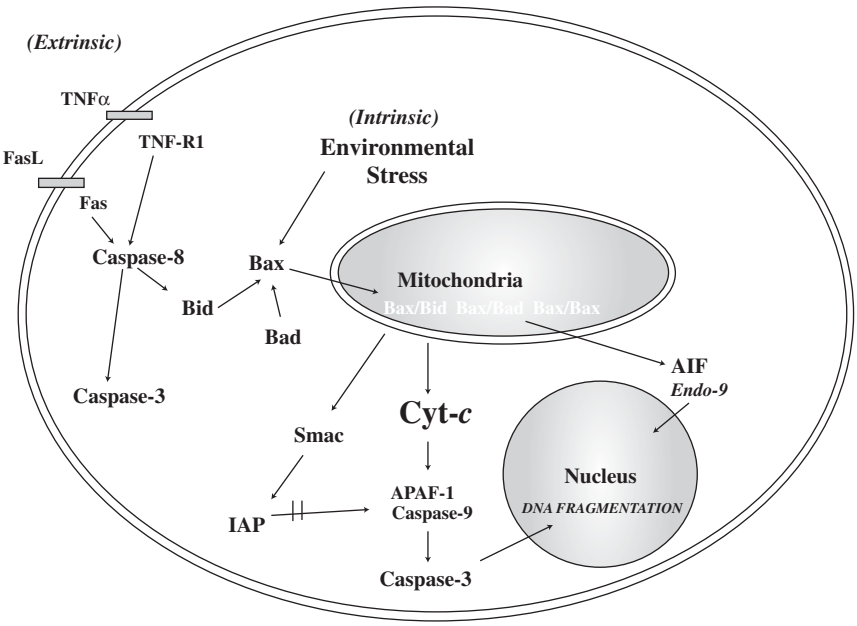

FIG. 4. Extrinsic and intrinsic apoptosis pathways. The schematic diagram displays the features of the extrinsic (receptor-dependent) and intrinsic (mitochondrial) apoptosis pathways. In the intrinsic pathway, environmental stress may cause direct mitochondrial damage, or promote signaling pathways, resulting in the activation of Bax. Bax translocates to the mitochondrial outer membrane, where it oligomerizes or forms complexes with other proapoptotic Bcl-2 related proteins such as Bid or Bad. Bax oligomers form pores in the outer mitochondrial membrane that facilitate the release of proapoptotic molecules such as cytochrome-c (Cyt *c*) or Smac. Cytochrome c forms a complex with Apaf-1 and caspase-9, leading to caspase-9 activation. Smac antagonizes the action of inhibitor of apoptosis proteins (IAP) in the cytosol, thus promoting indirect activation of caspases. In extrinsic apoptosis, a death-inducing ligand, such as tumor necrosis factor alpha (TNFα) or Fas ligand (FasL), initiates the death program upon interacting with its corresponding receptor (*i.e.,* TNF-R1 or Fas).These interactions lead to the recruitment and activation of caspase-8 in a death-inducing signal complex. Caspase-8 activation can lead to caspase-3 activation, or to the activation of Bid. Bid assists in the activation and mitochondrial translocation of Bax.

the principle that high energy levels are required for the execution of the apoptotic program, whereas they are dissipated during necrosis (205). Furthermore, apoptosis and necrosis have not been clearly delineated as mutually exclusive processes. Mixed-type cell death modes, containing features of both forms of cell death, have been reported. The so-called "aponecrosis" may represent aborted or partially executed apoptotic programs, that occur in the context of a final necrotic outcome (399).

The existence of necrotic cell death pathways regulated by an intrinsic death program distinct from that of apoptosis has also been proposed (173). A regulated Fas-dependent but caspase-independent nonapoptotic cell death, termed "necroptosis," appears morphologically similar to necrosis (74). Thus, the terminology "programmed cell death" (PCD), once reserved strictly for apoptosis, can indicate several forms of cell death mediated by an intracellular death program (334).

Autophagy, a type of PCD (Type II PCD) distinct from apoptosis (Type I PCD), is a regulated pathway for internal organelle or protein degradation (161). In this dynamic process the formation of cytoplasmic double membrane-bound vesicles sequesters organelles for delivery to the lysosome or vacuole where the delivered proteins are degraded and recycled (177, 335). Autophagy has been recognized as an essential function for cell homeostasis and adaptation to environmental stress conditions such as nutritional starvation and endoplasmic reticulum (ER) stress, hypoxia (ischemia), pathogen infection, and also oxidative stress (164, 177, 335). The morphological and biochemical features of autophagy and apoptosis are distinct. Cells undergoing autophagy display an increase in autophagic vesicles (autophagosomes and autophagolysosomes) (177, 335). Although partial chromatin condensation appears in autophagic cells, DNA fragmentation does not occur (177). Biochemically, caspases are not activated in autophagy, whereas apoptosis is caspase dependent (177). The increased expression of autophagic vesicles in dying cells may indicate that autophagy is involved with cell death; however, autophagy is not necessarily causally-related to cell death. Autophagy may constitute a defense mechanism against cellular damage potentially leading to cell death, whereas excessive intracellular damage causes the initiation of cell death (70). The discovery that protein factors which regulate apoptosis (*i.e.*, Bcl-2) can also downregulate autophagy, suggests an interrelationship between the two processes (334). The Bcl-2 interacting protein Beclin-1 the human homolog of the yeast autophagy gene atg6/vps30, represents a major regulator of autophagy (177, 209).

C. Apoptosis: pathways and proteins

a. Caspases. The caspase enzymes regulate many of the events leading to the cellular and biochemical changes associated with apoptosis (80). The term caspase originates from "cysteinyl aspartic acid-specific protease" and identifies distinct cysteine proteases with unique cleavage specificity for the carboxyl-side of aspartase residues in their target proteins (80). Over 13 caspases have been found to date in mammals, which share sequence homology with the *Caenorhabditis elegans* cell death protein Ced-3. The first caspase to be identified for its unique proteolytic activity: the interleukin-1-beta (IL-1β) converting enzyme (ICE), or caspase-1, defines a subclass (ICE) of caspases [-1, -4, and -5] involved in proteolytic activation of cytokines. Additional caspases, comprise a subfamily (*Ced3*) of apoptogenic caspases [-2, -3, -6, -7, -8, -9, and -10]. The apoptogenic caspases are further subdivided into initiator caspases (which function primarily to activate downstream caspases in a proteolytic cascade [-2, -8, -9, and -10], and effector caspases [-3, -6, and -7] that are activated by initiator caspases, and that are responsible for proteolytic events leading to apoptotic phenotype (371). The caspases are activated from inactive pro-forms by upstream caspases by proteolytic cleavage. Caspase–8/10 interact directly with death receptors through a specialized death effector domain (DED), and autoactivate upon ligand–receptor interactions (371, 394). Caspase-8 and caspase-10 appear to play apical roles in the pathway, by activating the downstream caspases, whereas caspase-3 appears to serve as the key executioner of apoptosis. Effector caspases act upon multiple substrates whose degradation can account for apoptotic changes. Caspases inactivate enzymes that catalyze the synthesis of poly(ADP-ribose), the 70-kDa subunit of U1 small nuclear ribonucleoprotein, and topoisomerase I, a nuclear factor involved in the maintenance of DNA superhelical structure, repair, and replication (45, 224, 314). Caspases also regulate factors involved in DNA degradation. The nucleosomal fragmentation of DNA associated with apoptosis is mediated by caspase-activated DNase (CAD) (214). The activation of CAD results from the caspase (*i.e.,* caspase-3) directed cleavage of its inhibitor (ICAD), or DNA fragmentation factor-45 (DFF45) (214). Finally caspases (caspase-6) also degrade proteins critical for the maintenance of nuclear architecture (*i.e.,* lamins), resulting in chromatin condensation and nuclear fragmentation (224).

b. BCl-2 family proteins. The Bcl-2 family consists of both proapoptotic (Bax, Bak, Bad, Bim, etc.) and antiapoptotic (Bcl-2, Bcl-X_L, Bcl-w) proteins, which respectively promote, or inhibit the execution of the apoptotic program. The Bcl-2 family of proteins control mitochondrial integrity, whereby the balance of proapoptotic proteins (*i.e.,* Bax) that translocate to the mitochondria, and antiapoptotic proteins (*i.e.,* Bcl-2, Bcl-X_L) that reside in the mitochondrial membrane, determines the relative sensitivity of cells to apoptotic stimuli (263). These proteins share sequence homology in Bcl-2 homology (BH) domains (162). Antiapoptotic proteins such as Bcl-2 and Bcl-X_L show homology in all four BH domains (BH 1–4). Proapoptotic proteins can be grouped into a "multidomain" subfamily whose members share homology in BH 1–3 domains (*e.g.,* Bax, Bak, Bok), and a "BH3-only" subfamily (*e.g.,* Bid, Bim, Bad) (162,323).

The *bcl-2* gene was originally identified as the translocated locus in B-cell leukemias and lymphomas. The *bcl-2* gene product localizes to the membranes of the endoplasmic reticulum (ER), nuclear envelope, and in the outer membranes of the mitochondria. A Bcl-2 related locus, the *bcl-X* gene, encodes two gene products that arise by alternate splicing, a long isoform Bcl-X_L, with anti-apoptotic properties, and a short form Bcl-X_S, with pro-death properties (33). Bcl-2 and Bcl-X_L can sequester BH_3 domain-only proteins in stable mitochondrial complexes, preventing the activation of Bax

(264). Bcl-X_L overexpression confers protection upon mitochondria, rendering it more difficult for apoptotic stimuli to induce permeability transition pore opening and Cyt-*c* release (90). The proapoptotic proteins Bax (Bcl-2-associated X-protein) and Bad (Bcl-X_L/Bcl-2-associated death promoter) were originally cloned as binding (heterodimerization) partners to Bcl-2. Bad competes against the interaction of Bcl-X_L with Bax by binding Bcl-X_L (420). A functional role of Bcl-2 family proteins as ion channels has recently been described (323). Bcl-X_L may form small ion channels that assume a mostly closed conformation, selective for the passage of cations; whereas the proapoptotic protein Bax tends to form larger channels, which assume a mostly open conformation selective for the passage of anions (323). The increased MMP observed after certain apoptotic stimuli is directly related to this property of proapoptotic Bcl-2 proteins (323).

c. Intrinsic apoptosis pathway. A broad spectrum of environmental and chemical stress agents including ionizing radiation, ultraviolet radiation (UVR), and H_2O_2, activate the "intrinsic apoptosis" or mitochondrial apoptotic pathway. These include agents that generate intracellular oxidative stress, or that alter ψ_m. Intrinsic apoptosis initiates with the activation and mitochondrial translocation of proapoptotic Bcl-2 family proteins (*i.e.,* Bax/Bak) in response to proapoptotic stimuli. The antiapoptotic proteins, which reside in the mitochondrial membrane, and preserve membrane integrity, compete for heterodimerization with activated proapoptotic Bcl-2 proteins. In the absence of a death signal, Bax adopts a conformation in which its carboxyl-terminal transmembrane signal-anchor domain cannot insert into membranes. The restriction on Bax targeting, dependent on the NH_2-terminal domain, is relieved by a proapoptotic stimulus, allowing the carboxyl-terminus signal-anchor of Bax to insert into the mitochondrial membrane (112). Upon incorporation into the mitochondrial membrane in excess of antiapoptotic proteins, Bax/Bak oligomerize to form pores that alter mitochondrial membrane permeability (MMP), which in turn facilitate the release of Cyt-*c* (309, 395), and several additional apoptogenic factors (*see* Section I-*C.c.*1) from the mitochondrial inner membrane space. Antiapoptotic Bcl-2 proteins protect the mitochondria by inhibiting Bax activation and subsequent mitochondrial translocation (55), thus preventing Bax from disrupting outer mitochondrial membrane integrity, and inhibiting the release of Cyt-*c* and subsequent procaspase activation (421). Once released, Cyt-*c* binds to apoptotic protease activating factor-1 (Apaf-1) and dATP in the cytosol to form an "apoptosome" complex (450). Apaf-1 binds to and cooperatively activates pro-caspase-9 through mutual caspase recruitment domain (CARD) interactions. The activated initiator caspase-9 in turn activates downstream caspases-3/-7, leading to compounded proteolytic activity characteristic of apoptotic cell death (162, 323).

1. Mitochondria-derived proapoptotic factors and inhibitors of apoptosis proteins. In addition to releasing Cyt-c following apoptotic stimuli, increases in MMP release a number of mitochondrial proteins from the inner mitochondria membrane. The first of these described after Cyt-c was Smac/Diablo [second mitochondria-derived activator of caspase/direct inhibitor of apoptosis protein (IAP)-binding protein with low pI]. The release of Smac/Diablo from the mitochondria is regulated by a separate mechanism from that of Cyt-c and requires caspases (1). Smac/Diablo acts as an indirect caspase activator by binding to cytoplasmic inhibitor of apoptosis proteins (IAPs) and antagonizing their inhibitory effect on caspase activation (306). IAPs contain conserved baculovirus IAP-repeat (BIR) domains that facilitate their interaction with caspases. The IAPs include the X-chromosome- linked inhibitor of apoptosis (XIAP), an endogenous inhibitor of caspases [-3, -7, and -9] (212). XIAP acts as a ubiquitin ligase that promotes the proteolytic degradation of caspase-3 (364). Following its release from the mitochondria, Smac/Diablo specifically targets XIAP. Other IAPs identified to date include neuronal apoptosis inhibitory protein (NAIP), cellular inhibitors of apoptosis (cIAP1, cIAP2), survivin, and Bruce/Apollon. Recently cIAP1 and cIAP2 have been redefined as caspase-binding proteins, though their role in direct inhibition of caspase activity has been questioned (81). cIAP1/cIAP2 function as E3: ubiquitin ligases that target Smac/Diablo and thus facilitate its proteolytic degradation. Bruce/Apollon is a high molecular weight membrane-bound IAP that appears in most normal cell types, whereas survivin typically appears only expressed in malignant tissue (11, 294). Bruce/Apollon binds to and ubiquitinates caspase-9 and Smac/Diablo, thus antagonizing the activity of these proteins, while survivin targets Smac/Diablo (294). A third mitochondria-derived factor, HtrA2/Omi is a nuclear-encoded mitochondrial serine protease. The proapoptotic function of HtrA2/Omi following its release from the mitochondria involves the inhibition of XIAP, through interactions with a conserved N-terminal IAP binding domain that is exposed in the mature form of the protein, resulting in indirect promotion of caspase activity (324, 363). Alternatively, HtrA2/Omi promotes apoptosis by proteolytic events mediated by its intrinsic serine protease activity. Recent studies demonstrating that HtrA2/Omi knockout mice develop neurodegenerative disorders have pointed to other homeostatic functions of this protein, and raised questions as to its relative role in apoptosis (231). The apoptosis inducing factor (AIF), and endonuclease-9 represent other mitochondria derived-species implicated in the execution of the apoptotic program. AIF and endonuclease-9 do not interact with IAP, but migrate to the nucleus upon their release, and directly contribute to the DNA degradation associated with apoptosis (150).

d. Extrinsic apoptosis pathway. The extrinsic apoptotic pathway refers to the initiation and propagation of the apoptotic program in response to activation of cell surface receptors, such as members of the tumor-necrosis factor receptor (TNF-R) superfamily of death receptors. The extrinsic apoptotic pathway initiates when a death ligand, such as the Fas ligand (FasL) or tumor necrosis factor alpha (TNF-α), interacts with its corresponding cell surface receptor such as Fas/APO-1/CD95, or the tumor necrosis factor receptor (TNF-R1/2). In the case of FasL-initiated apoptosis, the activation of Fas by its ligand, triggers its oligomerization, and the rapid recruitment of the adaptor FADD (Fas-associated death domain protein) and pro-caspase-8 to the cytoplasmic death domain of Fas, to

form a death-inducing signal complex (DISC) (248). A similar complex forms (complex II) with ligand-induced TNF-R1 activation, leading to recruitment of adaptors FADD and TRADD (TNF-R1-associated death domain), and the activation of pro-caspase-8/10 (246).

Cells can express Fas both intracellularly and at the cell surface. Cytoplasmic Fas localizes in the Golgi apparatus, a series of membrane-bound processing compartments that govern the secretion of macromolecules in eukaryotic cells (147). The recruitment of pro-caspase-8 to the DISC followed by its activation leads to a series of downstream events, including the subsequent cleavage of caspase-3, and multiple caspase substrates, leading to cell death (421).

The extrinsic pathway can be amplified by the DISC-dependent activation of Bid and subsequent Bax activation, leading to mitochondrial damage and release of apoptogenic factors. Activated caspase-8 subsequently cleaves Bid into truncated Bid (tBid), which translocates from the cytosol into the mitochondrial membrane, where it stimulates Cyt-*c* release and subsequent caspase-9 activation (220). The most efficient mechanism for Bid cleavage in various cell types is the Fas/FADD/caspase-8 pathway. However, alternative pathways to Bid activation have been proposed, including cleavage by granzyme B, or caspase-3 (29, 342). The activated form of Bid (tBid) can induce Cyt-*c* release from mitochondia by two possible mechanisms, dependent on association with either Bak or Bax (38). Bid assists in the auto-oligomerization of Bak (302). Bid facilitates a conformational change in Bax associated with its activation and subsequent translocation and insertion into the mitochondrial membrane to form functional oligomers, leading to Cyt-*c* release (83, 112). Bid does not necessarily require Bax to induce Cyt-*c* release (83). However, tBid cannot release Cyt-*c* from rat liver mitochondria, which lack both Bax and Bak. The maximum amount of Cyt-*c* release from the mitochondria occurs in presence of both Bax and Bak (38). Thus, the extrinsic and intrinsic apoptotic pathways converge through tBid. The activated caspase-8 can also directly activate caspase-3 in some cell types (320). Bcl-X_L can inhibit extrinsic apoptosis by blocking Bid redistribution, downstream of caspase-8 (220).

1. FLIP. Recently, an endogenous inhibitor of caspase-8 activation has also been described. This molecule, FLIP, also known as Fas-associated death domain protein (FADD)-like interleukin-1β-converting enzyme (FLICE)-like inhibitory protein, bears sequence homology to caspase-8 and inhibits apoptosis induced by death receptors such as Fas or the tumor necrosis factor-related apoptosis-inducing ligand receptors. A human cellular homolog of v-FLIP was found and termed cellular FLIP (c-FLIP; also called FLAME-1, I-FLICE, CASH, MRIT, CLARP, and usurpin) (240). The c-FLIP gene localizes to chromosome 2q33–34 in a cluster of 200 kb that includes caspase-8 and caspase-10, suggesting that these genes evolved by duplication (296). Multiple splice variants of c-FLIP have been found, but so far only two gene products, designated *c-FLIP$_S$* and *c-FLIP$_L$*, could be detected (240, 296). c-$FLIP_L$ contains tandem death effector domains (DED) and a caspase-like domain which lacks amino acid residues that are critical for caspase activity. c-$FLIP_S$ resembles its viral counterparts, consisting of two DED and a truncated C-terminus that differs from c-$FLIP_L$. The mechanisms of cell death attenuation by c-FLIP are not completely understood. c-FLIP, acting as a potential competitive inhibitor, precludes the recruitment of caspase-8/10 to the DISC and thereby prevents their activation (240, 296). FLIP is capable of binding to FADD yet cannot undergo cleavage to an active caspase because of a substitution of a tyrosine for an active site cysteine, thus preventing the initiation of the death pathway (145). Both $FLIP_L$ and $FLIP_S$ can be recruited to the DISC but they function differently: $FLIP_S$ prevents the initial cleavage step of caspase-8 activation between the p20 and the p10 subunit of the caspase homology domain; whereas $FLIP_L$ inhibits the final cleavage between the prodomain and the p20 subunit of the p43/41 intermediate (185). However, recent reports show that $FLIP_L$ when recruited to the DISC can also potentially promote caspase-8 activation by dimerizing with caspase-8 (370). Cells with high levels of FLIP relative to caspase-8 are generally resistant to apoptosis (321). In tumor cells, FLIP expression is regulated by the PI3-K/Akt signaling pathways (271). Assimilation of FLIP into the DISC potentially upregulates both NF-κB and ERK1/2-dependent survival pathways (158).

e. Protein kinase pathways in apoptosis signaling. Accumulating evidence indicates that many inducers of apoptosis activate protein phosphorylation-dependent signaling cascades that ultimately contribute to either inhibition or promotion of the apoptotic program. Recent studies have implicated a major role for the mitogen-activated protein kinases (MAPKs) in apoptosis signaling, though other kinases, including tyrosine kinases, phosphatidylinositol 3-kinase (PI3K)/Akt, protein kinase-C (PKC), and inhibitor of kappa-B (I-κB)-kinases (IKK), have also emerged as regulating mechanisms.

MAPKs belong to an evolutionary conserved and ubiquitous signal transduction superfamily of Ser/Thr protein kinases that regulate apoptosis, and other cellular programs such as growth, motility, differentiation, and responses to environmental stimuli. The MAPK superfamily comprises three primary signaling cascades named after their terminal MAPKs: the extracellular signal regulated kinases (ERK1/2 pathway), the *c*-Jun NH_2-terminal kinases or stress-activated kinases (JNK/SAPK), and the p38 MAPKs (formerly HOG-1 kinase). Each pathway consists of a multi-tiered hierarchy of kinases that sequentially phosphorylate and activate their downstream target kinases. Thus the MAPKs are phosphorylated by the mitogen activated protein kinase kinases (MKK or MEK); which are in turn regulated by the MEK kinases (MEKK or MAPKKK). Because each of these groups consists of many functionally-related kinases, this diversity generates a large repertoire of distinct signaling cascades. The terminal, activated MAPKs ultimately phosphorylate a number of target proteins, including multiple transcription factors involved in gene regulation (193).

Among the MAPKs, JNK and p38 MAPK are preferentially activated in response to a variety of stresses and proapoptotic signals, such as TNFα and FasL, H_2O_2, chemotherapeutics, and growth factor deprivation (189). The extracellular regulated kinases ERK1/2 preferentially respond to stimulation by growth-related signals, and also play key roles in the regulation of many cellular processes, such as cell

growth and proliferation, differentiation, and apoptosis. In many tissue culture studies, activation of ERK1/2, have been associated with survival pathways against proapoptotic stimuli (39, 135), or with promotion of the apoptotic program (204, 280). Likewise, the p38 MAPK has been implicated in both survival (62), and pro-death pathways (129, 188, 327, 414). Inhibitors of two members (α, β) of the p38 MAPK family have been shown to have anti-inflammatory effects in preclinical sepsis models, primarily through the reduced production of proinflammatory mediators (201). The role of the JNK pathway in apoptosis also remains controversial, as both proapoptotic and antiapoptotic effects have been observed dependent on cell type and apoptotic stimuli (332). Pharmacological inhibition of JNK can modulate the apoptosis response in a number of models discussed in this review, though again not always consistently towards inhibition of apoptosis (339). Thus, the specific role of MAPKs in apoptosis appears to vary in a cell type and inducer-specific fashion.

1. Dueling roles of JNK and NF-κB in cell fate. JNK phosphorylates a number of intracellular targets, including c-Jun, a component of the AP-1 transcription factor, and c-Myc, proteins involved in growth control and cell cycle regulation, respectively. JNK can also phosphorylate both pro- and antiapoptotic members of the Bcl-2 family (*i.e.,* Bad, Bim, Bcl-2, and Bcl-X_L) (332), as well as potentially downregulate ERK1/2-dependent survival pathways (333). In the example of cytokine (TNF-α)-induced apoptosis, TNF-α induces a biphasic activation of JNK, consisting of an early transient phase associated with antiapoptotic effects, and a sustained phase, associated with the promotion of cell death (387).

Early events in TNF-α signaling involve the formation of a signalosome (complex I) containing the TNF-R1 and adaptor molecules that signal to the inhibitor-of-κB kinase (IKK). IKK in turn, activates the multifunctional transcription factor NF-κB by the IKK-dependent phosphorylation of its cytoplasmic anchor I-κB, which releases the factor and permits its nuclear translocation (217). NF-κB directs a survival pathway that exerts inhibitory effects on apoptosis by regulating the expression of several antiapoptotic genes, including the caspase inhibitor XIAP, the caspase-8 inhibitor $FLIP_L$, zinc finger protein A2, and the inhibitor of JNKK2 kinase, thus inhibiting JNK activation, and suppressing TNF-α-induced cell death (337). TNF-α-induced apoptosis is initiated by subsequent complex II formation, which results in the TNF-R1-dependent activation of caspase-8/10.

In the presence of simultaneous activation of NF-κB, TNF-α induces transient JNK activation. When NF-κB activation is inhibited, TNF-α induces prolonged JNK activation, which is required for TNF-α-induced cell death. Despite its ability to promote TNF-α-induced cell death, independent stimulation of prolonged JNK1 activation in the absence of TNF-R1 activation, is insufficient to induce cell death, even in the absence of NF-κB activation (50). NF-κB potentially inhibits JNK activation in part, by inducing antioxidant enzymes that diminish ROS production, and prevent the ROS-mediated inhibition of protein phosphatases (153, 383). The negative regulation of JNK activation by NF-κB for cell survival appears to be specific for TNF-α, as NF-κB does not affect IL-1-induced JNK activation, and positively regulates UV-induced JNK activation for cell death (332). Recent developments indicate that TNF-α induces the degradation of the caspase-8 inhibitor $cFLIP_L$ via the ubiquitin-proteasome pathway and subsequent apoptosis in wild-type, but not *Jnk1*$^{-/-}$ hepatocytes (50). The link between prolonged JNK1 activation and degradation of $cFLIP_L$ is provided by a newly identified JNK1 substrate, the E3: ubiquitin ligase Itch (102). Phosphorylation and activation of Itch by sustained JNK1 activation is required for selective ubiquitination and subsequent proteolytic degradation of $cFLIP_L$ (50). Thus, prolonged JNK1 activation promotes apoptosis by targeting the $cFLIP_L$ that is induced by NF-κB for cell survival. Unlike the proapoptotic role of prolonged JNK1 activation in TNF-α-induced cell death, the function of transient JNK activation is less understood. Earlier studies suggested that JNK suppresses TNF-α-induced apoptosis through activation of JunD, which collaborates with NF-κB to induce antiapoptotic gene expression (102, 195). Recent studies that demonstrate that transient JNK activation is required for TNF-α-induced expression of antiapoptotic genes such as cIAP2, provide an important step toward understanding how the timing plays a part in the functional output of JNK activation (387).

2. PKB. The phosphatydyl inositol-3-kinase (PI3K)/protein kinase B (Akt) pathway is generally associated with survival pathways against multiple proapoptotic stimuli that induce its activation. PI3K is a ubiquitous lipid-modifying enzyme consisting of a p85 regulatory subunit and a p110 catalytic subunit. Activation of PI3K by a variety of stimuli, including growth factors, cytokines, and cytotoxic agents lead to phosphorylation of the serine-threonine kinase Akt. This stimulates the catalytic activity of Akt, resulting in the downstream phosphorylation of a number of proteins that affect cell survival, cell cycle regulation, protein synthesis, and cellular metabolism (336). Several Akt isoforms (*i.e.,* 1, 2, and 3) respond to activation by diverse stress agents. The pro-survival effects of Akt2 were recently ascribed to phosphorylation of IKKα, which activated the NF-κB survival pathway and suppressed JNK activation (429). There is evidence that the PI3K/Akt pathway can also upregulate cFLIP (271). Cells and mice lacking specific members of the PI3K-family develop a pro-inflammatory state implicating a role of PI3K/Akt in immunoregulation (183). Furthermore, the PI3K/(classI)-Akt/ mTOR pathway, which is activated in various cancers, negatively regulates autophagy (177). Dominant negative forms of Akt promote autophagy, whereas constitutive activation of Akt, inhibited autophagy (335).

3. PKC. Protein kinase C (PKC) comprises a family of ser/thr kinases, which can modulate the apoptotic program. The PKC family consists of 12 closely related isozymes that can be divided into three groups determined by their requirements for activation, the conventional (Ca^{2+}/diacylglycerol-dependent) cPKCs (α, β1, β2, and γ), the novel (Ca^{2+}-independent) nPKCs (δ, ϵ, ϕ, μ, and η), and the atypical (Ca^{2+}/diacylglycerol-independent) PKCs (ζ, λ, and τ) (253,275). Various studies have implicated the involvement of PKCs in the activation of PI3K (385), MAPK pathways (135, 303, 385), as well as inactivation of Bad during the inhibition of Fas-mediated signaling (385). PKCs can upregulate several antiapoptotic molecules such as FLIP (PKCμ) (375) and cIAP2 (PKCδ) (396), downregulate capase-8; as well as regulate

FADD recruitment and DISC formation (cPKCs) (111). A study which demonstrated the association of PKCε with Bax suggested an inverse relationship between the endogenous levels of PKC and the apoptotic effects of phorbol esters (236). Wang *et al.* recently demonstrate Bax suppression by association with PKCα, ζ in endothelial cells (400). Thus, recent evidence suggests that PKC isoforms may regulate various aspects of the apoptotic program, however the mechanisms and isoform specificity of these interactions are not completely understood. The roles of PKB/PKCs in specific models of oxidative stress are discussed in the later sections of this review.

f. Mitochondrial specific ROS and apoptosis. A relationship exists between $\Delta\psi_m$ and the production of ROS by the mitochondria (356). Apoptosis induced by many agents, (*i.e.,* staurosporine) is typically associated with ROS production, loss of membrane polarization (negative $\Delta\psi_m$), leading to permeability changes, and release of mitochondrial Cyt-*c* (186). Exogenous treatment with H_2O_2 causes membrane depolarization and Cyt-*c* release (318). Release of Cyt-*c* may cause increased mitochondrial O_2^- production, due to interruption of electron transport processes (54, 431). The negative $\Delta\psi_m$ is preceded in some cases by transient positive $\Delta\psi_m$ or hyperpolarization, as observed for cellular treatment with H_2O_2 or oxidized LDL (103, 341). Membrane hyperpolarization has also been associated with increased production of H_2O_2 in isolated mitochondria. The potential relationship between mitochondria–derived ROS and apoptosis was recently exemplified by rotenone-induced apoptosis. The mitochondrial poison rotenone inhibits the respiratory chain at complex 1. In cultured HL-60 cells, rotenone increased mitochondrial O_2^- production coincident with a Cyt-*c* and caspase-dependent apoptosis. The rotenone-induced apoptosis was inhibited by general antioxidants such as *N*-acetyl-L-cysteine (NAC). Although overexpression of Mn-SOD apparently protected cells from rotenone-induced apoptosis by removing O_2^-, this observation did not account for the relative role of H_2O_2 in apoptosis (207). General GSH depletion caused an apoptosis associated with increased MMP and Cyt-*c* release, which was reversible by inhibitors of respiratory complex III activity (18). These experiments indicated that loss of intracellular GSH, sensitizes cells to endogenous mitochondrial ROS production (18). Experiments with mitochondrial membrane selective antioxidants (*i.e.,* mito-VitE) (344) have further demonstrated a relationship between mitochondrial-specific ROS production and apoptosis. Mito-VitE, but not natural VitE, inhibited endogenous ROS production, caspase-3 activation, and DNA fragmentation associated with apoptosis in endothelial cells challenged with H_2O_2 or oxidized lipid (76). In contrast, Mito-VitE accelerated TNF-α–dependent apoptosis, leading to increased caspase-3 activation, and DNA fragmentation, relative to that observed with TNF-α alone. The proposed mechanism involved the delay (by ROS scavenging) of TNF-α–induced NF-κB activation, and hence inhibition of the antiapoptotic pathway (143).

Recently, an endogenous peroxidase activity of Cyt-*c* has been reported that selectively oxidizes membrane cardiolipin, that in turn facilitates Cyt-*c* release from the mitochondrial membrane (151). Since cyt-*c* is an iron containing protein, its release into the cytoplasmic compartment, may also promote secondary ROS generation from nonspecific iron-catalyzed reactions.

II. MECHANISMS OF CELL DEATH IN OXIDATIVE STRESS MODELS

In the following section, the mechanisms of cell death will be reviewed in the context of selected *in vitro* model systems of oxidative stress. H_2O_2 and redox-cycling compounds will be considered first, since they represent classical and commonly used models of exogenous and intracellular oxidative stress. Lipid metabolites will be considered both as exogenous stress, and as the metabolic consequence of other forms of cellular stress with intermediate signaling potential in regulating apoptosis pathways. The role of RNS in apoptosis will be discussed in brief, since this topic has been reviewed elsewhere (63). This section will conclude with a discussion of cell death pathways in response to several forms of radiation, including ionizing radiation (IR) and ultraviolet radiation(s) (UVR); and photodynamic therapy (PDT), a combination of irradiation and drug therapy used for therapeutic applications. Cigarette smoke exposure will also be considered as a specialized model of environmental/oxidative stress.

A. Hydrogen peroxide (H_2O_2)

Although H_2O_2 is a relatively weak oxidant compared to other ROS such as $^{\bullet}OH$, it has emerged as an important signaling molecule based on its unique biochemical properties: H_2O_2 is ubiquitously present in the biological system with a relatively long half-life; and more importantly H_2O_2 is soluble in both lipid and aqueous media (78). Thus it easily diffuses to its cellular targets. Recent research has suggested that the apoptosis signal can be transduced extracellularly by soluble factors. A population of cells stimulated with cytokine transmitted the apoptosis signal to neighboring cells through a soluble catalase-inhibitable factor, suggesting that H_2O_2 may act as a paracrine mediator of apoptosis (285).

a. Hydrogen peroxide-induced apoptosis. In studies of apoptosis, H_2O_2 has been widely used as a model of exogenous oxidative stress. Menadione and paraquat, compounds that produce O_2^- and H_2O_2 intracellularly upon redox cycling in the mitochondria, have been used as model compounds for endogenously produced ROS. Morphological and biochemical features of apoptosis, as defined by electron microscopy and TUNEL assays, have been observed after treatment of several cell types with these model compounds (68, 160, 203). For example, H_2O_2 stimulated apoptotic cell death in cardiomyocytes, associated with Bax/Bad mitochondrial translocation, upregulation of p53, loss of ψ_m, mitochondrial cyt-*c* release, caspase-3 activation, PARP cleavage, and DNA fragmentation (68). While the overall phenomenology of H_2O_2-dependent apoptosis is conserved, several studies report cell-type specific variations in the behavior of Bcl-2 related proteins.

As with other model systems, artificial modulation of Bcl-2 family proteins typically alters the outcome of oxidant-induced apoptosis (132, 276). For example, Bcl-2 expression

inhibited menadione-induced GSH depletion, ROS production, and the loss of ψ_m associated with apoptosis in murine fibroblasts (276). In contrast, one study reported that overexpression of Bcl-2 or Bcl-X_L, paradoxically increase mitochondria-specific H_2O_2 production (182). The relationship between increased mitochondrial ROS and the antiapoptotic action of these proteins was proposed to involve a chronic conditioning effect. Concurrent with inhibiting apoptosis, overexpression of Bcl-X_L and Bcl-2 in cells was reported to promote H_2O_2-dependent mutagenesis, implying increased survival and escape from apoptosis (56), and also reported to shift the balance from apoptosis to necrosis at lethal concentrations of H_2O_2 (79). Recent novel studies have shown that downregulation of Smac/Diablo by antisense oligonucleotides in C2C12 cells resulted in inhibition of H_2O_2-mediated apoptosis (148). By definition, antioxidants or the expression of antioxidative factors, generally inhibit oxidant-induced apoptosis. For example, mitochondrial-specific overexpression of catalase protected against H_2O_2-mediated cell death (17). Incubation with antioxidants such as NAC in cell culture also protected against H_2O_2 or menadione-induced cell death (157, 254).

b. Protein kinase pathways in oxidant-induced apoptosis. Activation of the MAPK pathways is a feature of oxidant-induced apoptosis. H_2O_2 treatment produced a sustained activation of all three major MAPK pathways (*i.e.,* ERK1/2, JNK, and p38 MAPK) in HeLa cells and cardiomyocytes (291, 397). Chemical inhibition of ERK1/2 promoted H_2O_2-induced apoptosis, whereas modulation of p38 MAPK did not alter H_2O_2-induced apoptosis in HeLa cells (397). H_2O_2 treatment of HL60 cells activated p38 MAPK (446). However, the p38 MAPK inhibitor did not protect against H_2O_2-induced apoptosis in HL60 cells, which depended on p38 MAPK-independent activation of caspase-8 (446). Sustained activation of ERK1/2 was associated with a pro-death pathway in H_2O_2-treated renal epithelial cells (202). Sustained activation of JNK was also observed in MLE12 and lung epithelial cells treated with H_2O_2 (208, 272). The selective inhibition of JNK, by dominant negative mutant (DNM) transfection, inhibited H_2O_2-induced apoptosis, in both HeLa and MLE12 cell lines (208, 397). More specifically, *Jnk1*$^{-/-}$ MEF cells were more resistant to H_2O_2 relative to wild-type or *Jnk2*$^{-/-}$ cells (331). Of the MAPK, the activation of JNK by oxidants has been perhaps the most extensively studied. Multiple mechanisms potentially involved in H_2O_2-induced JNK activation have recently been reviewed, which include the possible participation of death receptors, receptor tyrosine kinases (RTKs), MKKKs, and redox-related molecules (332) (Fig. 5).

1. Death receptors. There is evidence that H_2O_2-induced JNK activation involves, in part, extrinsic type apoptotic pathways involving activation of death receptors and/or associated adaptor molecules. In fibroblasts, TNF-R1 was required in part for H_2O_2-dependent JNK activation, since the response was inhibited in fibroblasts derived from *tnfr1*$^{-/-}$ mice (272). JNK activation in this model was proposed to follow recruitment of adaptor molecules TRADD and TRAF2 and JNK to the TNF-R1 (272). Overexpression of TRAF2 was also sufficient to induce JNK activation in this model. Following H_2O_2 stimulation, the degradation of the receptor-interacting protein (RIP1) by the complex was associated with the downregulation of the IKK/NF-κB-dependent survival pathway (272). In contrast, Shen *et al.* propose a distinct mechanism associated with H_2O_2-induced necrotic cell death in MEL cells. In this model,

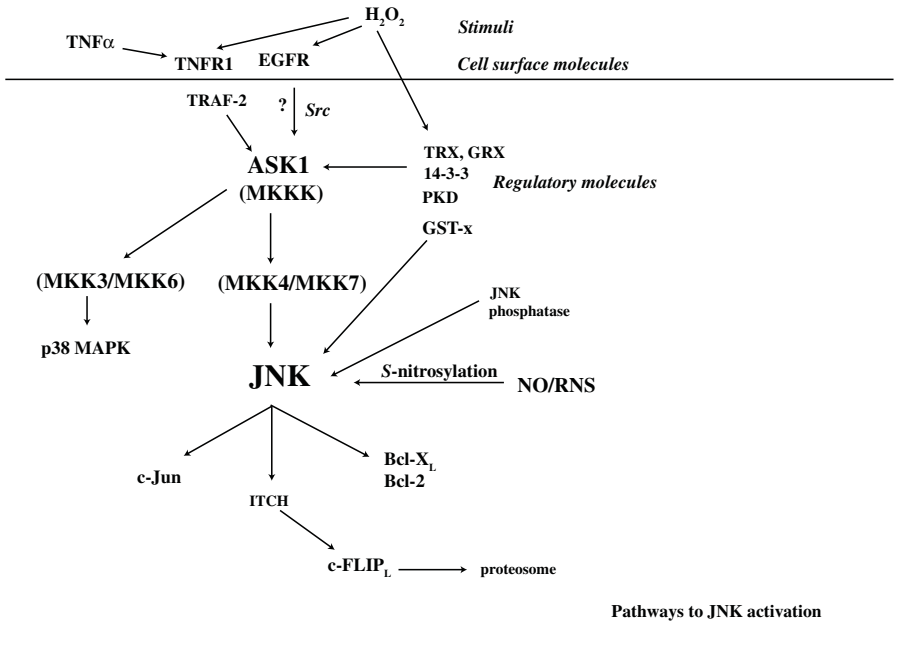

FIG. 5. Pathways to JNK activation. The activation of the *c*-Jun NH_2-terminal kinase (JNK) responds to extracellular proapoptotic stimuli such as H_2O_2 or TNFα. This activation pathway potentially involves cell surface receptors (*i.e.,* TNF-R1 or EGFR), leading to the transduction of the signal through MAP kinase kinase kinase (*i.e.,* ASK1), and MAP kinase kinase (*i.e.,* MKK4/7). Various regulatory proteins can interact with and influence the activity of ASK1 or JNK, including the thioredoxin or glutaredoxin proteins (Trx/Grx), protein kinase-D, glutathione-*S*-transferase-π, and the 14–3-3 proteins. JNK also can represent a target of *S*-nitrosylation. JNK regulates a number of possible proteins involved in apoptosis, including Bcl-2 family proteins (*i.e.,* Bcl-X_L, Bax), and the ubiquitin ligase ITCH, which promotes the degradation of FLIP.

JNK activation required the recruitment of JNK with RIP1 and TRAF2 to form a signaling complex in the lipid raft compartment of cell membranes, independently of TNF-R1. H_2O_2-induced cell death in MEL cells was inhibited in cells with *traf2*$^{-/-}$ and *rip*$^{-/-}$ genotype, and increased with *fadd*$^{-/-}$ genotype (331). Thus, TRAF2 appears to be essential for H_2O_2-induced JNK activation, but the relative role of RIP1 in H_2O_2-induced JNK activation remains unclear.

2. Receptor tyrosine kinases (RTK). There is increasing evidence that H_2O_2 can initiate signaling pathways by ligand-independent stimulation of RTKs (53). Among the receptors implicated in H_2O_2 signaling include the epidermal growth factor receptor (EGFR), vascular endothelial growth factor-2 receptor (VEGFR) and the platelet-derived growth factor-β receptor (PDGFR) (52, 53). Chemical inhibitors of various RTK, including Src family kinases, inhibited H_2O_2-induced JNK activation in endothelial cells, as did transfection with Src DNM, and antisense oligonucleotides against the EGFR (53). In this model, H_2O_2 stimulated EGFR tyrosine phosphorylation and association with Src and other adaptors (53). Cells genetically deficient in Src kinase (*src*$^{-/-}$) were also resistant to H_2O_2-induced JNK activation. The Src pathway and its downstream substrate Cas, as well as the adaptor protein Gab1, were shown to be specific intermediates for H_2O_2-mediated JNK activation (134, 426). The EGFR has recently been linked to an ERK1/2-dependent pro-death pathway in H_2O_2 stimulated epithelial cells (202).

3. ASK/JNK pathway. The apoptosis signal-regulating kinase-1 (ASK-1) appears to be one major mechanism by which oxidative stress stimuli regulate JNK in the context of apoptosis (233, 332). ASK1 belongs to the MKKK family and potentially activates both JNK and p38 MAPK pathways (144, 233, 403). ASK1 responds to cellular stimulation with oxidative stress and participates in oxidative stress-induced apoptosis (108). ASK1-dependent JNK activation phosphorylates Bcl-2, which results in the reduction of its antiapoptotic potential (416). Overexpression of wild-type or constitutively active mutant forms of ASK1 causes mitochondria-dependent apoptosis by releasing Cyt-*c* and activating caspase-3/-9 (125, 200). Several signaling molecules negatively regulate oxidative stress-induced ASK1 activation by direct binding. A yeast two-hybrid screen for ASK1-binding proteins revealed the ASK1-repressor function of thioredoxin (Trx) (310). Trx directly binds to the N-terminal region of ASK1 and inhibits its kinase activity. The binding of Trx to ASK1 requires the reduced form of an intramolecular disulfide bridge between two cysteine residues (Cys32/Cys35) in the catalytic site of Trx. An *in vitro* binding assay showed that oxidized Trx, or Trx mutants in which both of these residues have been altered, could not bind to or inhibit ASK1. Upon H_2O_2 stimulation of HEK293 cells, oxidized Trx dissociated from ASK1. The freed ASK1 is activated by formation of an oligomeric complex, followed by autophosphorylation at Thr845. This Trx-ASK1 interaction is also involved in TNFα signaling, such that TNF-α–induced intracellular ROS production promotes the dissociation of Trx from ASK1. Thus, Trx inhibits apoptosis signaling not only by general antioxidative protection by regenerating reduced thiols, but also by inhibiting the activity of ASK1 and downstream activation of JNK/p38 MAPK (310). A similar mechanism as shown for Trx, has been suggested for the related redox-active molecule glutaredoxin, which inhibits glucose deprivation-induced ASK1 activation (348). A number of other additional signaling molecules that potentially regulate H_2O_2-induced ASK1 and/or JNK activation have been recently reviewed by Shen *et al.* (332). Protein ser/thr phosphatase 5 (PP5) dephosphorylates Thr845 of ASK1 and inactivates its kinase activity both *in vitro* and *in vivo.* The association of PP5 with ASK1 is stimulated by H_2O_2, suggesting a negative feedback system of ASK1 activation (241). The 14–3-3 proteins, phosphoserine/phosphothreonine–binding molecules, may also act as negative regulators of ASK1 activation. 14–3-3 bind to ASK1 through phosphorylated Ser967 (located in the 14–3-3 binding motif of ASK1, which is phosphorylated in the inactive state), and suppress ASK1-induced apoptosis. H_2O_2 induces Ser967 dephosphorylation, hence increased ASK1 activation (437). In H_2O_2-treated endothelial cells, ASK1 associates with the phosphorylated form of protein kinase-D, which was required for H_2O_2-dependent JNK activation. Additional signaling pathways in ROS-mediated JNK activation potentially involve glutahione *S*-transferases (GST). The monomeric form of GSTπ binds to the C-terminal of JNK and suppresses its activity. H_2O_2 treatment induces GSTπ oligomerization and dissociation of the enzyme from GSTπ–JNK complex, leading to JNK activation (reviewed in Ref. 332).

4. PKB/PKC in oxidative stress. H_2O_2 can activate the PI3K/Akt survival pathway in various cell types (178, 254). Activation of Akt by H_2O_2 coincided with the increased association of Hsp27 with Akt (180). Activation of Akt by H_2O_2 depended on PI3K, as shown by wortmannin sensitivity, and also on EGFR-dependent signaling (293, 398). In CHO cells, H_2O_2-mediated apoptosis was sensitized by overexpression of PKCδ and desensitized by overexpression of PKBα/Aktα. Furthermore, Aktα prevented PKCδ phosphorylation in response to H_2O_2, implying that the antiapoptotic effect of Aktα involves targeted downregulation of PKCδ (179). Likewise, H_2O_2-mediated apoptosis was inhibited by insulin-dependent activation of the PI3K/Akt pathway in this cell type (6). The focal adhesion kinase (FAK) is an upstream regulator of PI3K/Akt. H_2O_2 caused the tyrosine phosphorylation and activation of FAK, which was associated with activation of PI3K/Akt in human glioblastoma cells (352). Overexpression of FAK in HL-60 cells inhibited H_2O_2-mediated apoptosis, by activating survival pathways dependent on the PI3K/Akt and NF-κB, leading to upregulated expression of IAPs (351). Conversely, the PI3K inhibitor wortmannin promoted H_2O_2-mediated apoptosis in various cell types (254, 352, 398).

5. Phosphoprotein phosphatases. Since protein kinases can either positively or negatively influence the progression of apoptosis, phosphoprotein phosphatases, which dephosphorylate target proteins represent a critical counter-regulatory mechanism. Protein phosphatases, like their kinase counterparts, belong to several classes: the Ser/Thr phosphatases (PP) and the protein tyrosine phosphatases (PTP). The PTP superfamily encompasses two broad categories of enzymes: the classical pTyr-specific phosphatases and dual specificity phosphatases (DSPs), which may also dephosphorylate Ser/Thr residues, and nonprotein substrates, such as inositol phospholipids (85, 374). The consensus peptide motif [I/V]

HCXXGXXR[S/T], characteristic of the PTP superfamily, contains an invariant Cys residue, which functions as a nucleophile during enzyme catalysis. Due to the unique chemical environment of the PTP active site, this Cys residue displays an unusually low pK_a, which enhances its nucleophilic properties but renders it susceptible to oxidation. Oxidation of the active site Cys abrogates its nucleophilic properties, thereby inhibiting PTP activity (115). Recent observations reveal that ROS signaling interacts with other physiological signaling pathways by acting on various protein phosphatases (299). The downregulation of PTPs by ROS, which removes the counterregulatory mechanism, may effectively act to facilitate the induction of tyrosine kinase signaling pathways by physiological stimuli (239, 298, 313). H_2O_2 downregulated both PTP and PP2A activities in Jurkat T-cells preceding the peak of MAPK activation (407). H_2O_2 specifically downregulated PP2A activity in Caco-2 cells, resulting in increased threonine phosphorylation of nonspecific proteins. This effect could be reversed by GSH supplementation, and by dithiothreitol, indicating a role for sulfhydryl oxidation and/or glutathionylation of the protein (93). PP2A, as the major MAPK phosphatase in the brain, was shown to be inhibitable by H_2O_2 in rat brain homogenates (93). H_2O_2 downregulated the JNK-specific phosphatase M3/6, albeit at the level of protein expression (53).

c. Glutamate-induced apoptosis. A number of endogenous compounds can generate ROS by redox cycling processes. Several of these, including glutamate, catecholamines, (*i.e.,* dopamine and its derivatives), and epinephrine, have been studied as models of endogenously produced oxidative stress, albeit specialized to neuronal cell cultures. The excessive release of glutamate has been linked to pathological conditions such as traumatic brain injury, Alzheimer's disease, and stroke. Excess glutamate release results in overstimulation of glutamatergic neurons, leading to increased ROS production, excitotoxicity, and neuronal cell damage (319). The ROS generation caused by glutamate was related in part to stimulation of extracellular calcium influx (118), and potentiated in the presence of lead (319). Glutamate causes depletion of intracellular GSH, by inhibiting cystine uptake in neurons, such that restoration of cystine or treatment with *N*-acetylcysteine protected against glutamate-induced neurotoxicity (97). Furthemore, glutamate causes cell death exhibiting some of the morphological features of apoptosis, such as cell blebbing and shrinkage (367). Exogenous glutamate treatment was demonstrated to cause activation of caspase-dependent apoptosis in cultured neural cells (118), associated with sustained activation of ERK1/2 MAPK (355).

B. Reactive nitrogen species and apoptosis

NO and related RNS can positively or negatively modulate the apoptotic program depending on dose, experimental conditions, and cellular context (63). In addition to a classical role as an activator of guanylyl cyclase, which regulates vessel tone, NO can initiate complex chemical interactions in biological systems, involving reactions with thiols, metals, heme groups, and other free radicals (410). NO can reversibly inhibit respiration at the sites of complex-I and cytochrome *c* oxidase (36, 37). At higher or prolonged exposure to NO/RNS irreversible inhibition of respiration may occur by inactivation of multiple targets, potentially involving protein tyrosine nitration. Inhibition of respiration may lead to loss of ATP production, which promotes necrotic death (36). $ONOO^-$ formation from the reaction of NO with O_2^-, in addition to reducing NO bioavailability, can exacerbate oxidative stress and participate in activation of signaling pathways (206). Important biological consequences of NO action include the *S*-nitrosylation of free thiol groups in proteins and the nitrosation of tyrosine residues (237). Cellular redox potential and nonheme iron content determine *S*-nitrosylation. Apoptotic cell death is potentially inhibited by NO-dependent *S*-nitrosylation of the redox-sensitive thiol in the catalytic site of caspase family proteases, which play an essential part in the apoptotic signal cascade (237). The susceptibility to *S*-nitrosylation was also observed for JNK1/2 and ASK1, at least *in vitro*, and this suggests other possible antiapoptotic mechanisms of NO through the potential direct inhibition of these activities (273). In many cell culture systems, prolonged or excessive NO production can promote apoptosis by the activation of intrinsic mitochondrial apoptotic pathways, involving the release of Cyt-*c*, and other factors from mitochondria, as well as the suppression of NF-κB activity (59). For example, $ONOO^-$ induces apoptosis at high concentrations in murine macrophages (315).

Similar to that observed with ROS, and other forms of stress, RNS have the capacity to modulate all major MAPK pathways (ERK1/2, p38 MAPK, and JNK) in a context-specific fashion. NO donor compounds induce JNK in a variety of cell types (332). The endogenous overproduction of NO by stimulation of iNOS, has been related to JNK activation and apoptosis induction by a variety of stimuli competent for iNOS activation, including lipopolysaccharide (LPS) (*see* Section II-*C*). The activation of JNK in endothelial cells by shear stress was attributed to the endogenous production of endothelial-derived $ONOO^-$ generation (104). The mechanisms regulating RNS-induced JNK activation are similar, but not identical to those proposed for H_2O_2, and have been recently reviewed elsewhere (332). The activation of JNK by RNS in murine alveolar type-II epithelial cells involved the death receptor Fas, in a ligand (FasL)-independent fashion, but did not involve TNF-R1. The activation of JNK by NO/RNS also potentially involved ASK1 activation, as demonstrated in human bronchial epithelial cells (149). The conflicting endpoints (*i.e.,* pro- or antiapoptosis) for NO/RNS treatments appear to vary in an inducer-specific and cell-specific fashion, further affected by concentration and kinetic parameters (25). Whereas H_2O_2-induced signaling is complicated by inhibition of PP and PTP activities, the effects of NO/RNS are potentially complicated by *S*-nitrosylation of regulatory proteins (332).

C. Toll-like receptor pathways and apoptosis

Microorganisms, including bacteria, fungi, and viruses, display various types of pathogen-associated molecular patterns (PAMP), which are recognized distinctively by Toll-like receptors (TLRs) (8). A number of TLRs respond differentially to distinct ligands, such as bacterial lipopolysaccharide, LPS (TLR4); peptidoglycan, PGN, or Pam (TLR2); double stranded RNA (poly(I:C), (TLR3); flagellin (Fla) (TLR5), and bacterial CpG (TLR9). Activation of TLRs initiate down-

stream signaling cascades involving NF-κB, interferon-related factor-3, (IRF-3), and/or MAPKs, resulting in the release of pro-inflammatory cytokines, chemokines, and the generation of ROS/RNS against the invading pathogens (8). In addition to pro-inflammatory responses, it is now evident that activation of TLR-dependent signaling pathways can also result in apoptosis. For example, LPS exposure can induce apoptosis with increased activation of caspase-3 in epithelial cells (252). Similarly, LPS can induce apoptosis in endothelial cells (25). Although macrophages or monocytes are more resistant to apoptotic cell death upon activation relative to other cell types, several TLR ligands, such as LPS, Pam, and poly(I:C), can induce apoptosis in macrophages and dendritic cells (73, 91, 142). Whereas CpG fails to induce apoptosis in macrophage cell lines (91), CpG treatment induced apoptosis in dendritic cells (73). The possible signaling pathways involved in TLR ligands-induced apoptosis have been examined. The protein kinase PKR is required for bacteria-induced or TLR3/4 ligand-induced apoptosis in macrophages (142). However, other studies in human breast tumor cells show that poly(I:C)-induced apoptosis is TLR3- and TRIF dependent, but PKR- and MyD88 independent (312). The apoptotic signaling pathway activated by TLR2 potentially involves FADD, the adaptor for FasL-induced apoptosis (9). The BH3-only protein Bim has a critical role in apoptosis induced by LPS or Pam treatment in macrophages (169).

The mediators released by PAMP *in vivo* activate and recruit immune cells in circulation to pathogen-localized tissue in a hyperactive state of the immune response. ROS/RNS generation, including O_2^-, H_2O_2, $ONOO^-$, have been suggested as important regulatory factors in TLR signaling pathways. In this regard, scavenging of ROS by antioxidants or treatment with NADPH oxidase inhibitors leads to inhibition of LPS-induced NF-κB activation and cytokine production (234, 274, 279). Recent studies revealed that the LPS-induced TLR4-dependent pathway shares similarity with the H_2O_2-mediated pathway in that it involves the ROS-stimulated release of Trx from ASK1, leading to MAPK activation (234). Thus, ROS caused by activation of TLR signaling appear to participate in the execution of the inflammatory response. On the other hand, ROS also potentially mediate apoptosis as an endpoint of the TLR signaling pathway. LPS-induced apoptosis in endothelial cells involved ROS generation (168). In cortex and hippocampus of the LPS-treated rat, ROS production correlated with an increased number of apoptotic cells and activation of caspase-3 (256). Neutrophils from patients with severe sepsis or septic shock upregulate both ROS generation and apoptosis relative to cells from control subjects (232). The modulation of apoptosis by LPS appears to also depend, in part, on endogenous NO production. For example, the elevated intracellular production of NO, as a consequence of increased endogenous iNOS activity, mediated the proapoptotic action of cytokine or LPS treatments in vascular smooth muscle cells (343). TLR2, TLR4, and TLR9 ligands induce iNOS gene expression and/or NO generation in monocytes (126). Redox factor-1 negatively regulates LPS-induced apoptosis in macophages by downregulating LPS-induced NO synthesis (425). In contrast, other studies show that NO donors such as *S*-nitro-*N*-acetylpenicillamine can antagonize LPS-induced apoptosis (75, 425). Increased production of NO from overexpression of iNOS suppressed LPS-induced endothelial apoptosis (46, 381). From the evidence at hand, ROS/RNS exert a variable downstream regulatory role in LPS-induced apoptosis. However it remains unclear the relative role of ROS/RNS in apoptosis induced by the other TLR-ligands.

An important function of cellular apoptosis induced downstream of TLR activation, in addition to the elimination of damaged cells, may involve the resolution of inflammation (326). In tissue, acute inflammation involves the rapid recruitment of neutrophils and monocytes, which mature into macrophages. Prolonged inflammation potentially causes profound cellular damages or organ dysfunction. To avoid this and to return to normal tissue homeostasis, the neutrophils and macrophages are eventually eliminated from the inflamed area. The abundance of these cells returns to normal through apoptosis occuring during the process of inflammation. Activated neutrophils begin to undergo apoptosis after entering the inflamed area and are cleared by activated macrophages, which is consistent with clinical studies of neutrophils from septic patients (232). At the same time, activated macrophages promote the apoptosis of resident cells and ingest them (326). Thus, apoptotic events in cells activated by pathogens are critical for adjusting the host defense mechanism. Arachidonic acid-derived prostaglandins and NO likely represent the principle mediators of the resolution of inflammation by TLR-dependent apoptosis (138). Despite increasing evidence that innate immune responses are significantly modulated by the cellular redox state, concise mechanisms of ROS-dependent signal transduction downstream of TLR activation remain poorly defined (176). A further understanding of the role of apoptosis in the resolution of inflammation may lead to additional therapeutic strategies for attenuating inflammation (326).

D. Lipid metabolites and apoptosis

Recent evidence suggests that the endogenous production of membrane-lipid derived metabolites, including 4-hydroxy-2-nonenal and ceramide, influences apoptotic signaling pathways.

a. 4-Hydroxynonenal. The peroxidative degradation of lipids yields the aldehyde 4-hydroxy-2-nonenal (4-HNE), a relatively stable α,β-unsaturated aldehyde, as a major product (84). The lipid aldehyde is an electrophile, which can attack nucleophilic amino acids such as Cys, His, and Lys. Using purified enzymes and isolated cells, various pathways for biotransformation of the lipid aldehyde have been identified, including enzyme-mediated oxidation, reduction, and GSH conjugation by glutathione-*S* transferases (GST) (354). Indeed, *in vitro* and *in vivo* production of 4-HNE in response to oxidant exposure has been demonstrated using antibodies against protein adducts of the lipid aldehyde. Recent evidence suggests a role for protein modification by 4-HNE in the pathogenesis of several diseases (*e.g.,* alcohol-induced liver disease). The precise mechanism(s) are currently unknown but likely involve the modification of proteins involved in cellular homeostasis or biological signaling. With regard to HNE-induced modulation of signaling kinases, experimental findings obtained thus

far for PKCs and MAPKs appear to indicate that lower concentrations of 4-HNE influence PKC-dependent physiological events such as protein trafficking and secretion, while relatively higher concentrations promote apoptotic death through involvement of novel nPKC isoforms and/or upregulation of JNKs (332). It is now clear that 4-HNE also potentially activates RTK-mediated signaling pathways. Further, inhibition of IKK by pathophysiological amounts of the aldehyde implies a link between lipid peroxidation and the NF-κB pathway (251). Overexpression of GSTα reduced apoptosis caused by agents known to cause membrane lipid peroxidation, including H_2O_2 and ROS-generating systems, as well as by exogenous treatment with 4-HNE. The antiapoptotic effect of GSTα was associated with downregulation of JNK activation (21).

b. Ceramide. The lipid-derived second messenger, ceramide, and its related metabolites, have been recognized as important mediators of apoptosis (Fig. 6). Ceramide (*N*-acylsphingosine) is synthesized *de novo* from the condensation of serine and palmitoyl-CoA. Ceramide is also generated from metabolism of the membrane lipid sphingomyelin in a salvage pathway consisting of acid and neutral sphingomyelinase activities (121). Ceramide can be converted to sphingosine by the action of acid ceramidase, which is then phosphorylated to sphingosine-1-phosphate (S-1-P) by the action of sphingosine kinase, and in turn cleared by sphingosine lyase (278). Ceramide has been recognized as a proapoptotic mediator that also causes cell cycle arrest, whereas S-1-P has opposing actions by promoting cell proliferation and angiogenesis (366). Thus, the relative ratio of S-1-P and ceramide has been proposed as a determinant of cell fate (223). Ceramide is specifically linked to proapoptotic pathways through its potential for activating JNK by tyrosine phosphorylation (292, 388, 406), whereas S-1-P differentially activates the ERK pathway (292). A number of pro-death stimuli induce sphyngomyelinase activity, and/or intracellular ceramide accumulation, including FasL, TNFα, pathogen infections, as well as in ionizing radiation or UVR exposures as described below (*see* Sections II E-G) (116). Ceramide release has also been implicated in apoptosis induced by oxidative stress, including H_2O_2 treatment and GSH depletion (199). Ceramide can concentrate in and enlarge lipid raft microdomains to potentially modulate intrinsic receptor activities (116). The existence of the sphingomyelinase pathway in mitochondria has also led to the suggestion that mitochondrial ceramide may participate in the initiation phase of apoptosis (340). Direct ceramide treatment was shown to induce apoptosis in A549 epithelial cells (191). Ceramide treatment promoted emphysema and lung cell apoptosis *in vivo*. In a model of VEGFR-blockage-induced emphsema, sphingomyelinase was required for the development of emphysema and lung cell apoptosis (281). Interestingly, ceramide treatment also induces autophagy accompanied with upregulation of beclin-1 (322).

E. Photodynamic therapy

Photodynamic therapy/treatment (PDT) is an experimental cancer treatment modality that involves the systemic application of a photosensitizer in combination with the targeted delivery of laser light, at a wavelength specific for the activation of the photosensitizer (110). Upon light-dependent activation, photosensitizers undergo complex photochemical reactions that can generate ROS under aerobic conditions, most predominantly $^1O_2$. The photochemical generation of ROS results in direct cell killing at the site of drug activation, which is harnessed therapeutically for the purpose of tumor ablation/reduction. A host of chemicals can generate $^1O_2$ upon irradiation including biochemicals (*i.e.,* protoporphyrin IX, chlorophylls-*a/b*, bilirubin-IXα, retinal, quinones, and flavins), or man-made dyes (*i.e.,* eosin, methylene blue, acridine orange, and rose bengal). One of the first sensitizers used for clinical PDT applications, hematoporphyrin, has fluorescence and tumor localizing properties exploited for tumor imaging. The chemical derivitization of hematoporphyrin by an acetylation/reduction process produces a mixture, hematoporphyrin derivative (HpD) with enhanced photosensitizing potential (110). Photofrin II (PH-II), a purified form of HpD, has received FDA approval for clinical use in esophageal and early lung cancer. Since the characterization

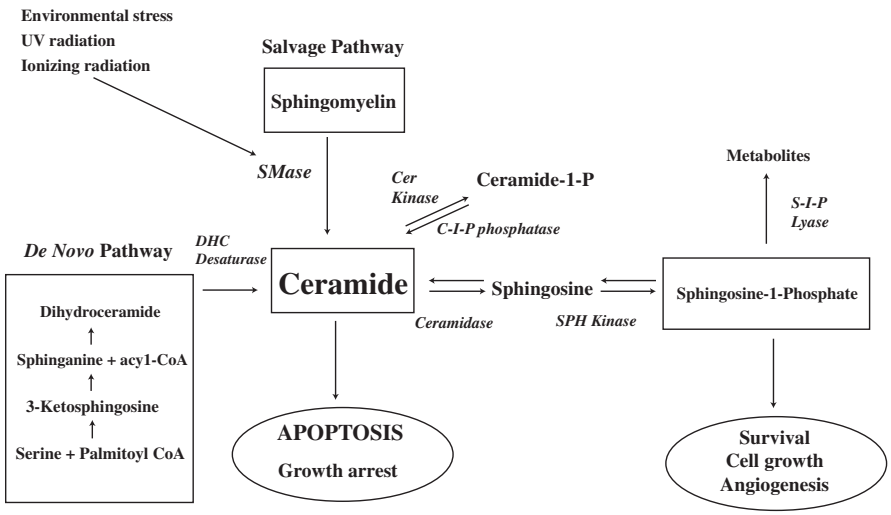

FIG. 6. Ceramide pathways in apoptosis. Ceramide and its metabolite sphingosine-1-phosphate (S-1-P) have emerged as important positive and negative regulators of apoptosis, respectively. Ceramide is synthesized by a *de novo* pathway and by a salvage pathway involving the metabolism of sphingomyelin by sphingomyelinases (*Smase*). Ceramide is converted to S-1-P by an enzymatic pathway, which is degraded by S-1-P lyase.

of PH-II, a second generation of potent synthetic photosensitizing compounds have emerged, which include phthalocyanines, bacteriochlorins, chlorins, purpurins, verdins, and benzoporphyrin derivatives (109). Unlike porphyrin-based photosensitizes that have no metal center, many synthetic photosensitizers contain a transition metal such as aluminum, zinc, tin, or silicon. These compounds also differ from PH-II by their specific subcellular localization properties, absorption maxima, and tissue photoactivation properties (109). An alternative form of PDT, δ-aminolevulinic acid (ALA)-PDT, depends on the stimulation of endogenous production of protoporphyrin-IX, which photosensitizes the cells to red light, achieved by tissue supplementation with the metabolic precursor ALA.

a. Induction of apoptosis by PDT in vitro. Since the principle therapeutic value of PDT lies in targeted cell killing (of neoplasia), by the site-specific generation of ROS ($^1O_2$), much research has been performed on elucidating the underlying mechanisms of photosensitizer-mediated or photooxidative cell death. In cell culture models of photodynamic action, a number of studies have demonstrated cell death with ultrastructural and biochemical features of apoptosis (262). In contrast to ionizing radiation, which induces apoptosis over a longer time interval, PDT of tumor cells appears to result in an early or "immediate" apoptosis, within 30–60 min of initial treatment (2, 218, 262) (Fig. 7).

As with other models of oxidant-induced apoptosis, the general phenomenology associated with initiation of apoptosis has been extensively documented in response to PDT protocols using a variety of photosensitizers, for example, aluminum phthalocyanine chloride (AlPc) and/or silicone phthalocyanine (PC-IV) in several tumor model cell lines. Typical observations include oligonucleosomal DNA laddering and chromatin condensation, Cyt-*c* release, inhibition of respiration, Ca^{2+} mobilization, caspase-3 activation, and PARP cleavage (2, 113). In several cases, activation of the extrinsic apoptotic pathway involving caspase-8 activation has also been proposed (113, 447). Similar to UVA and other radiation models, the release of C2-ceramide from the membrane has been implicated as an intermediate in the apoptosis signaling pathway (325).

Like with many other toxins, increasing the severity of applied dose, in this case determined primarily by the relative fluence of light applied to activate the sensitizer, correlates with transition from apoptotic to necrotic outcomes (218). Additionally, subcellular localization of photosensitizers, and hence the subcellular site of ROS production, can determine the differential induction of apoptosis or necrosis by PDT (163, 218, 219). Studies with multiple photosensitizers varying in subcellular localization properties concluded that the induction of apoptosis by PDT was associated primarily with mitochondrial damage (163). On the other hand cationic sensitizers, or incubation protocols favoring membrane localization of sensitizers, were associated with membrane damage and necrotic outcomes (163, 218).

The role of Bcl-2 proteins in PDT-initiated apoptosis has been extensively studied. Bcl-2 overexpression rendered Chinese hamster ovary (CHO) cells resistant to PC-IV mediated photokilling, and diminished the appearance of apoptotic markers (127). Conversly, retroviral delivery of antisense Bcl-2 transcripts sensitized cells to PDT (438). Overexpression of Bcl-X_L rendered HL-60 cells resistant to photokilling, DNA laddering, and caspase-3 activation triggered by PDT (113). Knockout cells deficient in Bax protein did not display overall differential sensitivity (clonogenicity) to PDT relative to Bax heterozygotic cells ($Bax^{+/-}$), though differential activation pathways were observed. Bax knockout displayed a delayed apoptotic response to PDT involving caspase activation, resulting in death but devoid of Cyt-*c* release (58).

Further studies indicated that PDT-mediated apoptosis coincides with cell growth arrest in G0/G1 phase. The induction

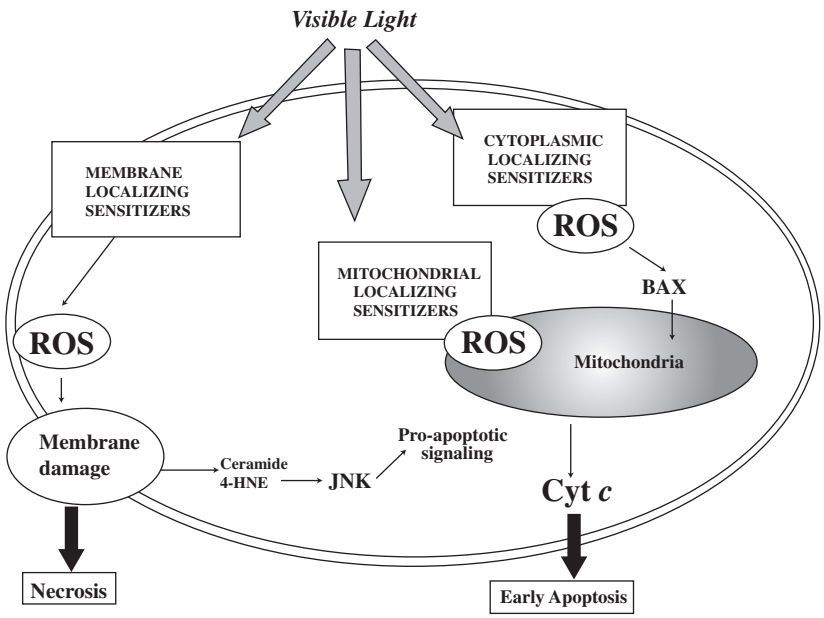

FIG. 7. Photodynamic therapy and cell death. The diagram depicts the pathways by which PDT triggers cell death. Activation of photosensitizers with visible light generates ROS, in particular, singlet molecular oxygen ($^1O_2$). Photosensitizers may localize in various subcellular compartments such as the plasma membrane, mitochondria, or cytoplasm, including lysozomes. Localization of the photosensitizer determines the site of ROS production. Membrane damage is associated with necrosis, but may also generate lipid derivatives involved in apoptosis signaling. Mitochondrial damage by photosensitization is associated with intrinsic apoptotic pathways.

of $p21^{Waf1/Cip1}$ and the downregulation of cyclins and cyclin-dependent kinases, were implicated as an essential component of PDT-mediated apoptosis (4). PDT affected G1-S transition by downregulating the expression of E2F family transcription factors, and decreasing the phosphorylation state of the retinoblastoma protein (pRB) (5). Fibroblasts expressing mutant p53 were found to be more resistant to PDT than normal human fibroblasts expressing wild-type p53 (373). Targeted disruption of the p53 locus in human colon carcinoma and murine MCF-7 breast cancer cells, however, apparently did not affect overall PDT sensitivity but moderately reduced apoptosis in the former cell type (92). PDT induced an early G1 block and pRB hypophosphorylation independently of cellular p53 status in this model, with inductions of $p21^{Waf1/Cip1}$ and p53 occurring at later intervals (92). On the other hand, the retroviral-mediated overexpression of p53 was recently shown to sensitize human tumor cells to PDT, by promoting growth arrest and apoptosis (210). Several studies have documented the relative role of protein kinases in PDT-dependent apoptosis. As with other forms of oxidative stress, PDT treatment can activate the major MAPK families, including p38 MAPK, ERK1/2, and JNK (49, 174, 372, 373, 414), with variations dependent on cell type and applied photosensitizer. Suppression of p38 MAPK or JNK with chemical inhibitors or DNM transfection was sometimes associated with cellular protection (414, 446), but variably also reported to cause sensitization to apoptosis (20), depending on cell type. On the other hand, sustained ERK1/2 activation during PDT correlated with cell survival (372). Interestingly, general PKC activation was associated with protection against PDT-induced apoptosis (447). Other inhibitors of PDT-mediated apoptosis include inhibitors of cycloxygenase-II (COX-2) (86), natural antioxidants such as curcumin (48), α-tocopherol, and $^1O_2$ scavengers (49). In conclusion, PDT represents a specialized model of oxidative stress where apoptosis has been extensively studied. Since the subcellular site of ROS production varies with the physicochemical properties of the chosen sensitizer, cellular experiments with PDT have provided unique mechanistic insight into the relationship between oxidative stress and apoptosis.

b. Induction of apoptosis by PDT in vivo. The overall mechanism of photodynamic killing *in vivo* remains unclear, though several investigations have proposed a primary mechanism involving tumor vascular damage, related to vascular inflammation and endothelial cell apoptosis/ necrosis, leading to decreased tumor blood flow and increased tumor hypoxia. The relative contributions of tumor cell apoptosis/ necrosis remain unclear. PDT treatment of radiation induced fibrosarcomas in mice with various photosensitizers (AlPc, PH-II, or PC-IV) activated by red light, caused rapid tumor cell apoptosis *in vivo*, also associated with chromatin condensation, oligonucleosomal DNA laddering, and formation of apoptotic bodies in excised tissue (430). Similarly, rapid apoptosis was observed in murine squamous papillomas subjected to PC-IV PDT. While tumor ablation occurred within 72–96 h, apoptosis markers were observed as early as 6 h post PDT (3). In experiments applying PC-IV PDT to human tumor xenografts in athymic nude mice, apoptotic markers, such as DNA fragmentation were observed within 15 min in PDT treated tumors. Induction of $p21^{Waf1/Cip1}$ and PARP-1 cleavage were also documented *in vivo,* using this model (66).

F. UV-radiation

Ultraviolet radiation (UVR) has been divided into several functional wavelength ranges, the UVC (<280 nm) which is excluded by the earth's atmosphere; and the UVB (280–320 nm), the UVA (320–380 nm), and near visible (380–420 nm) components, which reach the earth's surface. UVA1 (340–400 nm) is a clinical definition of UVA for therapeutic applications. The UVC and UVB regions overlap the DNA absorption spectra (379) and can cause direct DNA photodamage (*i.e.,* cyclobutane pyrimidine dimers), associated with mutagenesis and tumorigenesis (96). In contrast, the UVA region of the solar spectra is not absorbed directly by DNA. UVA exposure generates cellular oxidative stress, such that it stimulates the intracellular production of ROS by photochemical reactions (380). The oxygen-dependence of UVA photokilling, and the specific involvement of $^1O_2$ in UVA mediated gene regulation have been demonstrated, though the precise endogenous chromophores which mediate UVA-induced ROS production remain poorly defined (379, 380). UVA cause cellular damage characteristic of oxidative stress, including membrane lipid peroxidation and oxidation of intracellular reduced glutathione (GSH). Furthermore, DNA damage can occur after UVA exposure, including DNA strand breaks, and oxidative DNA damage such as 7,8-dihydro-8-oxo-2′-deoxyguanosine (8-OHdG) (192, 244, 365).

a. UVR-induced apoptosis. The mechanisms of apoptosis following cellular exposure to UVR appear to be wavelength specific (Fig. 8). To illustrate this, murine lymphoma cells were irradiated with UVA1, UVB, and UVC at isotoxic doses (107). The UVA1 radiation (340–400 nm) induced both an immediate (<4 h) and a delayed (>20 h) apoptosis mechanism, while UVB or UVC radiation induced only the delayed apoptosis with no early component. The delayed apoptosis seen at all wavelengths was comparable to that observed with DNA damaging agents, whereas the early apoptosis associated with UVA1 was inhibited by membrane antioxidants and inhibitors of the mitochondria transition pore (105–107). Apoptosis after UVA radiation has been observed in a number of physiologically-relevant skin cell models, including human dermal fibroblasts (77), epidermal keratinocytes (19,62), melanocytes (32); as well as transformed cell lines (107, 287, 436). Depending on the cell type, features of both extrinsic (Fas/caspase-8)-dependent and intrinsic (mitochondria-dependent) apoptotic pathways have been reported following cellular irradiation with UVA or UVB, involving modulation of Bcl-2 family proteins and typically culminating in caspase-3 activation (365, 448). A few studies have explored the role of apoptosis proteins in UVA sensitivity. Overexpression of Bcl-2 inhibited UVA-induced immediate apoptosis in rat-6 fibroblasts (287). In human B-lymphocytes, depletion of AIF by RNAi partially inhibited UVA-induced apoptosis, while maximal inhibition was achieved in the presence of both caspase inhibitors and AIF downregulation (428).

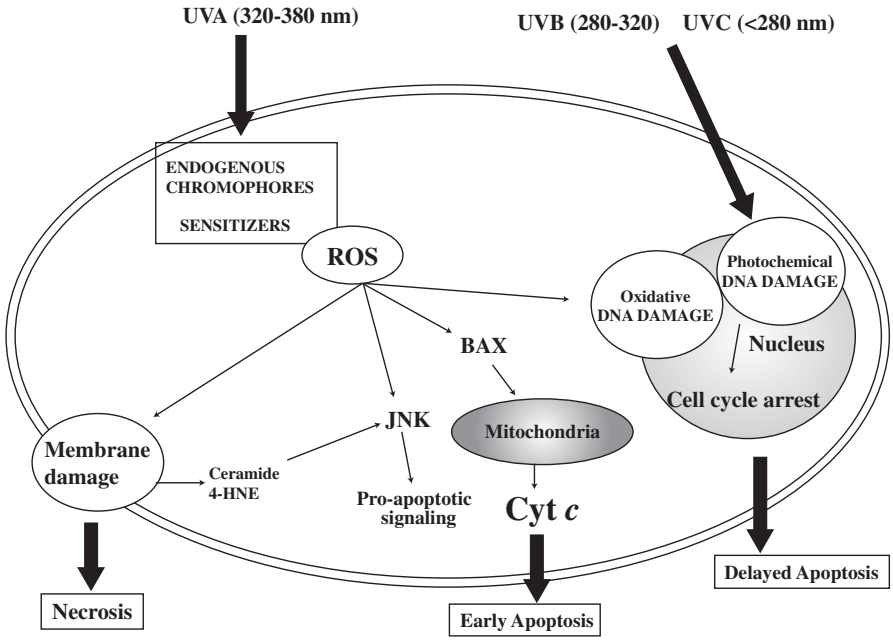

FIG. 8. UVR and cell death. The diagram depicts the pathways by which UVR triggers cell death. UVA (320–380 nm) generates ROS, in particular, singlet molecular oxygen ($^1O_2$). The precise intracellular chromophores remain unclear. Oxidative stress generated by UVA is associated with intrinsic apoptotic pathways. UVA can cause lipid peroxidation and membrane damage, depletion of intracellular glutathione, and oxidative DNA damage. UVC and UVB cause direct photochemical damage to DNA. DNA damage and subsequent cell cycle arrest may lead to the delayed apoptosis observed after exposure to these agents.

Additional mechanisms for UVA-mediated apoptosis potentially include the release of lysosomal proteases (cathepsins A/D) (32), and the generation of membrane lipid metabolites, which potentially serve a signaling function. For example, UVA-mediated apoptosis was associated with the activation of acid sphingomyelinase activity, and increased C-2 ceramide production. Conversely UVA-mediated apoptosis was inhibited in cells deficient in acid sphingomyelinase activity (444). The role of C-2 ceramide in apoptosis signaling is not clear but potentially relates to the modulation of MAPK activities such as JNK. S-1-P treatment protected melanocytes against UVB-mediated apoptosis by stimulating ERK1/2-dependent pathways (165). Since UVA can promote lipid peroxidation, associated increases in the level of 4-HNE may signal to proapoptotic pathways. For example, upon UVA radiation, 4-HNE production correlated with sustained JNK activation and apoptosis in human erythroleukemia cells (422).

Only few studies have addressed the mechanisms of UVA-induced apoptosis *in vivo.* In one example, human skin displayed increases of Fas in epidermal cells in biopsies after both UVA/B irradiation, whereas UVB radiation selectively decreased FasL expression in the epidermis (24).

b. Survival/death pathways in UVR-induced apoptosis. In parallel with many models of cellular stress, UVR can induce the major MAPK pathways in cultured cells, which redundantly and variably have been implicated in both pro-survival and pro-death pathways, in a tissue-specific and wavelength-specific fashion. With respect to JNK, sustained activation has been observed in UVA/B-irradiated cell cultures of various types and associated with the promotion of apoptosis (175, 422). Contradictory studies indicate that pharmacological inhibition of JNK can also sensitize cells to UVA-mediated apoptosis (339, 443).

With respect to p38 MAPK, cell culture experiments indicate that activation of p38 MAPK by UVA/B is generally associated with cell survival, for example, in normal and transformed human keratinocytes (22,62). *In vivo*, however, contrary results are reported in that p38 MAPK inhibitors apparently protected epidermal skin cells from UVB-mediated apoptosis (129).

ERK1/2 activation has also been associated with cell survival in various UVR models. A survival pathway dependent on delayed and prolonged ERK1/2 activation, was observed in UVA irradiated transformed keratinocytes (128). The shorter wavelengths UVB/C also induced the ERK1/2 survival pathways, though the activation appeared more rapidly by a mechanism dependent on EGFR activation (128, 171).

The significance of PKCs in UVA apoptosis remains incompletely understood. The UVA-induced activation of the ERK1/2 survival pathway depended on Ca^{2+}-dependent PKC-α activation (128). In contrast UVB-induced apoptosis required PKC-δ activity (347).

In UVA-irradiated human skin fibroblasts, survival pathways dependent on Nrf-2/Keap pathway activation have been proposed. This pathway, which is associated with the activation of stress proteins and antioxidant enzymes, contributed to apoptosis protection in this model (130). Cellular preconditioning with cytokines, leading to induction of iNOS and NO production, or supplementation of cultures with NO donors protected human skin fibroblasts from UVA-induced apoptosis (362). Upregulation of thioredoxin by transfection protected against UVA-mediated apoptosis (77). Natural antioxidants, such as green tea polyphenols, can also limit UVA/B mediated apoptosis (98).

The roles of p53-dependent and independent growth arrest in mediating UVR-induced apoptosis have also been extensively studied *in vitro*. UVC-mediated apoptosis and growth arrest, as it relates primarily to DNA damage rather than oxidative stress *per se*, lies beyond the scope of this review. In brief, UVC irradiation caused growth arrest in G1 phase associated with hypophosphorylation of pRB independent of p53 status, but induced p53 accumulation in association with

S-phase (119). In melanoma cells, p53 status correlated with sensitivity to UVA/B-induced apoptosis, such that cells expressing mutant p53, with loss of p53 function, were significantly more resistant to apoptosis triggered by both wavelength classes. Mutant p53 cells displayed reduced $p21^{Waf1/Cip1}$, and Bax expression after UVA/B radiation (436).

In conclusion, UVA mimics cellular models of oxidative stress, with respect to the induction of apoptosis-related phenomenon. UVC radiation which selectively promotes direct DNA damage without corresponding cellular oxidative stress, also causes apoptosis and cell cycle arrest, but by different mechanisms requiring longer latent periods.

G. Ionizing radiation

Ionizing radiation (IR) produces free radicals and ROS as the product of radiolysis of water. Radiation of tissue culture media generates electron paramagnetic resonance (EPR)-detectable hydroxyl and hydrogen radicals. The primary target of IR of cells appears to be DNA, with damage manifest as strand breaks, abasic lesions, and DNA base modifications (391). In cell types where IR caused apoptosis, the p53 status of human cells, correlated to the ability of IR to induce Bax (435), and upregulate Bcl-X_L protein expression (88, 434). IR induced p53-dependent apoptosis in immature rat thymocytes (225). In MCF-7 cells expressing wild-type p53, IR preferentially induced G1 arrest, when compared to other cell types deficient in p53 (346). Caspase-3 activation was generally associated with IR-induced apoptosis regardless of p53 status (427). IR caused strictly an intrinsic apoptosis in HL60 cells, resulting in Cyt-*c* release and caspase-3/9 activation, with no activation of Bid/Bax or caspase-8 observed (140). Although caspase-8 inhibitors decreased H_2O_2-mediated apoptosis in HL60 cells, they did not affect IR-induced apoptosis (140). Irradiated mice showed high levels of Bax expression and apoptosis in radiosensitive cell populations including lymphoid cells (170). Transgenic mice overexpressing Bcl-2 or Bcl-X_L resisted IR-mediated apoptosis in thymocyte cell populations (51). Overexpression of Bax sensitized MCF-7 breast cancer cells to IR-mediated apoptosis (311). Conversely, overexpression of Bcl-X_L inhibited IR induced apoptosis in human lymphoblastoid cells, associated with decreased apparent ROS production and decreased Bax expression (404). IR-induced apoptosis depended on p38 MAPK activation (61, 188) and/or activation of the JNK pathway (82). Suppression of the NF-κB activation pathway sensitized cells to IR-induced apoptosis by increasing activation of the JNK pathway (82). IR activated the PI3K/Akt survival pathway in endothelial cells and various tumor cell lines (346, 449), which depended on EGFR or VEGFR signaling (390, 433). Overexpression of Ha-Ras also activated the Akt-dependent survival pathway and protected against IR (61). A number of cytokines (HGF, IGF-I, and IL-6) and other factors that confer radioprotection to cells do so by activating PI3K/Akt (433). Lipid metabolites have been implicated in IR-induced apoptosis. Deletion of the acid sphingomyelninase in transgenic mice rendered lymphocytes resistant to apoptosis induced by IR, and this could be reversed by reconstituting the cells with ceramide (316). Conversely, S-1-P therapy protected against IR induced oocyte apoptosis *in vivo* (243).

In conclusion, since IR primarily causes DNA damage, the mechanisms for apoptosis likely are more closely related to those observed for other DNA damaging agents such as UVC radiation, for example, than to direct exposure to H_2O_2.

H. Cigarette smoke

Cigarette smoke (CS) is a complex mixture of over 4700 components, including heavy metals, aldehydes, aromatic hydrocarbons and phenolics, and high concentrations of ROS, free radicals, and other oxidants (64). Free radicals in CS are derived from both the gas and the tar phase. The gas-phase CS contains approximately 10^{15} radicals per puff, primarily alkyl and peroxyl radicals. In addition, NO is present in CS in concentrations of 500–1,000 ppm (290). NO reacts quickly with O_2^- in the gas phase to form peroxynitrite ($ONOO^-$), and with peroxyl radicals to generate alkyl peroxynitrites (ROONO). CS tar contains more than 10^{18} free radicals per gram (432). The radicals in the tar phase of CS are more stable and are predominantly organic, such as the semiquinone radical, which can react with oxygen to produce O_2^- and H_2O_2. CS tar is also an effective metal chelator and can bind iron as a tar-semiquinone-Fe^{2+} complex (411). Thus, ·OH formation can also be detected in the tar phase (290). Whereas short-lived radicals in the gas phase of CS may be quenched immediately in the epithelial lining fluid, redox reactions in CS condensate, which forms in the epithelial lining fluid, may produce ROS for considerable time (226).

CS represents the main causative factor in the development of chronic obstructive pulmonary disease (COPD) (28, 277), which ranks among the top five leading causes of death worldwide (277). To date, the exact pathophysiology of COPD remains unknown, thus very few effective treatment modalities exist (330). In susceptible smokers, CS exposure potentially results in chronic inflammation of the airways, leading to airways obstruction and an alveolar wall inflammatory response associated with lung cell death, lung tissue destruction, and emphysema (28). Injury of the alveolar epithelium by CS constituents plays a role in the pathogenesis of COPD (28). The mechanisms underlying CS-induced epithelial cell death, however, remain unclear.

Morphological and biochemical features of apoptosis have been observed in several models of pulmonary cells, as well as in other (nonpulmonary) cell types exposed to CS (Fig. 9). While some studies use mainstream cigarette smoke, the majority of studies are performed with either aqueous (or organic) cigarette smoke extract (CSE).

Both oxidative stress (ROS production) and cell death by apoptosis/necrosis exhibit a dose–response relationship with CSE concentrations (44). However both stimulatory and inhibitory potential of smoking on apoptosis have been demonstrated. CSE exposure caused strictly necrosis in lung epithelial cells, with associated inhibition of apoptosis (409). In this model, the antiapoptotic effects of CSE involved upstream inhibition of caspase-3/9 activation, and postmitochondrial regulation of apoptosis-related factors to inhibit active apoptosome formation (409). Cell death in response to CS by necrosis and not apoptosis may be responsible for the loss of alveolar walls and inflammation observed in emphysema (409). Liu *et al.* reported exclusively necrotic phenotypes in

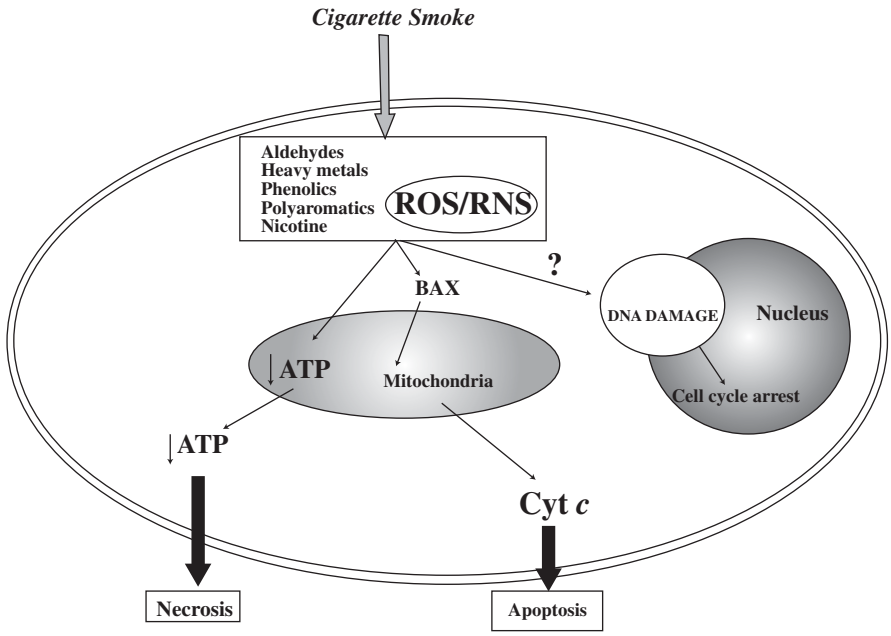

FIG. 9. Cigarette smoke and cell death. The diagram depicts the pathways by which cigarette smoke triggers cell death. Cigarette smoke contains thousand of compounds that may influence toxicity. Cigarette smoke contains ROS/RNS, which may also be generated endogenously as the result of exposure. ROS/RNS trigger intrinsic apoptosis pathways. Loss of mitochondrial ATP generation after smoke treatment has been associated with necrosis. The contribution of DNA damge during smoke exposure to cell death pathways is not clear.

CSE treated Beas-2b cells (213). Nevertheless, CSE was reported by others to cause apoptosis at low concentrations (< 5%) or less in eptithelial cells and necrosis at 10% or more (139). Transitions from apoptotic to necrotic phenotype with increasing CSE dose were also observed in other cell types (386).

In alveolar macrophages, apoptosis by CSE occurred in a dose- and time-dependent manner, with the majority of the cells showing apoptosis after 24 h exposure to a 10% by volume of CSE solution (16). Apoptotic phenotypes appeared in several other lung cell types exposed to CSE, including human lung fibroblasts (44), as well as in mainstream CS-treated rat bronchial/ bronchiolar epithelial cells (71). In alveolar macrophages, CSE induced apoptosis by activating an intrinsic mitochondria-dependent pathway, involving mitochondrial dysfunction (386). In a number of cell types, including nonpulmonary cell types apoptosis caused by CSE was dose dependent, and associated with increased ROS generation. The apoptosis-related phenomena observed resemble those of other oxidative stress models, including Bax protein accumulation, downregulation of Bcl-2, Cyt-*c* release, caspase-3/8 activation, and are variably reported to involve either p53-dependent or p53-independent mechanisms (16, 44, 297, 386, 392, 393). Activation of p38 MAPK and JNK in response to CSE was demonstrated in human aortic endothelial cells, such that pharmacological inhibition of JNK or p38 MAPK inhibited CSE-induced apoptosis (297). Activation of NF-κB by exposure to CS condensate was also reported, consistant with phosphorylation of I-κBα (338).

CSE has been reported to cause DNA damage. CSE-induced DNA damage was reversible, and cells proliferated when CSE was removed after 24 h exposure (166). Seveal avenues of experimentation indicate that ROS are the critical component of CSE-induced toxicity. Antioxidant compounds (*i.e.,* NAC) alone, or in combination with other scavengers (*i.e.,* aldehyde oxidase) protected against CSE-mediated apoptosis in several models, implying the involvement of CSE-derived and/or intracellular reactive species (16, 139, 386). Furthermore, overexpression of GST-π protected human lung fibroblasts against CSE-induced cell death (146). Stimulation of NO production, by eNOS activation, inhibited CSE-induced apoptosis (297).

In addition to ROS/RNS, nicotine represents a major component of CS with potential to modulate cell death programs. Nicotine exposure increased neuronal apoptosis during development (301). Nicotine can alter the cell death pathway by reducing the level of intracellular ATP, and that this effect may contribute to CS-induced tissue destruction (359). In the presence of nicotine, cells were unable to undergo apoptosis and instead died through a form of necrosis (359).

Several studies show that CS exposure can induce apoptosis *in vivo*. Chronic exposure of rats to mainstream CS produced a significant and time-dependent increase in the proportion of apoptotic cells in the bronchial and bronchiolar epithelium (71). Immunohistochemical evaluation of rat terminal bronchioles showed that CS exposure induces apoptosis *in situ*, associated with activation of Bid/Bax, and caspase-3; increased phosphorylation/activation of JNK, p38 MAPK, and p53; upregulation of FasL; and decreased expression of Bcl-2 (190, 413). Exposure to CS can increase apoptosis in the rat gastric mucosa through a ROS-mediated and a p53-independent pathway (222, 392). CS treatment was associated with depletion of serum EGF, and restoration of this factor protected against CS-induced apoptosis in the gastric mucosa (222). Mitochondrial dysfunction and impaired respiration occurred in brain tissue, during rodent CS exposure (15). Deletion of the Nrf-2 pathway, as in *nrf-2*$^{-/-}$ mice, resulted in increased pulmonary apoptosis after chronic CS exposure, increased oxidative stress, and increased susceptibility to emphysema relative to wild-type mice (295).

In conclusion, CSE can cause cell death by apoptosis and necrosis in a dose-responsive fashion depending on the acti-

vation of common pathways observed with other models of oxidative or nitrosative stress. While a majority of the toxicity is attributed to ROS/RNS, since it is inhibited by antioxidants, the model is complicated by the simultaneous presence of thousands of chemicals. Further complexity arises from difficulties in standardizing smoke concentrations for comparison of results between laboratories.

III. MECHANISMS OF CELL DEATH IN OXIDATIVE LUNG INJURY AND ISCHEMIA/REPERFUSION INJURY

A. Hyperoxia

The critical care management of severe respiratory disorders often requires supplemental O_2 therapy to increase arterial pO_2 and reduce tissue hypoxia. Exposure to an elevated oxygen tension (hyperoxia) may cause acute and chronic lung injury. Hyperoxia triggers an extensive inflammatory response in the lung that degrades the alveolar–capillary barrier, leading to impaired gas exchange and pulmonary edema (137). The pathological changes in hyperoxia-injured lungs coincide with the injury or death of pulmonary capillary endothelial cells and alveolar epithelial cells, which maintain the integrity of the alveolar–capillary barrier. Compromised epithelial cell function may permit fluid and macromolecules to leak into the airspace, resulting in clinical respiratory failure and death (228). Thus, the mechanisms of pulmonary cell death in response to high environmental O_2, have been examined *in vitro* and *in vivo*, though the signaling pathways involved remain incompletely understood.

a. Mechanisms of cell death in hyperoxia. The mechanisms underlying hyperoxic cell death *in vitro* have been reported to involve necrosis, apoptosis, or mixed cell-death phenotypes, dependent on the cell type analyzed.

Studies in human A549 lung epithelial cells indicated that hyperoxia killed these cells primarily by necrosis, with no observable manifestation of apoptotic cell death by fluorescence DNA labeling, *in situ* DNA end-labeling, or ultrastructural analysis (160). In contrast, lethal doses of H_2O_2 induced apoptosis in this cell type (160). Similar observations of cell death by necrosis were made in Type-I epithelial, and murine lung bronchial cells (160, 235, 257). Furthermore, pretreatment with hyperoxia inhibited subsequent oxidant (H_2O_2)-induced apoptosis in A549 cells (95). This antiapoptotic preconditioning effect of hyperoxia was related to activation of NF-κB (95). Hyperoxia caused a growth arrest in S-phase consistent with a partial G1 block, associated with observed increases in $p21^{Waf1/Cip1}$. The $p21^{Waf1/Cip1}$ deletion, however, did not prevent hyperoxia-induced growth arrest in A549 cells (235). In similar studies, in MC-12 cells, hyperoxia caused a type of cell death (oncosis) defined by cellular and nuclear swelling, vacuolation, and mitochondrial degeneration, associated with necrosis, while comparative H_2O_2 treatments caused primarily apoptosis, with evidence of caspase activation (300). Despite the difference in death phenotype, both hyperoxia and H_2O_2 treatment resulted in upregulation of similar molecular markers in this cell line, including activation of AP-1, JNK, and p38 MAPK (300). In mouse Type II alveolar epithelial (MLE12) cells, hyperoxia caused a biphasic activation of the JNK pathway, associated with oncotic cell death. In comparison, H_2O_2, which caused death consistent with apoptosis in these cells, caused a sustained JNK activation (208). Stable expression of JNK dominant negative mutant (DNM) protected against hyperoxia-mediated cell death (necrosis) in this cell line (208).

Despite the predominantly necrotic phenotypes observed in several types of lung cells exposed to hyperoxia, apoptosis has also been observed in response to hyperoxic stress in a cell type-specific fashion. When cultured RAW 267.4 murine macrophages were subjected to hyperoxia, increased apoptosis was observed in DNA laddering, TUNEL, and nucleosomal assays. In these cells, hyperoxia treatment selectively activated the MAPK pathway, as evidenced by the time-dependent phosphorylation of ERK1/2, but did not activate the JNK or p38 MAPK pathways. Chemical or genetic inhibition of the ERK1/2 MAPK pathway by the MEK inhibitor PD-98059, or transfection with ERK-DNM, respectively, inhibited hyperoxia-induced macrophage apoptosis. These data suggested that hyperoxia can induce apoptosis in cultured murine macrophages by an ERK1/2 MAPK-dependent mechanism (280). Studies in fibroblasts subjected to hyperoxia, also indicate apoptotic cell death. Rodent fibroblasts displayed increased DNA fragmentation, caspase activation, and Cyt-*c* release upon high oxygen treatment (40). Murine embryonic fibroblasts derived from $Bax^{-/-}$ $Bak^{-/-}$ mice resisted hyperoxia-induced cytotoxicity, indicating the involvement of Bcl-2 family proteins in hyperoxia killing of fibroblasts (40).

Recent studies have confirmed a predominant outcome of necrotic cell death in A549 cells subjected to hyperoxia (399). The necrosis occurred even in the presence of high glucose supplementation, which maintains ATP levels (10). Despite the final phenotypic outcome of cellular necrosis, however, early events in hyperoxia-induced epithelial cell death involved the activation of apoptogenic factors in both extrinsic and intrinsic apoptotic pathways (Fig. 10). The treatment of A549 cells with hyperoxia activated an apoptotic process that involved the increased formation of the Fas-related DISC, and the activation of caspase-8. Furthermore, the increased expression, activation, and mitochondrial translocation of both Bid and Bax were observed. Bid activation by caspase-8 involved cleavage to the p15 form, while Bax activation involved a Bid-dependent conformational change. Activation of both Bax and Bid stimulated the release of mitochondrial Cyt-*c* and cleavage of caspase-9. Compensatory increases in Bcl-X_L but not Bcl-2 expression were also observed. While overexpression of Bcl-X_L had no effect, the inhibition of caspase-8 by overexpression of FLIP protected A549 epithelial cells from hyperoxia-induced cell death, by reducing the levels of Bid and by reducing the activated form of Bax. Similarly, the $bid^{-/-}$ genotype significantly conferred resistance to hyperoxia-induced mortality in fibroblasts (399). This study suggested that cell death in cultured human A549 epithelial cells involves a cellular death pathway culminating in necrosis-like cell death, that shares features of both extrinsic and intrinsic apoptosis, and is insensitive to Bcl-X_L inhibition (399). Such mixed death phenotypes have

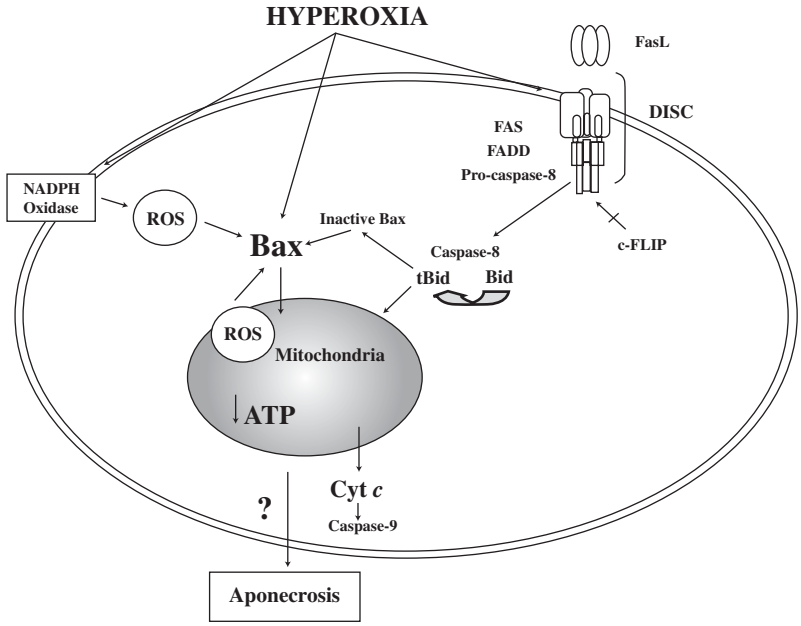

FIG. 10. Pathways to cell death in hyperoxia. The diagram depicts the pathways by which hyperoxia (high oxygen tension) triggers cell death. Hyperoxia increases intracellular ROS production. Both mitochondrial-derived ROS and activation of NADPH oxidase have been implied in this process. Hyperoxia triggers both mitochondrial (intrinsic) and death receptor-dependent (extrinsic) apoptotic pathways in pulmonary epithelial cells. Despite activation of apoptogenic factors, necrosis or mixed cell death (aponecrosis) appears to be the most common phenotype (399).

been described in other models and collectively referred to as "aponecrosis" though their functional significance as a distinct form of cell death remains unclear (94).

b. Hyperoxic lung injury. Morphological studies using animal models have described hyperoxia-induced lung injury. The first signs of injury include focal cytoplasmic swelling of microvascular endothelial cells, interstitial edema, and endothelial cell fragmentation. After 72 h of exposure, type-I pulmonary epithelial cells begin to die by necrosis (136, 228). The epithelial cell death from prolonged exposure leads to epithelial loss of alveolar integrity, airway fluid accumulation, and mortality. Several studies of hyperoxic lung injury in rodents have observed that lung cells can exhibit features of both necrosis and/or apoptosis *in situ,* including chromatin condensation, DNA fragmentation, changes in the expression of Bcl-2 family genes, and increases in TUNEL-positive cells (27, 235, 258, 268, 399). Intravenous infusion of the caspase inhibitor Z-VAD*fmk* into mice, however, did not protect pulmonary cells from hyperoxia-induced death, nor affect lung weights and DNA laddering (27). These features of hyperoxic lung injury suggest that apoptosis and necrosis may occur in discrete lung cell types, and as competing processes in the same cell type. Thus, the evidence indicates that hyperoxic lung injury involves histological features of both apoptosis and necrosis, and it remains difficult to ascertain how these forms of cell death are distributed among the various cell types *in vivo* (229).

Members of the death receptor superfamily, including Fas (27) and TNF-R1 (408), as well as Bcl family members (*i.e.,* Bax and Bcl-X_L) have been implicated in hyperoxic lung injury. Adult mice exposed to hyperoxia (>95% O_2) for 72 h displayed increases in whole-lung Bax and Bcl-X_L mRNA levels; unaltered Bak, Bad, or Bcl-2 mRNA levels; and decreased Bcl-w and Bfl-1 mRNA levels (27, 258). Increases in Bcl-X_L protein, but not in Bax protein, have been reported in response to hyperoxia in the mouse lung (235, 258, 399). Recent studies have confirmed lack of changes in total Bax expression, and observed increases in Bid protein in the mouse lung subjected to hyperoxia (399). Hyperoxia may induce other cell-death related molecules, such as p53 and $p21^{Waf1/Cip1}$ (27, 235, 259–261). Expression of the p53 protein responds to DNA damage, and in turn regulates genes involved in growth control, DNA repair, and apoptosis. By increasing the expression of proapoptotic Bcl-2 family members such as Bax, p53 may promote cell death. A major regulatory target of p53, the cyclin-dependent kinase inhibitor $p21^{Waf1/Cip1}$, may protect against oxidative lung injury by inhibiting cell proliferation and DNA replication, and promoting DNA repair (261).

In vivo studies using genetically deleted mouse strains have revealed the relative roles of apoptosis and cell growth-related proteins in oxygen sensitivity of the lung. With respect to cell-cycle proteins, $p21^{-/-}$ mice were more sensitive than wild-type mice, whereas $p53^{-/-}$ mice did not display any modulation of oxygen sensitivity (27, 258, 261). Hyperoxia induced the expression of $p21^{Waf1/Cip1}$ and of growth arrest and DNA damage-inducible (GADD) genes in $p53^{-/-}$ mice (258, 261). These observations suggest that regulatory targets of p53 such as $p21^{Waf1/Cip1}$ modulate cellular sensitivity to hyperoxia, though p53 itself is apparently not essential. $fas^{-/-}$ (lpr) mice (27), *tnfr1*/$2^{-/-}$ mice (288) and $fasl^{-/-}$ (gld) mice did not display resistance to hyperoxia relative to the corresponding wild-type mice (399). The activated form of Bid (p15), which occurs downstream of Fas in the extrinsic apoptotic pathway, appeared only in the lungs of wild-type mice but not $fas^{-/-}$ or $fasl^{-/-}$ subjected to hyperoxia, whereas equivalent Bcl-X_L expression and caspase-9 activation was observed in all strains after hyperoxia. Genetic deletion of Bid modulated hyperoxia sensitivity *in vivo*. Bid knock-out ($bid^{-/-}$) mice were significantly more resistant to oxygen

toxicity (>95% O_2) than the corresponding wild-type littermates (399). Overexpression of the caspase-8 competitive inhibitor FLIP, using adenoviral-mediated gene delivery in mice, resulted in hyperoxia resistance. In contrast, overexpression of Bcl-X_L did not confer protection against hyperoxia in mice. These results suggested that the caspase-8/Bid pathway represents a major pathway leading to pulmonary cell death during the hyperoxia response *in vivo*. The deletion of the death receptor Fas or its ligand FasL promoted increased basal Bax expression and further elevations of Bax expression during *in vivo* hyperoxia, relative to wild-type mice which did not express Bax protein following hyperoxia. Thus, an alternate pathway to death occurs in *fas*$^{-/-}$ or *fasl*$^{-/-}$ mice, likely mediated by a compensatory activation of the Bax-induced pathway, or by alternative mechanisms of Bid activation (399).

B. LPS-induced lung injury

Endotoxin (LPS) challenge in animals represents a model of acute lung injury. LPS challenge promotes a massive inflammatory response associated with lung tissue injury, lung cell apoptosis, and necrosis. The specific pathways of LPS receptor (TLR4) activation in macrophage apoptosis have been discussed previously (*see* Section II-C). Intratracheal administration of LPS into the lungs of mice caused epithelial cell injury within one day of administration (172). Increased TUNEL positive staining was observed in lung macrophages, neurophils, and in the alveolar wall within one day, coincident with upregulation of Fas (172). In addition to these cell types, analysis of TUNEL staining and DNA strand breaks also revealed extensive endothelial cell apotosis after LPS instillation (100). The caspase-3 inhibitor Z-VAD*fmk* inhibited LPS-inducible pulmonary cell apoptosis *in vivo* and increased survival after endotoxin challenge (159). Mice genetically deleted for cIAP (*ciap*$^{-/-}$) were sensitized to LPS-induced sepsis, and alveolar macrophages derived from these animals displayed increased apoptosis in response to LPS (67). Relative to the body of work on inflammatory responses, relatively little work has been performed on apoptosis following LPS-induced injury *in vitro* and *in vivo*.

C. Ischemia/reperfusion (I/R)

Ischemia/reperfusion (I/R) refers to the stoppage and subsequent restitution of blood flow as a component of disease, such as in cardiac arrest and myocardial infarction, shock, transplantation, respiratory failure, or by mechanical intervention. Interruptions in blood flow can lead to diminished O_2 tension (hypoxia) in tissues. Hypoxia represents a physiologically relevant stress that affects lung and cardiovascular function, and therefore contributes to the pathophysiology of common causes of mortality, including ischemic heart failure, stroke, cancer, chronic lung disease, and congestive heart failure. The reoxygenation of tissue following hypoxic episodes has long been associated with the increased production of ROS at the time of reperfusion, which may contribute to the appearance of tissue injury. Additionally I/R may cause injury through the recruitment of pro-inflammatory leucocytes. Endothelial cells represent the first cell type injured by ROS generated during I/R (360). *In vivo* models of I/R injury usually involve temporal clamping of arteries, whereas *in vitro* models of I/R injury, such as in cell culture models lacking a flow component, rely on manipulation of O_2 tension to generate an artificial hypoxia/reoxygenation (H/R), involving a sustained decrease of O_2, followed by restitution of ambient O_2 tension (308). It should be noted that ROS production can occur during reperfusion after minutes of ischemia *in vivo*. In tissue culture, however the same effect is typically observed *in vitro* after reoxygenation subsequent to many hours of hypoxia. This reflection of fundamental differences between the models is one indication that other factors contribute to I/R injury *in vivo* that cannot be modeled by H/R alone.

a. Mechanisms of lung cell death in hypoxia/reoxygenation. The cell death pathways induced by H/R in lung cells and their underlying regulatory mechanisms remain poorly understood, and may involve both necrotic and apoptotic forms of cell death. Numerous studies have suggested that H/R can induce apoptosis, dependent on the regulation of apoptotic factors. H/R stress can trigger the intrinsic apoptotic cascade in several cell types as the product of irreparable mitochondrial damage (247, 308). The potential expression of FasL during H/R may trigger Fas-dependent death pathways characterized by DISC formation and caspase-8 activation (147). When human fetal alveolar type II epithelial cells were subjected to H/R treatment, Bcl-2 displayed maximum abundance in hypoxia and mild reoxygenation. With increasing partial O_2 pressure, the Bcl-2 expression declined with reciprocal increase in Bax (120). Hypoxia also induced a time-dependent mitochondrial translocation of Bax, with the subsequent release of Cyt-*c* and apoptotic cell death upon reoxygenation (307). The antiapoptotic molecules in the Bcl-2 family, (i.e., Bcl-2, Bcl-X_L) may be downregulated in several cell types during H/R (307, 308).

Recent studies demonstrate that H/R causes cell death in mouse lung endothelial cells (MLEC) by stimulating both intrinsic and extrinsic apoptotic pathways (Fig. 11) (400–402). The cell death was associated with the activation and mitochondrial translocation of Bax, and caspase-9 activation. Additionally, a predominant role for the caspase-8/Bid pathway in signaling associated with H/R induced cell death was observed in MLEC (400–402). An increased expression of FasL was observed during H/R in MLEC and other cell types (147, 402). In MLEC, H/R induced a time-dependent cleavage of Bid at early kinetic points during the reoxygenation, which was attributed to DISC formation and activation of caspase-8. The mechanism by which Bid is proteolytically activated in the lung after hypoxia remains unclear. In addition to the appearance of activated DISC at the plasma membrane, H/R appeared to cause preassembly of DISC in the Golgi fraction which preceded its translocation to the plasma membrane (401). The mitochondrial Bax translocation following H/R treatment in MLEC, occurred without modulating total Bax protein levels (308, 401). The importance of Bid may increase during the hypoxic phase and at early reoxygenation times, whereas Bax may be important at later reoxygenation times, and likely does not cause cell death during the hypoxic phase. In accord with previous studies indicating that PKC can be induced by hypoxia (43), the expression and plasma

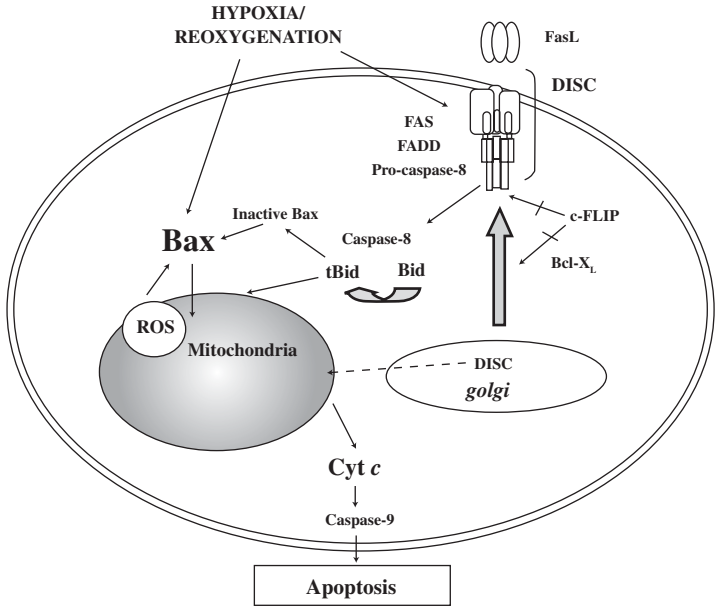

FIG. 11. Pathways to cell death in hypoxia/reoxygenation. The diagram depicts the pathways by which H/R stress triggers cell death. H/R triggers both mitochondrial (intrinsic) and death receptor-dependent (extrinsic) apoptotic pathways in MLEC. Bcl-X_L inhibited H/R-induced cell death by decreasing the formation of the DISC in the plasma membrane and Golgi apparatus, and diverting the DISC to the mitochondria. Bcl-X_L also inhibited caspase-8 activation and the mitochondrial translocation of Bid and Bax (401). Expression of c-FLIP inhibted caspase-8 activation and trafficking of the DISC from the Golgi apparatus (400).

membrane translocation of PKC was activated by hypoxia in MLEC, which preferentially involved the α and ζ isoforms (400). Under normoxic conditions PKCα/ξ were found in complex with Bax (400).

Expression of antiapoptotic factor Bcl-X_L in MLEC inhibited both intrinsic and extrinsic apoptosis pathways induced by H/R. Artificial Bcl-X_L expression inhibited Bax and Bid activation and translocation to the mitochondria, and ultimately Cyt-*c* release and pro-caspase-9 activation (401). Bcl-X_L inhibited caspase-8 cleavage and disrupted DISC formation in the plasma membrane of MLEC subjected to H/R stress. Bcl-X_L overexpression also antagonized DISC formation in the Golgi complex, and inhibited its association with Golgi associated proteins (401). In contrast, Bcl-X_L overexpression increased the appearance of the DISC in the mitochondrial fraction, where caspases-8 cannot undergo efficient processing (357). It remains unclear whether Bcl-X_L blocks Bid cleavage directly, or acts strictly by limiting the availability of active caspase-8 by promoting its mitochondrial sequestration. The effect of Bcl-X_L on the redistribution of DISC formation in these cellular compartments protected endothelial cells from the lethal effects of H/R. Bcl-X_L overexpression also stimulated the expression of FLIP, which may have contributed to the overall anti-apoptotic effect.

In MLEC, artificial overexpression of FLIP also inhibited H/R-induced cell death by blocking both extrinsic and intrinsic apoptosis (400). FLIP prevented caspase-8 processing, and inhibited Bid and Bax activation and mitochondrial localization, and subsequent Cyt-*c* release. FLIP overexpression also upregulated Bcl-X_L. FLIP inhibited Bax activation in both wild-type and in *bid*$^{-/-}$ MLEC, indicating independence from the caspase-8/Bid pathway (400). FLIP expression inhibited the expression and activation (membrane translocation) of PKCα/ζ during H/R, and promoted an association of these forms of PKC with Bax, resulting in Bax inhibition. The mechanism by which FLIP inhibits PKC translocation remains unclear. Surprisingly, FLIP expression also inhibited DISC formation at the plasma membrane, by retaining the DISC in the Golgi. Unlike Bcl-X_L overexpression, FLIP overexpression did not prevent DISC formation in the Golgi (400).

In MLEC, conditioning with hepatocyte growth factor (HGF) also markedly inhibited H/R-induced endothelial cell apoptosis (402). HGF is a multifunctional cytokine involved in tissue repair and angiogenesis, which acts as a mitogen and motogen for epithelial and endothelial cells. HGF has been reported to be a survival factor for endothelial cells (221), and protects against human endothelial cell death during H/R *in vitro* by promoting Bcl-2 expression (417). In MLEC, the cytoprotection afforded by HGF was mediated in part, by the stimulation of FLIP expression, which inhibited DISC formation, caspase-8 activation, and Bid cleavage. HGF also decreased Bax activation and mitochondrial translocation in response to H/R (402). HGF preserved the expression of the antiapoptotic Bcl-X_L protein, which was downregulated during the reoxygenation phase. HGF has been shown in other cell types to activate signaling pathways directly leading to modulation of Bcl-2 family proteins such as Bcl-X_L (249).

b. Lung I/R injury. Ischemia/reperfusion, which generates cytotoxic ROS, and promotes the recruitment of inflammatory leukocytes, causes lung injury and cell death involving both necrotic and apoptotic events. Endothelial cells appear to be the first cell type injured by ROS generated during I/R (360). Latent, but potentially lethal, ischemic damage may cause cells in different regions of the lung to sustain reperfusion injury by restitution of blood flow. Cell death may also arise as a secondary consequence of inflammation around dead tissue. The inflammatory response can play a deleterious role in I/R-induced lung injury (369). Pulmonary I/R induced biochemical features of apoptosis in mouse lung, including increased expression of Fas, FasL, and activation of caspases (3-, 8-, 9-), modulation of Bcl-2-related proteins, PARP cleavage, and Cyt-*c* release (441).

c. Mechanisms of cardiac cell death in hypoxia/reoxygenation. The cardiomyocyte has been studied extensively as an *in vitro* model for cardiac I/R injury. As in other cultured cell models, reoxygenation of hypoxic cultures is associated with ROS production which leads to cell injury and death. For example, H/R treatment caused reoxygenation-dependent apoptosis in cultured cardiomyocytes independent of p53 status (405), which was associated with the typical markers, including Bax mitochondrial translocation, Cyt-*c* release, and DNA fragmentation (117, 155). Simulated ischemia also caused Bax translocation to mitochondria, which depended on p38 MAPK (42).

The application of mild stress, by stimulating endogenous adaptive processes, often confers cellular or tissue protection against subsequent insult. In addition to their role in cellular damage after reoxygenation, ROS have also been implicated in ischemic preconditioning. For example, pretreatment with hypoxia protected cardiomyocytes from subsequent simulated I/R, presumably by enhancing mitochondrial ROS generation. Directed application of H_2O_2 in this model also protected cardiomyocytes against subsequent I/R, whereas this preconditioning effect was blocked by antioxidants (384). The relative role of MAPK pathways, especially between *in vitro* and *in vivo* models, in promotion or inhibition of cardiomyocyte apoptosis remains unclear. Exposure of cardiomyocytes to repeated cycles of H/R caused the reoxygenation–dependent activation of JNK, which required ROS production since it was inhibited by antioxidants (194). Antisense oligonucleotides specific to JNK1 or transfection with JNK-pathway specific DNM protected against reoxygenation-induced apoptosis in H/R-treated cardiomyocytes (141). While JNK activation is associated with H/R induced apoptosis *in vitro*, simultaneous inhibition of JNK and p38 MAPK aggravated I/R injury in the rat heart (329).

Apoptosis is a histochemical feature of myocardial tissue from heat transplant/ heart failure patients (156). Apoptosis of cardiac cells has been observed in animal hearts, and in isolated heart models after cardiac I/R. For example, I/R treatment of isolated hearts, but not ischemia alone, caused a reperfusion-dependent myocardial apoptosis, also independent of p53 status (405). The apoptosis observed in isolated hearts after I/R depends on intrinsic apoptotic pathways, since mice genetically-depleted of Bax, (*bax*$^{-/-}$) displayed reduced cardiomyocyte apoptosis following I/R (131). A role for extrinsic apoptosis has also been implied, since isolated hearts from *fas*$^{-/-}$ (lpr) mice also resist I/R-induced apoptosis (147).

d. I/R injury and apoptosis in other organ systems. Organ I/R injury resulting as a general complication of surgery or transplantation, may limit the success of these procedures (154). Thus, apoptosis has been studied in models of kidney, intestinal, liver, and cerebral I/R injury. Experimental I/R of the kidney induces oxidative injury to proximal and distal renal tubular cells. Ligation of the superior mesenteric artery caused apoptosis associated with DNA fragmentation associated with ischemia, which was further exacerbated as a function of reoxygenation (255). In rats, renal I/R increased O_2^- production in the kidney, and caused apoptosis in the proximal and distal tubles, involving Fas, caspase-3 activation, PARP cleavage, and decreased Bcl-2/Bax ratio. Following renal I/R in mice, transcripts corresponding to apoptosis-associated proteins were upregulated in tubule cells (361). Adenoviral-mediated expression of Bcl-2 inhibited renal I/R injury and apoptosis in the proximal and distal tubles (57). Renal I/R induced p38 MAPK and JNK1/2. While p38 MAPK activation occurred as a function of ischemia, activation of JNKs and JNK substrates occurred as a function of the reoxygenation (424). Ischemic preconditioning with FK506 or cyclosporin-A *in vivo* prevented renal cell apoptosis induced by renal I/R, in a mechanism dependent on stress protein (Hsp70) induction (418). Preconditioning with erythropoietin *in vivo* also reduced apoptosis associated with renal I/R, by increasing Hsp70 levels and Bcl-2 expression, leading to decreases in JNK activation and caspase activation (419). As in other models, I/R injury to the intestine causes epithelial cell apoptosis associated with caspase activation and DNA fragmentation. In the rat, intestinal I/R stimulated p38 MAPK after reperfusion, such that treatment with inhibitors of p38 MAPK reduced epithelial cell apoptosis (445). Overexpression of Bcl-2 in transgenic mice protected intestinal epithelial cells from I/R induced apoptosis (69). As in other models, preconditioning, for example, with recombinant HGF, protects against intestinal I/R injury (187).

Hepatic I/R causes apoptosis of sinusoidal endothelial cells and hepatocytes (154). Adenoviral-directed overexpression of Bcl-2 generally protected against hepatic I/R injury in the mouse and prolonged survival (31). In contrast, a more recent study in a similar model reported that Bcl-2 expression promoted hepatic I/R-induced hepatocyte apoptosis (265). Overexpression of constitutively active Akt protected against hepatic I/R-induced apoptosis by increasing Bad phosphorylation and inhbiting Cyt-*c* release (123). Similarily, treatment with caspase-3 inhibitors reduced hepatic I/R injury and improved the outcome of liver transplatation (245).

In a model of focal cerebral ischemia in mice, ischemic neuronal apoptosis involved the activation of the caspase-8/Bid-mediated mitochondrial pathway leading to Cyt-*c* release (284). The transcription and expression of Bcl-2 and Bcl-X_L increased after sublethal forebrain ischemia, but Bax remained unchanged suggesting that upregulation of Bcl-X_L may participate in protective ischemic preconditioning (412).

IV. HEME OXYGENASE-1/CO IN CELL DEATH/APOPTOSIS

When mammalian cells are subjected to stress, they respond by alterations in cellular protein synthesis, characterized by the transient induction of distinct protein species above basal levels, against an overall attenuation of cellular protein and mRNA synthesis. These "stress protein responses" contribute to overall cellular defense mechanisms and/or survival pathways against the stress conditions that induce their expression. Of these, the classical heat shock proteins, which include a number of distinct proteins (HSPs) (*i.e.,* Hsp70, Hsp90, and Hsp27) are transcriptionally regulated by thermal stress. The HSPs confer adaptive thermotolerance by binding and sequestering denatured or malfolded

proteins, thus preventing their aggregation. In addition to thermoprotection, it has become clear that HSPs participate in immunomodulation, and can also regulate the apoptotic program. A subclass of these proteins, the glucose regulated proteins (GRPs), provides a chaperoning function in the context of ER stress. The relative roles of these stress proteins in apoptosis has been reviewed elsewhere (353). A distinct class of stress proteins is uniquely represented by the heme oxygenase enzymes (HO; E.C. 1:14:99:3). Heme oxygenase-1 (HO-1), the rate-limiting step in heme degradation identical to the low molecular weight stress protein (p32, HSP32), has emerged as a key player in cellular defense against environmental stress. HO-1 is particularly responsive to various forms of ROS/RNS generating systems, but also responds to a myriad of other stress conditions, which include cytokines, hormones, volatile anaesthetics, thiol-reactives substances, heavy metals, endotoxin, and UVA radiation (133, 304). HO-1 has been associated with pleiotropic protective properties in cell culture and *in vivo* associated in part with antioxidative effects, and with the suppression of inflammation, proliferation, and apoptosis. HO-1 confers protection against oxidative stress in numerous *in vivo* models, including hyperoxia, hypoxia, I/R injury, and sepsis (see Ref. 304 for review). The HO-directed degradation of heme, generates biliveridin-IXα, with the concomitant liberation of Fe (II) and carbon monoxide (CO) derived from the heme α-carbon (368). All of these byproducts have been implicated in cytoprotective effects of HO-1 (133, 304). HO deficiency in humans leads to anemia and extensive endothelial cell damage (415). Endothelial cells derived from *ho-1*$^{-/-}$ mice display an oxidative stress sensitive phenotype *in vitro* (286). The application of CO at low concentration mimics the cytoprotective effects observed with HO-1 expression *in vitro* (35, 266). Low dose CO exerts potent anti-inflammatory (266), antiapoptotic (35), and antiproliferative (242, 270) effects in cell culture and *in vivo* by modulating intracellular signaling pathways (Fig. 12). As the extensive biology of the HO/CO system has been described elsewhere (304), only those features directly relevant to apoptosis mechanisms will be described further.

A. Effects of heme oxygenase-1 on cell death

HO-1 overexpression conferred antiapoptotic protection in a model of TNFα-induced cell death in murine lung fibroblasts *in vitro,* which involved increases in cGMP (282). This was not observed within cells overexpressing HO-antisense RNA. Similar functions of HO-1 expression that reduced cell death during oxidative stress conditions could be demonstated in multiple *in vitro* as well as *in vivo* models (304). The pathway through which HO-1 exerts its function seems to be independent of Fas/FasL, since antiapoptotic features were demonstrated in Fas-deficient mice that were treated with adenoviral HO-1 (AdHO-1) in a model of pulmonary fibrosis (376). There is some evidence that HO-1 acts via the induction of Bcl-X_L and p38 MAPK in human hepatocytes (377). In addition, the antioxidative effects of HO-1 and its prevention of oxidant-induced apoptosis potentially involve secondary increases in antioxidant enzymes (e.g., SOD and catalase) (378).

B. Effects of HO-derived reaction products on cell death

For each of the products of HO, such as iron (Fe), biliverdin (BV), and carbon monoxide (CO), effects on cell death have been proposed.

a. HO-derived iron. Despite the known pro-oxidant properties of iron, including that which is liberated from heme by HO-dependent heme degradation, the effect of endogenous HO-1 expression appears to be protection, rather than sensitization, to oxidative stress. In HO overexpression models, however, immediate early sensitivity to oxidative stimuli were observed related to transient iron accumulation (reviewed in Ref.

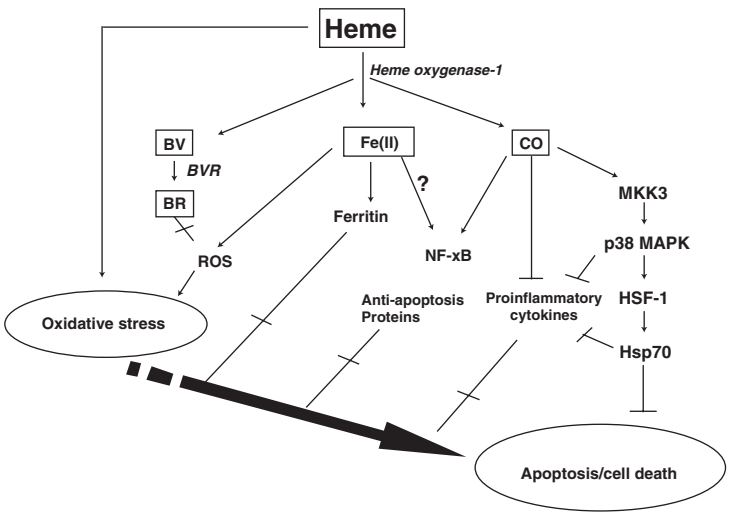

FIG. 12. Antiapoptotic potential of the heme oxygenase-1/carbon monoxide system. Heme oxygenase (E.C. 1:14:99:3) catalyzes the rate-limiting step in the oxidative metabolism of heme to form three reaction products: Biliverdin IXα (BV) which is converted to bilirubin-IXα (BV) by the enzyme NAD(P)H:biliverdin reductase (BVR), as well as carbon monoxide (CO) and Fe(II). Each of these end product pathways have been implicated directly or indirectly in antiapoptotic protection conferred by heme oxygenase-1. BV and BR have antioxidant properties, which may result in general protection from ROS scavenging. Fe(II) stimulates the synthesis of ferritin which sequesters iron in an inert form. Ferritin has been implicated in cytoprotection and tissue protection. An iron-dependent antiapoptotic pathway involving NF-κB activation has also been proposed. CO protects against endothelial cell apoptosis by modulating the mitogen activated protein kinase kinase-3 (MKK3)/p38 mitogen-activated protein kinase (p38 MAPK) pathway. This pathway has been implicated in both antiapoptotic and anti-inflammatory (*i.e.,* downregulation of cytokine production) effects of CO, as well as in the secondary increases of stress proteins (*i.e.,* Hsp70), which may contribute to tissue protection.

304). This apparent paradox might be explained by the fact that HO stimulates iron efflux from cells (87), and also promotes the synthesis of ferritin, which eventually neutralizes potentially reactive iron (389). Iron release from HO activity leads to post-translational release of translational repression of ferritin, therefore ferritin synthesis is increased (389). HO-1 induction following UVA radiation provided cellular resistance to subsequent UVA irradiation, which could be blocked by HO-1 antisense oligonucleotides (389). This cytoprotective effect was linked to HO-dependent increases in ferritin, and was blocked by scavenging of reactive iron with desferrioxamine (389). HO-1 induction resulted in cellular resistance to PDT treatment or oxidant challenge, which was reversible by incubating cells with antisense oligonucleotides against ferritin mRNA (211). Ferritin overexpression reduced apoptosis in a model of I/R injury after liver transplantation (30). Thus, ferritin appears to confer cytoprotection against oxidative challenge, and potentially plays an intermediate role in HO-mediated antiapoptotic protection. Furthermore, the ATP-dependent iron pump colocalizes with HO-1 in the microsomal membrane. This pump also might facilitate the exocytosis of HO-derived iron (26). A possible antiapoptotic mechanism of intracellular HO-derived iron has recently been suggested. HO-derived iron promotes NF-κB activation in HO-1 overexpressing cells, which in turn mediates an antiapoptotic pathway (60). Nevertheless, the role of intracellular iron in apoptosis sensitivity/resistence remains unknown. Iron loading sensitizes endothelial cells to oxidant-mediated cell killing (23). On the other hand, complete deprivation of iron leads to apoptosis, as suggested by pro-apoptotic effects of metal chelator treatments, suggesting that at least a minimal amount of iron is needed to serve for vital cellular processes (114).

b. Biliverdin/bilirubin. Biliverdin originates in the human body from the degradation of heme, primarily that derived from hemoglobin. Biliverdin is further reduced to bilirubin by the enzyme NAD(P)H:biliverdin reductase. Biliverdin, as well as bilirubin, exert potent antioxidative and antinitrosative effects in diverse cell culture models, including endothelial, vascular smooth muscle, HeLa cells, and cardiomyocytes (reviewed in Ref. 304). Moreover, various *in vivo* studies investigating disease models, such as I/R, transplantation, pulmonary fibrosis, or organ injury, demonstrated a reduction of cell death when bilirubin or biliverdin were administered or present at elevated levels (reviewed in Ref. 304). The underlying mechanisms remain unclear, but potentially also include anti-inflammatory, antiapoptotic, and antiproliferative effects. Since bilirubin has antioxidant properties as potent as α-tocopherol in *in vitro* systems of liposomal lipid and LDL oxidation (358), it remains reasonable to speculate that any implicit antiapoptotic effect of bilirubin is at least in part based on ROS scavenging effects.

c. Carbon monoxide. CO administered in a dose range between 15 and 1000 parts per million (ppm) provides antiapoptotic effects *in vitro* as well as *in vivo* (35, 282, 451). The antiapoptotic potential of CO was first demonstrated *in vitro*. Exposure of cell cultures to exogenous CO inhibited TNFα-initiated apoptosis in mouse fibroblasts (282), and endothelial cells (35). Several underlying mechanisms for CO-dependent antiapoptotic effects have been proposed. The antiapoptotic effect of CO *in vitro* depended on soluble guanylyl cyclase (sGC)(216, 282), and/or p38 MAPK (35). The increase of p38 MAPK by CO is preceded by the activation of MKK3/6, which do not activate other MAPK (*i.e.,* ERK or JNK). In the endothelial cell model, the inhibitory effect of CO on TNFα-induced apoptosis could be abolished with the chemical inhibitor of p38 MAPK, SB203580, or a p38 MAPK DNM (35). Furthermore, HO-1 or CO-induced NF-κB-dependent antiapoptotic genes (cIAP2 and A1) to protect against TNFα-mediated endothelial cell apoptosis (34). Overexpression of I-κB resulted in a loss of CO-mediated protection. The activation of p38 MAPK by CO induces heat shock factor-1 (HSF-1), which upregulates the heat shock protein 70 (Hsp70), and thus promotes another possible antiapoptotic mechanism (167). CO acts as a potent anti-inflammatory substance, thereby indirectly inhibiting cytokine-mediated apoptosis (215, 266). The antiapoptotic effect of CO on cytokine-treated rat aortic smooth muscle cells involved the activation of sGC and was associated with suppression of p53 and inhibition of Cyt-*c* release, though p38 MAPK was not implicated in this study (216). CO also appears to inhibit L-type Ca^{2+} dependent channel activity that might protect from ischemic cell death (382). CO is not necessarily antiapoptotic in all cell models. In Jurkat T-cells, CO treatment increased Fas/CD95-induced apoptosis, associated with the downstream activation of caspases, and the inhibition of anti-apoptotic Bcl family members (*i.e.,* Bcl-X_L). In this cell type, the proapoptotic effect of CO in the context of Fas/CD95-induced apoptosis was associated with downregulation of ERK-1/2 activation by CO (350).

C. HO/CO-mediated cellular protection in organ injury models

CO exposure dose-dependently modulates apoptosis *in vivo*. In numerous models of disease and/or tissue injury in rodents, including I/R injury and lung transplantation, an antiapoptotic effect of low dose CO pretreatment has been observed *in vivo* (270, 349). Nonetheless, higher concentrations of inhalation CO in rodent models cause tissue apoptosis, particularly in brain regions, associated with CO poisoning and tissue injury (283).

a. HO/CO in hyperoxia-induced lung injury and cell death. Data from *in vitro* and *in vivo* studies revealed that CO administration increased cell survival after hyperoxia challenge (268, 269). The cytoprotective effect *in vitro* depended on the activation of MKK3 and p38β MAPK (269). Furthermore, intratracheal administration of adenoviral HO-1 (AdHO-1) protected rat lungs from hyperoxia-induced apoptosis and increased survival when administered before the hyperoxia treatment (267). In this model, exogenous application of CO at a dose of 250 ppm by inhalation reduced apoptosis and other histological markers of hyperoxia-induced lung injury (268, 269). A more recent study demonstrated that *ho-1* gene transfer rescued TLR4-deficient mice (*tlr4*$^{-/-}$) from their inability to upregulate Bcl-2 and phospho-Akt, and thereby prevented apoptosis and mortality from hyperoxic stress (442).

b. HO/CO-mediated cell protection in ischemia/reperfusion injury. Apoptosis occurs regularly after I/R injury in many tissues and organs (12, 101). The HO/CO system potentially provides a major defense mechanism to protect from reperfusion injury. This has been demonstrated by studies in which HO-1 deficiency led to a dramatic increase of cellular death and mortality after lung I/R (101) or cardiac I/R (423). In contrast, HO-1 overexpression confered cellular protection and resistance to reperfusion injury in a number of models (reviewed in Ref. 304). Likewise, low dose CO treatment provided tissue protection against I/R injury (65, 198), which depended on activation of p38 MAPK (13, 439). Exogenously applied CO at low concentrations inhibited H/R-induced apoptosis in pulmonary artery endothelial cell cultures, associated with the CO-dependent activation specifically of the p38β MAPK isoform with concomittant suppression of ERK and JNK activation. The antiapoptotic effect of CO was associated with inhibition of Fas/FasL expression, and other apoptosis-related factors including caspases [-3, -8, -9] mitochondrial Cyt-c release, Bcl-2 family proteins, and PARP cleavage (441). Further studies also demonstrated that antiapoptotic functions of CO after anoxia-reoxygenation *in vitro* depended on activation of the PI3K/Akt and the p38 MAPK-dependent STAT3 pathway (440). CO exposure also protected against I/R induced lung injury *in vivo*. Chemical inhibition of p38 MAPK activity, or the use of the MKK3$^{-/-}$ mice abolished the antiapoptotic effects of CO during lung I/R, by preventing the modulation of caspase-3 activity (439). CO inhalation (1,000 ppm) compensated for HO-1 deficiency in *ho-1*$^{-/-}$ mice, and improved survival following lung I/R. The protection provided by CO involved the derepression of fibrinolysis, by the cGMP-dependent inhibition of plasminogen activator inhibitor-1, a potent smooth muscle cell proliferation activator produced by macrophages (101). Mice treated with an sGC inhibitor, ODQ, were not protected from I/R-induced lethality by CO (101). In a model of acute coronary artery ligation and release, HO-1 gene transfer was accompanied by decreased Bax and increased Bcl-2 protein levels (238). Likewise, the pharmacological application of CO by CO-releasing molecules, reduced the infarction size after I/R in the heart (65). In the same model, CO (1000 ppm) by inhalation reduced the infarct area after occlusion of a cardiac artery. The protective effect of CO was mediated by the increased production of cGMP, and activation of p38 MAPK, leading to activation of the Akt-eNOS pathway (99). Certainly, the antiapoptotic effects of CO are not only based on a direct effect of CO on signaling pathways leading to apoptosis, and indirect CO-mediated pathways may also be considered. It is well known that inflammation or cytokine release are important proapoptotic effectors and, as mentioned above, CO has potent anti-inflammatory properties (266). CO potentially dilates vessels via the activation of sGC/cGMP. As a consequence, CO reduced microcirculatory dysfunction after I/R in many organs, including the liver and skin (124).

c. HO/CO-mediated cell protection in organ transplantation. Organ transplantation represents a specific form of I/R injury. The reperfusion injury that frequently occurs after organ transplantation leads to cell death and determines early graft function or rejection. This remains a major problem for patients undergoing transplantation. Much emphasis has been undertaken to resolve or attenuate the degree of reperfusion injury under these conditions. Interestingly, HO-1 expression has been positively correlated with graft survival in several models of organ transplantation in rodents (12, 317, 345). For instance, HO-1 gene therapy or expression, following preconditioning or chemical induction, protected against acute transplant rejection, reduced apoptosis, and prolonged survival in different transplantation models (12, 304). CO has been shown to mimic the beneficial effects of HO-1 overexpression, and when administered exogenously, reduced apoptosis, proinflammatory mediators, platelet aggregation, and increased survival in different models of rodent organ transplantation (152, 250, 270, 317, 349). The antiapoptotic effect of CO in transplantation involves the downregulation of Bax, and the upregulation of Bcl-2, in a cGMP-dependent pathway (250). The induction of Hsp70 potentially contributed to the antiapoptotic effect of CO after liver transplantation (152). The antiapoptotic function has been proposed to be of major influence to protect transplanted organs from dysfunction and failure (7), though improvement of blood circulation by CO within the reperfused transplanted organ cannot be discounted (270).

V. CONCLUDING REMARKS

A considerable amount of redundancy occurs in the phenomenology of apoptosis across model systems of oxidative stress. Caspase activation, modulation of Bcl-2-related proteins, and mitochondrial events associated with the intrinsic apoptotic pathway and Cyt-*c* release are recurring themes in oxidative stress-mediated apoptosis. However, it has recently become evident, as in H/R models, that extrinsic and intrinsic pathways are not necessarily mutually exclusive and elements of both may co-participate in the regulation of the apoptotic program in response to a single stimuli. Subcellular damage to mitochondrial targets favors apoptosis, whereas membrane damage favors necrosis, as demonstrated in PDT-specific models of oxidative stress. As exemplfied in IR and short-wave UVC models, apoptosis can also occur in delayed fashion as the consequence of prolonged cell cycle arrest and unrepaired DNA damage. The transition of apoptosis to necrosis is typically a dose-responsive event with most stimuli, including oxidants. However, the apoptosis and necrosis are not necessarily mutually exclusive, as demonstrated by high oxygen stress, where mixed death phenotypes have been observed. Diverse protein kinase activities including three major MAPK families can modulate the apoptotic program in both positive and negative fashion depending on cell type or inducing agent, and, in the case of JNK, even may exert both effects in the same cell type depending on activation kinetics (331, 387). In this regard, the protein phosphatases, which counterregulate kinase activities, have emerged as an important regulatory target of oxidants. While IKK and PKB/Akt are well established as initiatiors of cell survival pathways, the variable roles of the multiple isoforms of PKC in apoptosis remain intriguing and enigmatic. It is clear that the pathological generation of ROS can cause sufficient cellular damage that, in the case of insufficient or incomplete repair processes, can cause the cell to engage in apoptosis. With re-

spect to recent findings, it remains appropriate to speculate that ROS production can also serve a signaling or intermediate function in the regulation of the death program in response to diverse stimuli. A number of adaptive mechanisms operate to protect cells against damaging cellular events potentially leading to apoptosis, including inducible stress proteins such as heat shock proteins, ER stress proteins, and HO-1. HO-1 and its reaction product CO, have recently attracted much attention as potential cellular antiapoptotic mechanisms, especially in models of I/R injury and transplant rejection (304). An understanding of the mechanisms that regulate cell death programs in response to environmental stimuli will contribute to the development of therapeutic strategies in a multiplicity of disease states.

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The following online content was accessed during the preparation of this manuscript and provides pertinent background information.

http://www.sgul.ac.uk/depts/immunology/~dash/apoptosis/receptors.html [June 23, 2006]
http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/A/Apoptosis.html [June 23, 2006]
http://www.princeton.edu/~ygshi/research.htm#background [June 23, 2006]
http://focosi.immunesig.org/apoptosis.htm [June 23, 2006]
http://metallo.scripps.edu/PROMISE/NOS.html [June 23, 2006]

ABBREVIATIONS

$\Delta\psi_{m:}$ mitochondrial membrane potential difference; 4-HNE: 4-hydroxynonenal; 8-OhdG, 7,8-dihydro-8-oxo-2′-deoxyguanosine; Ad-HO-1, *ho-1* containing adenovirus; ALA, δ-aminolevulinic acid; AlPc, (chloro)-aluminum phthallocyanine; AP-1, activator protein-1; APAF-1, apoptotic protease activating factor-1; AIF, apoptosis inducing factor; ASK1, apoptosis signal-regulating kinase-1; ATM, *ataxia telangiectasia mutated* kinase; BH, Bcl-2 homology domains; cIAP, cellular inhibitor of apoptosis; CO, carbon monoxide; CS, cigarette smoke; CSE, cigarette smoke extract; Cyt-c, cytochrome c; DED, death effector domain; DISC, death-inducing signal complex; DNM, dominant negative mutant; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinases-1/2; FADD, Fas-associated death domain protein; FAK, focal adhesion kinase; FasL, Fas-ligand; FLIP, Fas-associated death domain protein (FADD)-like interleukin-1β-converting enzyme (FLICE)-like inhibitory protein; GSH, glutathione (reduced form); GST, glutathione *S*-transferase; HaCAT, transformed human keratinocytes; HGF, hepatocyte growth factor; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase-1; H/R, hypoxia/reoxygenation; IAP, inhibitor of apoptosis protein; I-κB, inhibitor of κB; IKK, inhibitor of κB kinase; IL, interleukin; IR, ionizing radiation; I/R, ischemia/reperfusion; JNK, c-Jun NH_2-terminal kinase/stress-activated protein kinase; LPS, bacterial lipopolysaccharide; MAPK, mitogen-activated protein kinase; Mito-VitE, 2-[2-(triphenylphosphonio)ethyl]-3,4-dihydro-2,5,7,8-tetramethyl-2H-1-benzopyran-6-ol bromide; MKK: mitogen activated protein kinase kinase; MKKK, mitogen activated protein kinase kinase kinase; MMP, mitochondrial membrane permeability; NAC, *N*-acetyl-L-cyteine; NF-κB, nuclear factor kappa-B; NO, nitric oxide; NOS (I/II/II), nitric oxide synthase-I/II/III; NOX, NADPH oxidase; $^1O_2$, singlet molecular oxygen; O_2^-, superoxide anion radical; $^{\bullet}OH$, hydroxyl radical; p38 MAPK, p38 mitogen-activated protein kinase; PAMP, pathogen associated molecular patterns; PARP-1, poly(ADP-ribose) polymerase-1; PC-IV, silicon phthallocyanine; PCD, programmed cell death; PDT, photodynamic treatment/therapy; PH-II, photofrin-II; PI3K/ Akt, phosphatydylinositol-3-kinase/Akt; PKC/D, protein kinase-C/D; PLA_2, phospholipase-A2; PLC, phospholipase-C; PP, phosphoprotein phosphatase; PTP, phosphotyrosine phosphatase; RIP, receptor interacting protein; RNS, reactive nitrogen species; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; S-1-P, sphingosine-1-phosphate; Smac/DIABLO, second mitochondria-derived activator of caspase/direct IAP binding protein with low p*I*; SnET2, tin etiopurpurin; SOD, superoxide dismutase; TLR, Toll-like receptor; TNFα, tumor necrosis factor-α; TNF-R1/2, tumor necrosis factor receptor-1/2; TRADD, TNF-R1-associated death domain; TRAF2, tumor necrosis factor receptor associated factor-2; Trx, thioredoxin; TUNEL, terminal deoxynucleotidyltransferase dUTP nick end-labeling; UVA, ultraviolet-A (320–380 nm) radiation; UVA1, ultraviolet-A1 (340–400 nm) radiation; UVB, ultraviolet-B (280–320 nm) radiation; UVC, ultraviolet-C (<280 nm) radiation; UVR, ultraviolet radiation (general); XIAP, X-chromosome-linked inhibitor of apoptosis; zVAD-fmk, benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone.

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