Annu. Rev. Pharmacol. Toxicol. 2006. 46:411–49
doi: 10.1146/annurev.pharmtox.46.120604.141053
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First published online as a Review in Advance on September 30, 2005

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CO AS A CELLULAR SIGNALING MOLECULE

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Key Words carbon monoxide, guanylate cyclase, mitogen-activated protein kinase, stress response

■ **Abstract** Many biological functions of heme oxygenase (HO), such as cytoprotection against oxidative stress, vasodilation, neurotransmission in the central or peripheral nervous systems, and anti-inflammatory, anti-apoptotic, or anti-proliferative potential, have been attributed to its enzymatic byproduct carbon monoxide (CO), although roles for biliverdin/bilirubin and iron have also been proposed. In addition to these well-characterized effects, recent findings reveal that HO-derived CO may act as an oxygen sensor and circadian modulator of heme biosynthesis. In lymphocytes, CO may participate in regulatory T cell function. A number of the known signaling effects of CO depend on stimulation of soluble guanylate cyclase and/or activation of mitogen-activated protein kinases (MAPK). Furthermore, modulation of caveolin-1 status may serve as an essential component of certain aspects of CO action, such as growth control. In this review, we summarize recent findings of the beneficial or detrimental effects of endogenous CO with an emphasis on the signaling pathways and downstream targets that trigger the action of this gas.

INTRODUCTION

Living organisms have developed highly conserved enzymatic systems that generate small gaseous molecules, such as nitric oxide (NO),* carbon monoxide (CO), and hydrogen sulfide (H_2S) (1–4). Coinciding with the development of industry,

*Abbreviations: bHLH: basic helix loop helix; cGMP: guanosine 3′,5′-monophosphate; CNS: central nervous system; CO: carbon monoxide; EC: endothelial cells; HBP1: high mobility group-box protein-1; HO: heme oxygenase: HO-1: heme oxygenase-1; HO-2: heme oxygenase-2; Hsp70: 70-kDa heat shock protein; I/R: ischemia/reperfusion; LDL: low-density lipoprotein; MAPK: mitogen activated protein kinase; NO: nitric oxide; NPAS-2: neuronal PAS domain protein-2; p38 MAPK: p38 mitogen activated protein kinase; PDGF: platelet-derived growth factor; PKG: protein kinase G; pRB: retinoblastoma protein; sGC: soluble guanylate cyclase; SnPP-IX: tin-protoporphyrin IX; SMC: (vascular) smooth muscle cells; TGF-β1: transforming growth factor-β1; TNF-α: tumor necrosis factor-alpha; UVA: ultraviolet-A; ZnPP-IX: zinc protoporphyrin-IX.

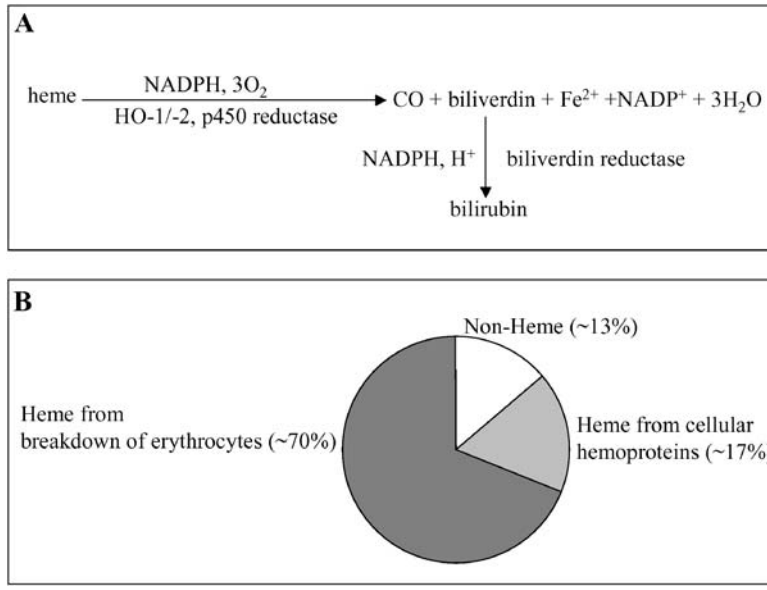

Figure 1 Catabolism of heme by heme oxygenase (HO). Equimolar CO, iron, and biliverdin are produced by HO enzymatic activity. Biliverdin is further metabolized by biliverdin reductase to bilirubin (*A*). A major source of endogenous CO arises from the degradation of erythrocytes and hemoproteins (*B*).

these molecules are also widely known as toxic air pollutants. Regardless of their notoriety, recent findings reveal that trace amounts of these gaseous molecules are indispensable for maintaining the biological system and defending the host from hostile environments (5). Physiological NO, as implicated in vasoregulation and immune function, arises from the conversion of L-arginine to L-citrulline by constitutive and inducible nitric oxide synthase (NOS) enzymes. On the other hand, endogenous CO evolves primarily from the enzymatic degradation of heme by the heme oxygenase enzyme system (HO; E.C. 1:14:99:3) (6–8) (Figure 1*A* and *B*). HO provides the first and rate-limiting step in the oxidation of heme, leading to the formation of biliverdin-IXα, with the concomitant liberation of CO and reduced heme iron. Heme metabolism concludes with the enzymatic reduction of billiverdin-IXα by NAD(P)H:biliverdin reductase (6, 9). At least two distinct isoforms of HO exist, a constitutive form (HO-2) and an inducible form (HO-1) responsive to transcriptional activation by a broad array of chemical and physical stress (8, 10).

Over the past decade, HO-1 has attracted intensive interest as a mediator of tissue protection and host defense. Efforts to dissect the underlying mechanisms of cell and tissue protection have revealed possible contributory mechanisms based on the evolution of all the major HO end-products, including CO (reviewed in 11). Because this represents primarily a review on the role of CO in intracellular

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signaling, we refer the reader to other recent reviews for discussion of the possible roles of biliverdin/bilirubin and iron metabolism in HO-mediated protection (11–13).

HO-derived CO was formerly considered as a catabolic elimination product with no physiological significance (14). Indeed, elevated CO concentrations cause tissue hypoxia by virtue of competitive binding with the oxygen binding sites of hemoglobin (15, 16). A signaling role for CO first emerged from observations that CO can weakly stimulate soluble guanylate cyclase (sGC) in vitro by heme binding to produce guanosine 3′,5′-monophosphate (cGMP), as well as stimulate the production of cGMP when directly applied to vascular smooth muscle cells (SMC) (17–19). HO-derived CO and downstream effects on cGMP formation have been implicated in a number of neuronal signaling processes, including olfactory neurotransmission (5, 20, 21–24). Furthermore, CO has been implicated in vascular processes such as regulation of vessel tone (25–30), SMC proliferation (31–34), and platelet aggregation (34–36). An exclusive or unequivocal role for sGC in all signaling processes triggered by CO has not been established, leaving the question open for the resolution of other possible molecular targets. Indeed, CO has been shown to modulate the activation state of mitogen-activated protein kinases (MAPK) critical for cellular signal transduction in response to stress and inflammation. CO exerts novel anti-inflammatory, anti-apoptotic, and anti-proliferative effects dependent on the modulation of the p38 MAPK signaling pathway (Figure 2). Over the past decade, CO applied at low concentration has been shown to confer cyto- and tissue-protective effects akin to HO-1 elevation in numerous models of tissue injury and disease, including oxidative lung injury, inflammation, and organ transplantation (37–39, reviewed in 40). Recent observations from this laboratory

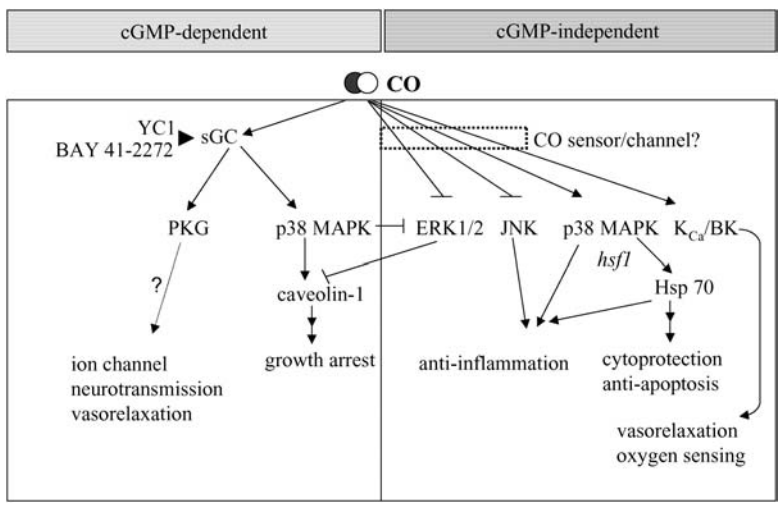

Figure 2 c-GMP-dependent or -independent CO signaling.

reveal additional candidate molecules that function as downstream targets of CO signaling, including the 70-kDa heat shock protein (Hsp-70) and caveolin-1 (31, 41). This review describes the major signaling pathways by which CO exerts potent and diverse actions on cellular homeostasis.

TRANSCRIPTIONAL REGULATION OF HO-1

HO-1 is transcriptionally upregulated as a sensitive cytoprotective protein by various types of oxidative stress, such as oxidized low-density lipoprotein (LDL), ultraviolet-A (UVA) radiation, thiol-reactive substances and by growth factors, hormones, disease states, and dietary antioxidants including various classes of natural products. There is no commonality among HO-1 inducers, which have diverse chemical structures ranging from proteins to small organic compounds to a gas molecule (NO) (reviewed in 42). HO-1 is widely accepted as a cellular defense mechanism against harmful or noxious stimuli, such as sodium arsenite or metal ions (43, 44, reviewed in 45). Although clearly depictive, we further categorize the HO-1 induction depending on the modes of action mechanism.

Synergistic Induction

If the induction and function of HO-1 parallels with the physiological activity of a given stimulus, it may be grouped in the category of a synergistic response. In such examples, the presence of HO-1 is required for the therapeutic effect of the primary stimuli, which is mediated presumably by the reaction products of HO activity. In this way, HO-1 can amplify the therapeutic effects of certain stimuli, such as the anti-inflammatory cytokine IL-10 (46), the anti-proliferative rapamycin (47), 15-PGJ_2 (48), and aspirin/salicylic acid (49). For instance, IL-10 stimulates the upregulation of HO-1, and subsequently a product(s) of the degradation of heme by HO-1 mediates the therapeutic effect of IL-10. Accumulating data with clinical therapeutics and Oriental medicines also support that HO activity may amplify therapeutic potential. Cholesterol-independent, pleiotropic actions of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) exert anti-inflammatory and antioxidant action (50). Grosser et al. show that HO-1 is a target site of statins in endothelial cells. In cultured human umbilical vein endothelial cells, simvastatin and lovastatin increase HO-1 mRNA levels in a concentration- and time-dependent, but NO-independent fashion. The increased transcriptional expression of HO-1 was associated with elevated HO-1 protein and reduction of free radical formation (50). Recently, antioxidants (vitamin E, polyphenols) have received much attention as potential anti-atherosclerotic agents (51, 52). Among the polyphenols that induce HO-1, resveratrol, a phytoalexin of grape, may protect the vascular wall from oxidation, inflammation, platelet aggregation, and thrombus formation (52). Both caffeic acid and curcumin are plant extracts that exert potent anti-inflammatory effects, which have also been shown to function through upregulation of HO-1 (53) (see Table 1).

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TABLE 1 Various stimuli induce HO-1 induction

Growth factor
- FGF (178)
- HGF (179)
- VEGF (180)
- NGF (181, 182)
- TGF-β (183)
- KGF (184)
- BMP-7 (185)
- PDGF (186)

Disease state (reviewed in 187)
- Ischemia reperfusion
- Inflammation
- Immune dysfunction
- Transplantation
- Myocardial infarction
- Atherosclerosis
- Hypertension
- Vascular restenosis
- Acute renal failure
- Glomerulonephritis
- Diabetic kidney disease
- Hypoxia/hyperoxia induced lung injury
- Emphysema
- Asthma
- Spinal cord injury
- Cerebrovascular injury
- Alzheimer's disease

Hormone
- Estrogen (188)
- Prolactin (189)
- Adrenocorticotrophin (190, 191)
- Atrial natriuretic peptide (192)
- Melatonin (193)
- Angiotensin II (55, 194)
- Progesterone (195)
- Glucocorticoid (regulation of HO-2; 196)
- Chorionic gonadotropin (testis) (197)

Medicines/chemicals
- *Immunosuppressant/anti-inflammatory*
- IL-10 (46)
- Aspirin/salicylic acid (49)
- Cyclopentenone PG (15d PGJ2, PGA2; 48, 198)

Oxidative stress
- Endoplasmic reticulum stress (205)
- Heavy metals (206)
- Oxidized LDL (207, 208)
- Hydroperoxide (209)
- Diphenyl- and dithiol-compounds (210)
- HNE (208, 211)
- Dieldrin (212)
- Cigarette smoke extract (213)
- Alcohol (214)

Dietary antioxidant/natural product
- Synthetic terpenoid (215)
- Quercetin/flavonoid (216)
- Mycotoxin (food contaminant; 217)
- Ferulic acid/ethyl ferulic acid (218)
- Zerumbone (sesquiterpene; 219)
- Selegiline (220)
- Turpentine oil (221)
- 3-O-caffeoyl-methyl quinic acid (222)
- Diallyl sulfide (garlic; 223)
- Chalcone/rosolic acid (224)
- Isoflurane (225)
- Taurine (226)
- Curcumin (53)
- Cafestol/kahweol (227)
- Avicins (triterpenoid; 228)
- Resveratrol (52, 229)

Physiological changes
- Hypertonic saline (osmotic pressure; 230)
- Transient glucose deprivation (231)
- Acidosis (232)
- Nitric oxide (233–242)
- Cytokine (LPS, IFN-γ, TNF-α, IL-1β; 243)
- Mechanical shear stress (244, 245)

Miscellaneous
- Dopamine (246)
- Nicotine (247)
- β-amyloid (248)
- Cysteamine (249)

(*Continued*)

TABLE 1 (*Continued*)

Rapamycin (47)	UV irradiation (250)
Statins (50, 199)	Co-protoporphyrin (251)
Antioxidant	Proteasome inhibitor (252)
Vit E (51)	
Selenium (ebselen; 200, 201)	
Probucol (202)	
Paclitaxol (*antitumor;* 203)	
Hydralazine (*vasodilator;* 204)	

Abbreviations: FGF, fibroblast growth factor; HGF, hepatocyte growth factor; VEGF, vascular endothelial cell growth factor; NGF, nerve growth factor; TGF, transforming growth factor; KGF, keratinocyte growth factor; BMP, bone morphogenic protein; PDGF, platelet derived growth factor; oxLDL, oxidized low density lipoprotein; HNE, hydroxynonenal; LPS, lipopolysaccharide; IFN, interferon; IL, interleukin; UV, ultraviolet.

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Antagonistic Induction

In response to certain stimuli, the organism may induce HO-1 to counteract the action of the stimuli in a feedback mechanism (54, 55). For example, serum stimulates HO-1 gene expression and subsequent CO synthesis in SMC (54). CO acts in a negative feedback fashion to inhibit vascular SMC growth by regulating specific components of the cell cycle machinery, including retinoblastoma protein (pRb) phosphorylation or the expressions of $p21^{Waf1/Cip1}$ and cyclin A. The ability of serum components to stimulate HO-1 gene expression is also observed after the administration of platelet-derived growth factor (PDGF), transforming growth factor-β1 (TGF-β1), or angiotensin II, and it may represent a counterregulatory mechanism against mitogen-stimulated SMC growth (55). In some cases, the inhibitor of HO-1 or scavenger of CO tends to exaggerate the effect of a given stimulus. For example, serum-stimulated DNA synthesis is augmented in the presence of HO inhibitors zinc- or tin-protoporphyrin IX (SnPP-IX, ZnPP-IX), indicating a growth inhibitory role for HO-1. In another example, angiotensin infusion causes hypertensive effects involving increased blood pressure and also induces HO-1 in the vasculature. Inhibition of HO-1 with metalloporphyrins aggravates the hypertensive effects of angiotensin, thus highlighting HO-1 as an antagonistic response to the stimulus (55).

HEMOPROTEINS AS CO RECEPTORS

The affinity of CO for metal atoms allows it to interact with a number of metalloproteins (56). This property implicates all heme-containing proteins as possible candidate biological CO sensors even though they are known to have other physiological ligands. These include proteins in which heme functions as a prosthetic group, for example, hemoglobin, myoglobin, sGC, cyclooxygenase, cytochrome p450, cytochrome *c* oxidase, inducible NOS, NADPH: oxidase, and the transcription factors Bach-1 and -2 (57, reviewed in 58). Furthermore, proteins that contain PAS (Per-Arnt-Sim) motifs, such as neuronal PAS domain protein-2 (NPAS-2),

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are known to be gas responsive. CO can modulate the biological activity of these hemoproteins by virtue of its ability to bind the central iron group contained within their heme prosthetic groups (59, 60). When this occurs, CO induces conformational changes in these proteins that can regulate their biological activity (56). CO also potentially binds to proteins that contain other metal ions, such as zinc, copper, and manganese (58).

Soluble Guanylyl Cyclase

Vertebrate sGC is a heterodimeric (α/β) heme protein that senses NO (61, 62). sGC is expressed in the cytoplasm of almost all mammalian cells and mediates a wide range of important physiological functions (61). Based on the lipophillic property of NO and its site of generation, the plasma membrane localization of sGC was examined in rat heart and human platelets (63). Zabel et al. proposed that sGC dynamically translocates to the plasma membrane, where it is sensitized to NO. When NO binds to the heme motif of sGC, its activity in converting GTP to cGMP is enhanced by several hundredfold. cGMP acts as a second messenger that plays a pivotal role in a variety of physiological processes, including vasodilation and neuronal signal transduction (61).

The overall structure of sGC is unknown, but its catalytic domain is composed of the C-terminal regions of the both subunits, which have sequence homology to regions in the particulate sGC and adenylate cyclase. Although both subunits are essential for catalytic activity, the N-terminal region of the ß-subunit alone binds the heme prosthetic group (64). The presence of the heme prosthetic group is required for activation of sGC by NO (17). NO has been shown to trigger a conformational change in sGC through the cleavage of the proximal histidine ligand, His105, resulting in a five-coordinate high-spin NO adduct (65). The reconstitution of sGC with a series of metalloporphyrins supports the hypothesis that the cleavage of the His-Fe bond is critical for activation (66, 67). For example, Mn(II)-protoporphyrin IX-reconstituted sGC binds NO but is not active, consistent with the role of the retention of the His-Fe bond. Conversely, Ni(II)- or Cu(II)-protoporphyrin IX-reconstituted sGC are active without NO. Ni(II) or Cu(II) protoporphyrin IX favors four-coordinate geometry, and therefore these reconstituted sGC variants lack the His-Fe bond. sGC with a free-base protoporphyrin IX, lacking an iron and therefore incapable of forming the His-Fe bond, is also active. However, the observation that porphyrin-free sGC is not active indicates that cleavage of the His-Fe bond is not sufficient and that the heme-vicinity also plays a crucial role in the activation mechanism of sGC.

Recently, CO has been shown to inhibit platelet aggregation and to relax vascular smooth muscle (35, 68), which are activities also attributed to the action of NO on sGC. These CO-dependent activities have been shown to be cGMP-dependent (35, 68–70). CO can enhance sGC activity in vitro, although its fourfold increase is much lower than that of NO and does not seem to explain the degree of the visible physiological responses. Indeed, because CO binding to sGC leads to a six-coordinate low-spin heme adduct, with an intact His-Fe bond, the

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activation mechanism of CO must differ from that of NO. Importantly, however, the presence of YC-1 [3-(5′-hydroxymethyl-2′-furyl)-1-benzylindazole], or BAY-41–2272, small synthetic molecules that have been found to enhance the CO effect in vitro, allows activation by CO to reach the same level as that of NO-stimulated sGC (71–73). The molecular basis for the stimulation mechanism of YC-1 to the CO-bound sGC is unclear, but YC-1 apparently does not force the cleavage of the Fe-His bond (73), as might be expected if it also led to a five-coordinate adduct. However, the production of substantial amounts of the five-coordinate CO adduct upon addition of the BAY 41-2272 was demonstrated (72). Thus, several out-of-plane heme deformation modes are simultaneously activated, an observation similar to that realized upon NO activation. The question remains whether CO is a physiological ligand of sGC and whether there exists a physiological modulator in vivo that mimics the synergism triggered by YC-1 or BAY 41-2722. Although there is no evidence available for the latter question, there are strongly suggestive data in support of the former. First, CO-induced vasorelaxation can be blocked by inhibiting sGC activity (36), consistent with a direct role in vivo for CO and sGC. Second, there is the striking evidence that HO, the source of CO in nerve cells, colocalizes with sGC in cells with little or no NOS expression, supporting a link between CO and sGC (74, 75). Although the possible role of sGC in mammalian CO sensing is tantalizing but firmly unproven, the participation of other hemoprotein species in CO-sensing remains likely.

GC-INDEPENDENT EFFECTS OF CO CO has potential actions distinct from modulating cGMP levels. Wang et al. noted that CO-induced relaxation of rat-tail arteries was not completely blocked by inhibitors of the cGMP pathway, and that the residual relaxation could be blocked by inhibitors of large conductance calcium-activated K^+-channels (K_{Ca}) (76). When activated, these channels relax smooth muscle by hyperpolarizing the membrane. CO (1 μM) activates these channels to relax smooth muscle by membrane hyperpolarization (28, 76). CO increases the single channel open probability of K_{Ca} channels by a direct action on the channel. Chemical modification of a single histidine on the extracellular surface of the channel blocks the activation by CO (76). The effects of CO on K_{Ca} channels in SMCs have been confirmed by multiple laboratories (29, 30, 76). CO can also increase the activity of other families of K^+ channels (77). These findings establish an sGC-independent mechanism for the relaxant actions of CO on smooth muscle. Hemin and NADPH, HO substrates, mimic the effects of exogenously added CO when applied to excised membrane patches containing K^+ channels, and these effects are reversed by HO inhibitors (77). This suggests that HO is tightly associated with the K^+ channels on the plasma membrane.

NPAS2, Circadian Clock, and CO

The circadian clock is the central timing system that controls numerous physiological processes (78, 79). In peripheral tissues, the circadian clock generates

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transcriptional rhythms (80, 81). The gases NO and CO are increasingly appreciated as major neurotransmitters (5). One of the principal means by which NO and CO transmit signals between neurons is through binding to a heme moiety at the active site of sGC and generation of the intracellular second messenger molecule cGMP. Recently, HO-derived CO has also been implicated in the regulation of circadian rhythms through transcriptional mechanisms. Dioum et al. have characterized a mammalian transcription factor NPAS2 that regulates circadian rhythm and that is regulated by CO binding (60, 82). NPAS2 modulates circadian activity in the suprachiasmatic nucleus but is also present in cells outside the central nervous system (CNS). NPAS2 was first identified as a member of the basic helix-loop-helix (bHLH) family of transcription factors (83). NPAS2 together with its binding partner BMAL1, another bHLH transcription factor, binds DNA as an obligatory heterodimer (60). The NPAS2 monomer contains two heme moeities that can act as CO-binding sites, which are both six-coordinate in their resting states. The binding of CO to NPAS2 inhibits the DNA binding of active NPAS2-BMAL1 complexes, which confer negative modulation of circadian clock machinery. CO binding to NPAS2 results in the accumulation of the BMAL1 homodimers at the expense of NPAS2-BMAL1 heterodimers. When Takahashi et al. (84, 85) identified Clock as a crucial regulator of circadian rhythms, they noted its close sequence similarity to NPAS2. Clock and NPAS2 regulate the activating portion of the circadian transcriptional feedback cycle by heterodimerizing with BMAL1. NPAS2-BMAL1 and Clock-BMAL1 heterodimers direct the transcription of period (Per) and cryptochrome (Cry) proteins, which are the negative regulatory components of the circadian clock. Per and Cry inactivate the Clock-BMAL1 and NPAS-BMAL1 heterodimers, thus completing the transcriptional loop. Considering that Clock displays significant sequence homology to NPAS2 in both PAS domains, it therefore might also bind to CO (85, 86).

One of the features of circadian clocks is their entrainment by environmental stimuli such as light, temperature, activity, and food intake (60). The molecular mechanisms that enable environmental stimuli to abruptly alter circadian rhythms remain obscure. However, modulation of Clock and NPAS2 activity according to the redox state of the cell may provide a clue (86). The reduced cofactors NADH and NADPH greatly enhance binding of Clock-BMAL1 and NPAS2-BMAL1 heterodimers to DNA, whereas the oxidized forms of the same molecules, NAD^+ and $NADP^+$, inhibit the DNA binding of these dimers (86). Alterations in DNA-binding activity occur with modest changes in the ratio of oxidized to reduced cofactors. This implicates the cofactors as molecular switches that direct NPAS2-BMAL1 and Clock-BMAL1 dimers to bind to DNA in response to changes in cellular redox state. PAS domains with modules of 130 amino acids, previously characterized in organisms ranging from bacteria to mammals, respond to variations in stimuli, including oxygen, voltage, light, and redox potential. The PAS domains of some bacterial proteins operate as oxygen sensors via a heme prosthetic group. Because both PAS domains of the NPAS2 monomer contain a heme molecule, the absorption spectrum of heme-bound NPAS2 resembles that of gas-sensing proteins from

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bacteria, including the CO-sensor protein CooA from *Rhodospirullum rubrum* (56). Furthermore, CO bound to heme-containing NPAS2 with a dissociation constant of about 1 μM but failed to bind to NPAS2 lacking heme. In addition, CO inhibited the DNA-binding capacity of NPAS2-BMAL1 heterodimers with a similar molar potency. By contrast, NO did not bind to NPAS2 at physiologic concentrations, and O_2 bound irreversibly (60). In contrast, sGC is activated by nanomolar concentrations of NO but requires high micromolar concentrations of CO for activation. Because the characterization of CO regulation of NPAS2 results from in vitro experiments, it remains necessary to determine whether CO regulates NPAS2 in intact cells and organisms. If CO regulates NPAS2 in vivo, it would represent the first example of a mammalian protein selectively regulated by CO.

CO is formed in neurons exclusively by HO-2 (87, 88). The enzyme occurs in neuronal populations in numerous parts of the brain and partially overlaps with the distribution of NPAS2 (23, 42). HO-2 activity is dynamically regulated by neuronal impulses through a kinase cascade in which protein kinase C activates casein kinase-2, which in turn phosphorylates and activates HO-2 (23). HO-2 activity generates low micromolar concentrations of CO in the intact brain, which is sufficient to regulate the DNA-binding activity of NPAS2 (60). Dioum et al. suggest that the production of CO fluctuates according to the circadian rhythm of heme metabolism. Recent findings propose that the heme biosynthesis pathway, rate-limited by δ-aminolevulinate synthase-1 (ALAS1), falls under the control of circadian rhythm (78, 79). Indeed, heme controls the activity of the BMAL1-NPAS2 transcription complex in vitro by inhibiting DNA binding in response to CO. Heme differentially modulates expression of the mammalian *Period* genes mPer1 and mPer2 in vivo by a mechanism involving NPAS2 and mPER2. mPER2 positively stimulates the activity of the BMAL1-NPAS2 transcription complex and, in turn, NPAS2 transcriptionally regulates ALAS1. Vitamin B_{12} and heme compete for binding to NPAS2 and mPER2, but they exert opposite effects on mPer2 and mPer1 expression in vivo (78). These data show that the circadian clock and heme biosynthesis are reciprocally regulated and suggest that porphyrin-containing molecules as potential candidates for therapy of circadian disorders (Figure 3). Elevated heme levels are likely to inhibit heme synthesis by modulating circadian transcription factors through mPer2 or through HO-derived CO, which thus may constitute a cellular feedback loop for heme homeostasis.

SIGNALING GAS: p38 MAPK AND CO

Of the signaling pathways influenced by CO, we will emphasize the role of MAPK, especially p38 MAPK (Figure 4). Accumulating evidence suggests that p38 MAPK activation is essentially involved in the cytoprotective, anti-inflammatory, anti-apoptotic, and anti-proliferative effects of CO (31, 38, 41, reviewed in 89). Recently, Zhang et al. reported that CO inhibits apoptosis via p38 MAPK-STAT

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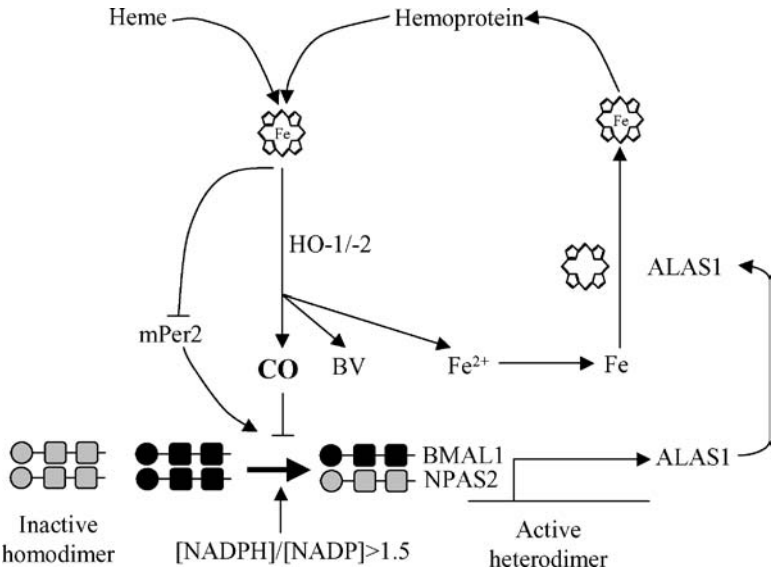

Figure 3 Reciprocal modulation of heme biosynthesis by NPAS-2 and possible involvement of CO in the processes.

or Akt/PKB-STAT pathways during ischemia reperfusion (I/R) injury (90–92). Hence, we discuss the specific roles of p38 MAPK in the following sections.

Properties of p38 MAPK Members

p38α (p38) was first isolated as a 38-kDa protein rapidly tyrosine phosphorylated in response to lipopolysaccharide (LPS) stimulation (93, 94). p38 MAPK was cloned as a molecule that binds pyridinyl imidazole derivatives, which are known to inhibit biosynthesis of inflammatory cytokines such as interleukin-1 (IL-1) and tumor-necrosis factor-alpha (TNFα) in LPS-stimulated monocytes (95). To date, four splice variants of the p38 MAPK family have been identified: p38α, p38β (96), p38γ (ERK6, SAPK3) (97, 98), and p38δ (SAPK4) (99, 100). Of these, p38α and p38β are ubiquitously expressed, whereas p38γ and p38δ are differentially expressed depending on tissue type. All p38 MAPKs can be categorized by a Thr-Gly-Tyr (TGY) dual phosphorylation motif (101). Sequence comparisons have revealed that each p38 MAPK isoform shares ~60% identity within the p38 MAPK group but only 40%–45% to the other three MAPK family members. Mammalian p38 MAPKs show similar roles and activation has been shown to occur in response to extracellular stimuli such as UV light, heat, osmotic shock, inflammatory cytokines (TNF-α and IL-1), and growth factors (94, 102). This plethora of activators conveys the complexity of the p38 MAPK pathway. Activation of p38α is not only dependent on stimulus but also on cell type (103). For example, insulin can stimulate p38 MAPK in 3T3-L1 adipocytes (104), but downregulates

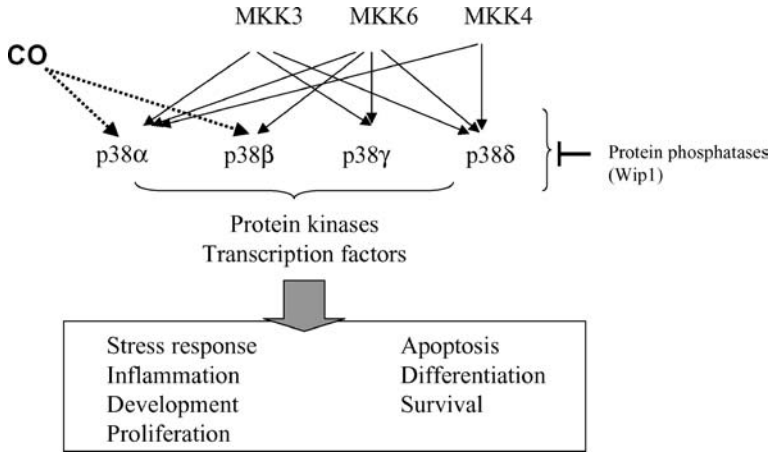

Figure 4 Effects of CO on diverse biological processes through p38 MAPK. The α- and β-isoforms of p38 MAPK actively participate in the functions of CO including anti-apoptotic, anti-proliferative, and anti-inflammatory activity.

p38 MAPK activity in chick forebrain neuron cells (105). Although the other three p38 MAPK isoforms have been cloned, little is known regarding their activation. Despite all four p38 MAPK group members displaying similar activation profiles (103, 106), differences have been observed in the kinetics and level of activation of these isoforms. Furthermore, the activation of p38 MAPK isoforms can be specifically controlled through different regulators and coactivated by various combinations of upstream regulators.

CO, p38 MAPK, and Apoptosis

We and others showed that expression of HO-1 or exposure of endothelial cells (ECs) to exogenous CO enhances p38 MAPK activation by TNF-α (41, reviewed in 89). Specific inhibition of p38 MAPK activation by SB 203580 or through overexpression of a p38 MAPK-dominant negative mutant abrogates the anti-apoptotic effect of HO-1. To the contrary, evidence exists for the concomitant activation of p38 MAPK and apoptosis induced by a variety of agents, such as nerve growth factor withdrawal and Fas ligation (107). In Jurkat T cells, Fas/CD95-induced cell death is augmented by exposure to CO, and this occurs in part via inhibition in the activity of ERK MAPK (108, 109). Thus, the role of p38 MAPK in apoptosis is cell type- and stimulus-dependent. Although p38 MAPK signaling can promote cell death in some cell lines, it may enhance survival, cell growth, and differentiation in others (reviewed in 106).

More recently, we demonstrated that Hsp70 mediates the cytoprotective activity of CO in ECs. The expression of Hsp70 appears as a downstream target of p38β MAPK (41). Several studies demonstrate the protective capacity of Hsp70

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against heat shock and other toxic stimuli. In rats, ischemic preconditioning of the liver strongly induced Hsp70, resulting in resistance to subsequent hepatic I/R injury (110). The downregulation of Hsp70 can facilitate the induction of apoptosis, whereas the upregulation of Hsp70 inhibits TNF-α-induced apoptosis (111, 112). The expression of Hsp70 conferred resistance in models of cardiac I/R injury or acute respiratory distress syndrome (113). Accumulating evidence demonstrates that the heat shock response can confer anti-inflammatory effects involving the inhibition of pro-inflammatory gene expression (114, 115). Hyperthermia pretreatment protected against the lethal effect of LPS or TNF-α treatment in mice, which correlated with systemic Hsp70 induction (111). Similarly, Zhang et al. have reported that p38α MAPK activation is important for modulation of apoptosis during lung I/R injury (90–92). In a model of hepatic I/R injury, p38 MAPK activation was essential to exert the effect of CO (116).

We also suggested a critical role for the β-isoform of p38 MAPK in mediating the effects of CO on cytoprotection and Hsp70 expression because these effects were abrogated in endothelial cells by SB 203580, a selective inhibitor of α and β isoforms, and in p38β-null fibroblasts. The observed inhibition of Hsp70 expression by SB 203580 results from inhibition of HSF-1 activation potentially involving phosphorylation and nuclear localization. The augmentation of p38 MAPK by CO over the TNF-α/Act D-induced background led to the significant increase in HSF nuclear translocation. Activation of HSF-1 by CO was also expressed as increased HSF DNA-binding activity. CO, however, did not further modulate the phosphorylation of HSF, which was also determined to require p38 MAPK activity (41).

CO, p38 MAPK, and the Cell Cycle

The participation of p38α in cell growth has been observed in yeast and mammals (117). Overexpression of p38α in yeast led to significant inhibition of proliferation, whereas treatment in mammalian cells with p38α/β inhibitor SB 203580 increased proliferation. Likewise, inactivation of protein phosphatase 2C (Wip1) inhibited cellular growth and tumorigenesis by activating p38 MAPK (118, 119). p38 MAPK has been implicated in G1 and G2/M phases of the cell cycle (120–122). G1 arrest of NIH 3T3 cells caused by microinjection of Cdc42 was found to be p38α-dependent. Also, a link between p38 MAPK and G1 cell cycle control has been proposed through the regulation of the p38 MAPK substrates high mobility group-box protein 1 (HBP1) and p21 (117). HBP1 is thought to have a role in regulating G1 cell cycle progression through the repression of cell cycle regulatory genes, similar in function to pRB, whereas the p21 CDK inhibitor is established as a crucial factor in preventing G1 progression through blockage of CDK activity. Several examples implicate p38 MAPK involvement in G2/M phase as well. p38α is activated in mammalian cells upon M phase arrest by disruption of the spindle with nocodazole (120). Furthermore, p38α and p38γ are required for UV-induced G2 cell cycle arrest (122). Interestingly, p38α activity increases in confluent cultures of human

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fibroblasts compared with proliferating cultures, implying that α-isoform of p38 MAPK is required for contact inhibition (123). Lee et al. have demonstrated that overexpression of the *ho-1* gene delays the growth of A549 lung epithelial cells (124). This slowing of cell growth was associated with an increased number of cells in G0/G1 phase during the exponential growth phase and decreased entry into the S phase. Furthermore, the transgenic cells accumulated in the G2/M phase and failed to progress through the cell cycle when stimulated with serum, whereas the control cells exhibited normal cell cycle progression. Similarly, exogenous administration of CO recapitulated the same phenomena, resulting in the accumulation of SMC in G0/G1 phase (34).

Anti-Proliferative Effect of p38 MAPK

A common feature of tumor cells is a loss of senescence. p38 MAPK appears to play major roles in tumorigenesis and senescence (125–127). The activation of MKK6 and MKK3 led to a senescent phenotype dependent on p38 MAPK activity (126, 127). Also, p38 MAPK activity was shown to be responsible for senescence in response to telomere shortening, H_2O_2 exposure, and chronic *ras* oncogene signaling (106). Furthermore, p38 MAPK activation may be reduced in tumors. The loss of components of the p38 MAPK pathway, such as MKK3 and MKK6, resulted in increased proliferation and tumorigenic conversion regardless of the cell line or the tumor-inducing agent used in these studies (128). Bulavin et al. describe the critical role of p38 MAPK in inhibiting tumorigenesis or cell proliferation (118, 119). Wip1 is a serine-threonine phosphatase encoded by *Ppm1d*. It was first identified as a gene that is induced by the p53 tumor-suppressor protein in response to DNA damage. The importance of the activation of this phosphatase by p53 became clear when it was found that Wip1 specifically inactivates the protein kinase p38 MAPK, which can activate p53 to cause cell cycle arrest and apoptosis in response to certain environmental stress. In addition, p38 MAPK can inhibit cell cycle stimulatory proteins, such as cyclin D1 and the Cdc25 phosphatases. Thus, *Ppm1d* activation by p53 constitutes a negative feedback loop responsible for downregulation of genotoxic stress-induced signaling, which leads to suppression of the cellular stress response. Consistent with a role for Wip1 in cell proliferation is the finding that *Ppm1d* can cooperate with an activated *Hras* oncogene in transformation of primary mouse embryo fibroblasts. Conversely, Wip1-null cells have a reduced proliferative capacity in vitro and suffer from premature senescence. Suppression of *Ppm1d* expression in neuroblastoma cell lines suppressed growth and induced apoptosis. Together, these data establish Wip1 as a central component of the cellular stress response, whose inhibition enhances anti-proliferative effects of environmental stress signals by modulating p38 MAPK activity. Based on these findings, it is also important to note that upregulation of caveolin-1 expression is found in senescent cells, mice, rat, and human subjects (129). Collectively, the interaction between caveolin-1 expression and p38 MAPK activity may control a variety of key biological programs, such as cell proliferation, differentiation, and

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senescence (31, 127, 129). Because trace amounts of exogenous CO treatment can cause upregulation of caveolin-1 expression and p38 MAPK activation, we also speculate that CO modulates cell growth or differentiation. We showed that CO inhibits the vascular SMC proliferation and neointima formation during balloon injury in rats by modulating the GC-cGMP-p38 MAPK-caveolin-1 signaling pathways (31).

EFFECTS OF CO ON PROLIFERATION AND NEOINTIMA FORMATION: INVOLVEMENT OF CAVEOLAE The importance of HO-1 as a protective gene in humans is supported by two population studies. First, individuals vary in terms of the strength of their HO-1 response to a given stimulus based on a GT-length polymorphism in the promoter of the *ho-1* gene. Individuals with a robust HO-1 response (short GT repeats) are less likely to have restenosis after balloon angioplasty, as well as less likely to have chronic rejection of an allograft and to undergo other pathological processes (reviewed in 130). Individuals with longer GT repeats, who respond more weakly in terms of upregulating HO-1 activity to a particular stress stimulus, are more likely to experience restenosis or chronic rejection. Thus, the ability to upregulate HO-1 more strongly to a specific stress stimulus appears to be physiologically important. Second, multiple studies show that individuals with high normal or just above normal levels of bilirubin, which is produced as a consequence of HO-1 action, have less atherosclerosis-related diseases than individuals with low normal levels of bilirubin (131). The combination of these association studies with experimental findings that administration of either CO or biliverdin suppresses atherosclerosis-related pathologies in rodents (31, 34, 132, 133) strongly supports the importance of HO-1, bilirubin/biliverdin, and CO as protective products in humans. Intimal hyperplasia is a major morphological feature of various arterial pathologies, such as atherosclerosis, postangioplasty restenosis, and transplantation arteriopathy (33).

Substantial evidence indicates that HO-1 is a negative regulator of growth in vascular SMCs, and the inhibition of SMC proliferation by HO-1 appears to be mediated via release of CO (31, 32, 34). The exogenous administration of CO at concentrations of 100 to 250 ppm can substitute for HO-1 in blocking SMC proliferation (31, 34). The CO scavenger, hemoglobin, enhances the proliferative response of vascular SMC to several growth factors. CO appears to block SMC growth by increasing the intracellular levels of cGMP. CO activates sGC and elevates cGMP levels in SMC. In fact, inhibition of sGC blocks the rise in cGMP and proliferative action of HO-1 (134). Recent studies clarified that inhibition of HO-1 activity by ZnPP-IX potentiates the mitogenic action of serum, angiotensin II, PDGF, endothelin-1, and hypoxia in SMCs (31, 55, 89). Thus, SMC-derived CO is an important regulator of SMC proliferation. Moreover, vascular SMCs obtained from HO-1 knockout mice exhibit enhanced proliferation and DNA synthesis compared with those from wild-type animals (32, 34). HO-1 may also indirectly modulate cell growth by affecting the release of growth factors. Alternatively, the induction of HO-1 by gene transfer

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or hemin administration blocks SMC proliferation and neointimal formation (32, 34).

We have further investigated the signaling pathways that mediate the anti-proliferative effects of CO. We showed that the activation of the p38β MAPK signaling pathway by CO led to an enhanced expression of caveolin-1 in fibroblasts and SMC, which in turn mediated the increased expression of $p21^{Waf1/Cip1}$ and the down-regulation of cyclin A, leading to growth arrest. The inhibition of intimal hyperplasia by CO treatment in a vascular injury model involved the enhanced expression of caveolin-1 in vascular SMC (31).

Besides the anti-proliferative effect of CO in SMCs, CO may act as a multi-functional level against every stage of neointimal development owing to its potential anti-inflammatory and anti-apoptotic activity. In line with this notion, treatment with anti-inflammatory cytokines (i.e., IL-10), rapamycin (135, 136), cell migration inhibitors (Rho kinase inhibitor and endothelin B null) (137, 138), receptor signaling modulators (PDGFR) (139), and regulators of extracellular matrix formation (MMP, TIMP) (140, 141) inhibit neointimal formation in various models. The inhibitory role of IL-10 or rapamycin against neointimal development may depend on the induction of HO-1. Moreover, the latter three events, namely growth factor receptor signaling, cell migration, or extracellular matrix metabolism, occur at caveolae or lipid rafts directly or indirectly (see Table 2). Recent studies in caveolae-deficient animals show that caveolae sequester and regulate a variety of signaling intermediaries (142). Both G protein–coupled receptors and tyrosine kinase receptors are believed to cluster in caveolae, and the possibility that caveolae provide a platform for interactions between the sarcoplasmic reticulum and plasmalemmal ion channels is emerging (143, 144). Moreover, messengers involved in Ca^{2+} sensitization of myosin phosphorylation and contraction may depend on caveolae or caveolins. Caveolae, indeed, appear to constitute an important signaling domain that plays a role not only in regulation of smooth muscle tone but also in proliferation, such as seen in neointima formation and atherosclerosis.

CO in Innate Immunity: Effect on Macrophages

A strong link has been established between the p38 MAPK pathway and inflammation. Rheumatoid arthritis, Alzheimer's disease, and inflammatory bowel disease may be influenced in part by the p38 MAPK pathway (106). p38 MAPK plays essential roles in the production of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) (93–95) and in the induction of enzymes such as COX-2 and iNOS and in the induction of VCAM-1 and other adherent proteins and inflammatory-related molecules. In addition, a regulatory role for p38 MAPK in the proliferation and differentiation of immune system cells by factors such as GM-CSF, EPO, CSF, and CD-40 has been established (107). If, however, macrophages overexpress HO-1 or are exposed to CO in vitro before stimulation with LPS, the pro-inflammatory (i.e., TNF-α and IL-6 production) response

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TABLE 2 Caveolae-residing proteins. Some are localized to caveolae endogenously, whereas others localize transiently by stimuli

Growth factor receptor	Calcium and eNOS signaling
EGF receptor (253)	IP3 receptor like protein (282, 283)
VEGF receptor-2 (Flk-1/KDR; 254)	PLA2 (284)
TGF-β receptor (255)	Estrogen receptor (285)
Insulin receptor, Insulin-like growth factor receptor (256)	Cationic amino acid transporter (CAT) 1 (286)
PDGF receptor (257)	eNOS (287, 288)
NGF receptor (258)	Na/Ca Exchanger (NCX-2; 289)
Angiotensin II type I receptor (259)	Bradykinin receptor (290)
TNF receptor 1 (260)	
Cell migration/contraction	Heme oxygenase system (291, 292)
Integrin (261)	Heme oxygenase 1
RhoA/Rac (262, 263)	NADPH:cytochrome P450 reductase (NPR)
Endothelin receptor A (264)	Biliverdin reductase (BVR)
MT-MMP1 (265)	Heme oxygenase 2
MMP-2 (266)	
uPAR (267, 268)	
Protein kinase	Chemokine/Toll-like receptor signaling
PKA (269)	CCR5 (HIV-1 co-receptor; 293)
PKC (270)	TLR2 (294)
JAK/STAT (271)	MyD88 (295)
	IRAK-1 (296)
Structural protein	Ion channel
Caveolin (272)	Maxi-K channel (297)
Flotillin (273, 274)	BK channel (298)
Actin (275–278)	TRPC1 (calcium channel; 299)
Dynamin (279–281)	Ca^{2+}-ATPase (300)
Vimentin (278)	
Miscellaneous	
Adenylyl cyclase/guanylyl cyclase (301, 302)	Na/K ATPase (303)
Glucose transporter GLUT4 (304)	Nogo-B (305)
Prostacyclin synthase (306)	src family kinases (272)
Heterotrimeric G proteins (307)	H-ras (308)
CD36 (309)	

Abbreviations: EGF, epidermal growth factor; TNF, tumor necrosis factor; MT-MMP, membrane type matrix metalloproteinase; MMP, matrix metalloproteinase; PKA, protein kinase A; PKC, protein kinase C; JAK/STAT, janus kinase-signal transducers and activators of transcription; PLA2, phospholipase A2.

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is markedly inhibited, whereas the anti-inflammatory (i.e., IL-10 production) response is enhanced (38, 145). Three other modes of CO action contribute to its anti-inflammatory effects. First, CO prevents platelet activation and aggregation, thereby suppressing thrombosis and the pro-inflammatory response stimulated by activated platelets (34–36). Second, CO downregulates the expression in macrophages of plasminogen activator inhibitor type 1; this action appears to be crucial for the ability of CO to exert a protective effect in a model of lung I/R injury (36, 146). Third, CO prevents apoptosis in several cell types, including endothelial cells (41, 147, 148), fibroblasts (149), hepatocytes (150), and pancreatic β-cells (151). The anti-thrombotic effect of CO in platelets requires GC-cGMP and p38 MAPK. CO suppresses production of TNF-α and induces IL-10 in macrophages through activation of p38 MAPK but not by activation of the sGC/cGMP pathway. However, the action mechanisms underlying the anti-inflammatory effect of CO via p38 MAPK are quite different from the main paradigm where activation of p38 MAPK triggers pro-inflammatory reactions (152). It remains necessary to clarify the isotype-specific contributions of p38 MAPK to its anti-inflammatory action.

Regulation of the p38 MAPK pathway is not an isolated cascade and many different upstream signals can lead to p38 MAPK activation. These signals may be p38 MAPK specific (MKK3/6), or involve general MAPKKs (MKK4) or MAPKK-independent signals (TAB1 and ASK1) (153, 154). Downstream signaling pathways of p38 MAPK are quite divergent, and each component may interact with other cellular components, both upstream and downstream, to coordinate cellular processes such as feedback mechanisms. Furthermore, in vivo p38 MAPK is a complex event and exists in the presence of other MAPK and a plethora of other signaling pathways. The subcellular localization of p38 MAPK activation may also determine the end-point biological effect and may add yet another order of complexity. Future work would benefit from attention to the interaction between different pathways, the balance/regulation among signaling events, and the subcellular compartmentalization of p38 MAPK activation.

CO in Adaptive Immunity: Effect on Regulatory T Cells

A decade ago, Sakaguchi et al. suggested that a relatively small population of $CD4^+$ T cells coexpressing CD25 (the α-chain of the IL-2R) was responsible for the prevention of autoimmunity (155). Since then, a plethora of studies have supported the notion that $CD4^+CD25^+$ T cells, often referred to as regulatory T cells (Treg), play a major role in suppressing immune reactivity (156, 157). The forkhead box P3 transcription factor (Foxp3) was identified as required for the development and maintenance of the $CD25^+$ Treg cell compartment (158–161). The disruption in this gene leads to multi-organ-specific autoimmunity in both mice (scurfy mouse phenotype) and in humans [immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome] (162). We and others have demonstrated that CO/HO-1 is a potent modulator of innate immunity including

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monocyte/macrophage cells (38, 41, 145, 163). Recent reports implicate that CO/HO-1 might be involved in cell-mediated, adaptive immunity, including transplant rejection (39, 164–165). Pae et al. have demonstrated that HO-1 is differentially expressed between $CD4^+CD25^+$ and $CD4^+CD25^-$ T cell populations in a manner analogous to the aforementioned findings for human FOXP3 expression (166). Upon anti-CD3/anti-CD28 costimulation, human $CD4^+CD25^-$ T cells could also be induced to express HO-1; a finding that once again paralleled the expression pattern of human FOXP3. Stable transfection of HO-1 into Jurkat T cells inhibited cellular proliferation (166). This latter observation, when applied to natural Treg, could explain the anergic and refractory phenotype of this cell population. Interestingly, transfection of Foxp3 into Jurkat T cells reveals that Foxp3 subsequently induced expression of HO-1 (159). HO-1 gene expression in these regulatory cells suppressed proliferation and cytokine production of nontransfected cells in a cell-cell contact-dependent manner. Furthermore, the suppressive capacity of Foxp3-transfected Jurkat T cells and primary human $CD4^+CD25^+$ T cells was blocked in the presence of an HO-1 inhibitor, SnPP-IX. CO produced by HO-1, but not the other reaction products (iron or bilirubin), is capable of mediating the anti-proliferative effects of HO-1 in human $CD4^+$ T cells (108, 109). Specifically, CO was shown to block production of IL-2, a principal cytokine responsible for T cell proliferation (159, 167). The anti-proliferative effect of CO in T cells is independent of the sGC/cGMP pathway and p38 MAPK and may involve caspase activation (108).

sGC and p38 MAPK Activation by CO

It is well established that p38 MAPK can be activated by a large number of environmental factors, and all of them do not activate the same signaling mechanism. For example, NO activates p38 MAPK via the sGC-protein kinase-G (PKG) pathway, whereas TNF-α uses ASK1 (153, 168, 169). Owing to the complexity of upstream signaling pathways of p38 MAPK in response to stimuli, it is possible that the intensity or duration of the kinase activation could be dependent on the specific signaling pathways that they utilize. Now, we have evidence that CO activates p38 MAPK by sGC-dependent or –independent pathways dependent on the experimental model (Figure 2). For example, the anti-inflammatory effects of CO in macrophages were determined to depend on p38 MAPK but not sGC. The induction of Hsp70 by CO is also not likely to use sGC as an intermediate signaling protein. However, caveolin-1 expression by the gas adopts sGC-p38 MAPK cascades, as assessed by chemical inhibitors and genetic deletion experiments. The role of sGC in caveolin-1 expression through p38 MAPK is also supported by the recent observation that reduced cGMP signaling is associated with neointimal proliferation and vascular dysfunction in hypercholesterolemic rabbits. Whether CO also uses PKG for the upregulation of caveolin-1 and growth inhibition in response to PDGF treatment or balloon-injured neointimal hyperplasia remains under investigation.

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OXYGEN SENSING

Animals require oxygen to survive, and have evolved different mechanisms to sense and respond to low-oxygen tensions. When faced with low blood oxygen levels (hypoxia), humans and other mammals reflexively increase the lung ventilation rate to restore normal oxygen tensions to vital organs (170). This compensatory mechanism relies on oxygen-sensing glomus cells in the carotid body located in the carotid artery. Glomus cells sense hypoxia and respond by rapid membrane depolarization. This results in production of action potentials, influx of calcium ions (Ca^{2+}) into the glomus cells through voltage-gated Ca^{2+} channels, and release of the neurotransmitter dopamine. Dopamine then activates postsynaptic sensory neurons, and this afferent discharge initiates a variety of responses by the CNS that ensures appropriate oxygenation of different organs.

A recent study showed that the sensitivity of BK channels to hypoxia may be mediated by CO and that the underlying mechanism may involve an increasingly common principle in cellular signal transduction: a spatially tuned local signaling pathway mediated by a large protein complex of NPR, HO-2, and BK channel formed in the CNS (170).

On the vascular bed, CO can dilate blood vessels by directly acting calcium-dependent potassium channel (K_{Ca}). Kaide et al. demonstrated that decreased CO production was accompanied by a decreased number of open potassium channels in SMCs and increased vascular contractility; these effects were reversed with exogenous CO (30). In a study investigating the mechanisms of CO-mediated dilation of porcine cerebral arterioles, CO was found to dilate arterioles by increasing the effective coupling of calcium sparks to channels. The mechanism by which CO mediates these effects is still unclear, but the authors suggest the involvement of cGMP, another membrane-associated heme protein, or even direct action of CO on the receptors.

Moreover, chronic inhalation of CO (50 ppm) attenuates hypoxic pulmonary artery hypertension development presumably through activation of BK_{Ca} channels because CO inhalation slightly increases single-channel conductance of BK_{Ca} channels and induces a large increase in the sensitivity of BK_{Ca} channels to Ca^{2+} of pulmonary artery myocytes from normoxic and chronic hypoxic rats (171, 172). Consequently, BK_{Ca} currents are increased and play a more prominent role in controlling resting membrane potential of myocytes. From these observations, it is questioned whether the proposed mechanism for CO-dependent oxygen sensing in the CNS through BK channel is effective in peripheral vascular SMCs.

CO AND CAVEOLAE/CAVEOLIN-1: A NEW HYPOTHESIS

The membrane systems in any type of cell exhibit substantial and specific differences in their lipid compositions. In addition, specific differences exist between the two leaflets of most bilayers, and lipids in individual leaflets are not distributed

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homogeneously in the plane of the membrane. Mainly because of their distinct biophysical properties, sphingolipids and cholesterol play a predominant part in generating microdomains in biological membranes. These sphingolipid- and cholesterol-dependent microdomains are designated as lipid rafts or caveolae (173). Lipid rafts are first assembled at the Golgi, and take major roles in specific trafficking of proteins and lipids to and from cellular compartments. Different types of cells can differ substantially in their raft contents, and association with lipid rafts influences cell signaling. Therefore, it is plausible that if a molecule can affect the composition of lipid rafts or caveolae, or the status of the structural protein caveolin, the molecule may play a role in cell signaling or trafficking. Li et al. proposed that endothelial nitric oxide synthase (eNOS)-dependent signaling could be terminated by a NO/cGMP-dependent process that leads to the disruption of caveolin-1 oligomers (174). Furthermore, they provided evidence that NO interferes with the integrity of caveolin-1 scaffolding function. Intracellular trafficking of caveolin and lipid microdomains may correspond to plasmalemmal caveolae after budding from the plasmalemmal membrane. Indeed, dynamin, which is known to play an essential regulatory role in the process of endocytosis through clathrin-coated pits, was recently found to promote cholera toxin B chain internalization within caveolae after budding from the plasmalemmal membrane. Therefore, both caveolar fission and apparent caveolin deoligomerization could represent the same phenomenon. Collectively, these data show that the integrity of the scaffolding function of caveolin-1 is potentially important for the spatial organization of signaling systems localized to caveolae and that NO modulates signal transduction by dissociating caveolin-1 oligomers (175). On the other hand, CO increased the oligomerization of caveolin-1 in the rat pulmonary artery endothelial cells (H.P. Kim & A.M.K. Choi, unpublished observation).

Caveolae have been proposed to play an important role in cell signaling and trafficking. Epidermal growth factor and platelet-derived growth factor receptors, endothelin-A and bradykinin B2 receptor, MAPKs, src-family nonreceptor tyrosine kinase, G proteins, protein kinase C, eNOS, and HO-1, among others, are concentrated in these signalosomes (Table 2). Caveolar-coat protein caveolin forms high-molecular-weight Triton-X-100 insoluble complexes through oligomerization mediated by N-terminal residues 61–101. NO can modulate signaling initiated via receptors (i.e., M2 muscarinic acetylcholine receptor) residing in caveolae. On the contrary, the involvement of CO in receptor-mediated signaling remains unclear. Hyperactivation of p38 MAPK by CO in response to PDGF-BB treatment provides a clue. Because the balance of upstream kinases and phosphatases may determine the phosphorylation strength by growth factor receptor signaling, CO may play a role in the signaling of growth factor receptor-mediated events by altering the activities of kinases, phosphatases, or both. Interestingly, some kinases and phosphatases are localized to caveolae to act properly in response to stimuli (176, 177). Because the effects of the two gases, NO and CO, can yield similar or different outcomes depending on the cells or stimuli, we need to investigate their roles in terms of caveolin-1 oligomerization or trafficking case by case.

It would be reasonable to speculate that, however, especially in acute phase, CO may modulate the signaling in a fashion opposite to NO owing to the apparent effects of the gases on caveolin-1 oligomerization. The questions arising from this paradox are (*a*) Can oligomerization of caveolin-1 inhibit signaling generally? (*b*) Can caveolin-1 oligomeric status modulate signaling depending on stimuli or cell type? (*c*) Can pretreatment of CO modulate activation of eNOS by agonists such as bradykinin? (*d*) Can oligomerization of caveolin-1 affect the activation of sGC, which is a well-known protein activated by both gases? Answering the above questions may not only shed light on the biology of caveolae, a signalosome, but also on the understanding of the crosstalk between the two gases.

CONCLUSION

In this review we have summarized the major known mechanisms by which CO, an endogenously produced gas, can affect cellular signaling pathways. Activation of sGC appears to be a functional intermediate in some of the biological effects of CO, including neurotransmission and vasodilation. The lack of involvement of sGC in some processes triggered by CO suggests that additional proximal targets of CO action may exist. Of these, modulation of K^+-channel activity by CO has recently been described. MAPK signaling pathways, including p38 MAPK appear to represent major mediators of CO action, with respect to anti-inflammatory, anti-proliferative, and anti-apoptotic effects. An understanding of the molecular mechanisms of CO action at the cellular level may be useful in the rational design of therapeutic strategies for the treatment of inflammatory or proliferative disorders.

ACKNOWLEDGMENTS

We have limited the scope of this article to cover recent advances in CO signaling and classical studies. A comprehensive account of the vast literature in the HO/CO field is not possible in this space, and we regret many omissions. We thank K. Nakahira for preparing the tables. Supported by American Heart Association award AHA 0335035N (S.W.R.); AHA 0525552U (H.P.K.); and NIH grants R01-HL60234, R01-AI42365, and R01-HL55330 (A.M.K.C.).

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LITERATURE CITED

1. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. 1987. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc. Natl. Acad. Sci. USA* 84:9265–69
2. Sjöstrand T. 1949. Endogenous production of carbon monoxide in man under normal and pathophysiological conditions. *Scand. J. Clin. Lab. Invest.* 1:201–14

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3. Coburn RF, Blakemore WS, Forster RE. 1963. Endogenous carbon monoxide production in man. *J. Clin. Invest.* 42:1172–78
4. Stipanuk MH, Beck PW. 1982. Characterization of the enzymic capacity for cysteine desulphhydration in liver and kidney of the rat. *Biochem. J.* 15:267–77
5. Boehning D, Snyder SH. 2003. Novel neural modulators. *Annu. Rev. Neurosci.* 26:105–31
6. Tenhunen R, Marver HS, Schmid R. 1968. The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. *Proc. Natl. Acad. Sci. USA* 61:748–55
7. Vremen HJ, Wong RJ, Stevenson DK. 2000. Carbon monoxide in breath, blood, and other tissues. In *Carbon Monoxide Toxicity*, ed. DG Penney, pp. 19–60. Boca Raton, FL: CRC Press
8. Maines MD. 1997. The heme oxygenase system: a regulator of second messenger gases. *Annu. Rev. Pharmacol. Toxicol.* 37:517–54
9. Tenhunen R, Ross ME, Marver HS, Schmid R. 1970. Reduced nicotinamide adenine dinucleotide phosphate dependent biliverdin reductase: partial purification and characterization. *Biochemistry* 9:298–323
10. Maines MD, Trakshel GM, Kutty RK. 1986. Characterization of two constitutive forms of rat liver microsomal heme oxygenase. *J. Biol. Chem.* 261:411–19
11. Ryter SW, Choi AM. 2005. Heme oxygenase-1: redox regulation of a stress protein in lung and cell culture models. *Antioxid. Redox. Signal.* 7:80–91
12. Foresti R, Green CJ, Motterlini R. 2004. Generation of bile pigments by haem oxygenase: a refined cellular strategy in response to stressful insults. *Biochem. Soc. Symp.* 71:177–92
13. Watts RN, Richardson DR. 2004. Differential effects on cellular iron metabolism of the physiologically relevant diatomic effector molecules, NO and CO, that bind iron. *Biochim. Biophys. Acta* 1692:1–15
14. Barinaga M. 1993. Carbon monoxide: killer to brain messenger in one step. *Science* 259:309
15. Von Berg R. 1999. Toxicology update. Carbon monoxide. *J. Appl. Toxicol.* 19: 379–86
16. Coburn RF. 1979. Mechanisms of carbon monoxide toxicity. *Prev. Med.* 8:310–22
17. Ignarro LJ, Degnan JN, Baricos WH, Kadowitz PJ, Wolin MS. 1982. Activation of purified guanylate cyclase by nitric oxide requires heme. Comparison of heme-deficient, heme-reconstituted and heme-containing forms of soluble enzyme from bovine lung. *Biochim. Biophys. Acta* 718:49–59
18. Furchgott RF, Jothianandan D. 1991. Endothelium-dependent and -independent vasodilation involving cyclic GMP: Relaxation induced by nitric oxide, carbon monoxide and light. *Blood Vessels* 28:52–61
19. Morita T, Mitsialis SA, Koike H, Liu Y, Kourembanas S. 1997. Carbon monoxide controls the proliferation of hypoxic vascular smooth muscle cells. *J. Biol. Chem.* 272:32804–9
20. Verma A, Hirsch DJ, Glatt CE, Ronnett GV, Snyder SH. 1993. Carbon monoxide: a putative neural messenger. *Science* 259:381–84
21. Morita T, Perrella MA, Lee ME, Kourembanas S. 1995. Smooth muscle cell-derived carbon monoxide is a regulator of vascular cGMP. *Proc. Natl. Acad. Sci. USA* 92:1475–79
22. Morita T, Kourembanas S. 1995. Endothelial cell expression of vasoconstrictors and growth factors is regulated by smooth muscle cell-derived carbon monoxide. *J. Clin. Invest.* 96:2676–82
23. Boehning D, Moon C, Sharma S, Hurt KJ, Hester LD, et al. 2003. Carbon monoxide neurotransmission activated by CK2 phosphorylation of heme oxygenase 2. *Neuron* 40:129–37
24. Raub JA, Benignus VA. 2002. Carbon

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
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monoxide in the nervous system. *Neurosci. Biobehav. Rev.* 26:925–40
25. Johnson RA, Columbari E, Columbari DS, Lavesa M, Talman WT, Nasjletti A. 1997. Role of endogenous carbon monoxide in central regulation of arterial pressure. *Hypertension* 30:962–67
26. Caudill TK, Resta TC, Kanagy NL, Walker BR. 1998. Role of endothelial carbon monoxide in attenuated vasoreactivity following chronic hypoxia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 275:R1025–30
27. Suematsu M, Kashiwagi S, Sano T, Goda N, Shinoda Y, Ishimura Y. 1994. Carbon monoxide as an endogenous modulator of hepatic vascular perfusion. *Biochem. Biophys. Res. Commun.* 205:1333–37
28. Wang R, Wu L, Wang Z. 1997. The direct effect of carbon monoxide on KCa channels in vascular smooth muscle cells. *Phlügers Arch.* 434:285–91
29. Leffler CW, Nasjletti A, Yu C, Johnson RA, Fedinec AL, Walker N. 1999. Carbon monoxide and cerebral microvascular tone in newborn pigs. *Am. J. Physiol. Heart Circ. Physiol.* 276:H1641–46
30. Kaide JI, Zhang F, Wei Y, Jiang JH, Yu C, et al. 2001. Carbon monoxide of vascular origin attenuates the sensitivity of renal arterial vessels to vasoconstrictors. *J. Clin. Invest.* 107:1163–71
31. Kim HP, Wang X, Nakao A, Kim SI, Murase N, et al. 2005. Caveolin-1 expression by means of p38β mitogen-activated protein kinase mediates the antiproliferative effect of carbon monoxide. *Proc. Natl. Acad. Sci. USA* 102:11319–24
32. Duckers HJ, Boehm M, True AL, Yet SF, San H, et al. 2001. Heme oxygenase-1 protects against vascular constriction and proliferation. *Nat. Med.* 7:693–98
33. Ndisang JF, Tabien HEN, Wang R. 2004. Carbon monoxide and hypertension. *J. Hypertension* 22:1057–74
34. Otterbein LE, Zuckerbraun BS, Haga M, Liu F, Song R, et al. 2003. Carbon monoxide suppresses arteriosclerotic lesions associated with chronic graft rejection and with balloon injury. *Nat. Med.* 9:183–90
35. Brüne B, Ullrich V. 1987. Inhibition of platelet aggregation by carbon monoxide is mediated by activation of guanylate cyclase. *Mol. Pharmacol.* 32:497–504
36. Fujita T, Toda K, Karimova A, Yan SF, Naka Y, et al. 2001. Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by derepression of fibrinolysis. *Nat. Med.* 7:598–604
37. Otterbein LE, Mantell LL, Choi AM. 1999. Carbon monoxide provides protection against hyperoxic lung injury. *Am. J. Physiol. Lung Cell Mol. Physiol.* 276:L688–94
38. Otterbein LE, Bach FH, Alam J, Soares MP, Tao Lu H, et al. 2000. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. *Nat. Med.* 6:422–28
39. Soares MP, Lin Y, Anrather J, Csizmadia E, Takigami K, et al. 1998. Expression of heme oxygenase-1 can determine cardiac xenograft survival. *Nat. Med.* 4:1073–77
40. Ryter S, Otterbein LE, Morse D, Choi AM. 2002. Heme oxygenase/carbon monoxide signaling pathways: regulation and functional significance. *Mol. Cell. Biochem.* 234–235:249–63
41. Kim HP, Wang X, Zhang J, Suh GY, Benjamin IJ, et al. 2005. Heat shock protein-70 mediates the cytoprotective effect of carbon monoxide: involvement of p38β MAPK and heat shock factor-1. *J. Immunol.* 175:2622–29
42. Otterbein LE, Soares MP, Yamashita K, Bach FH. 2003. Heme oxygenase-1: unleashing the protective properties of heme. *Trends Immunol.* 24:449–55
43. Keyse SM, Applegate LA, Tromvoukis Y, Tyrrell RM. 1990. Oxidant stress leads to transcriptional activation of the human heme oxygenase gene in cultured skin fibroblasts. *Mol. Cell Biol.* 10:4967–69
44. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. 1987. Bilirubin is

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
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an antioxidant of possible physiological importance. *Science* 235:1043–46
45. Takahashi T, Morita K, Akagi R, Sassa S. 2004. Heme oxygenase-1: a novel therapeutic target in oxidative tissue injuries. *Curr. Med. Chem.* 11:1545–61
46. Lee TS, Chau LY. 2002. Heme oxygenase-1 mediates the anti-inflammatory effect of interleukin-10 in mice. *Nat. Med.* 8:240–46
47. Visner GA, Lu F, Zhou H, Liu J, Kazemfar K, Agarwal A. 2003. Rapamycin induces heme oxygenase-1 in human pulmonary vascular cells: implications in the antiproliferative response to rapamycin. *Circulation* 107:911–16
48. Koizumi T, Negishi M, Ichikawa A. 1992. Induction of heme oxygenase by delta 12-prostaglandin J2 in porcine aortic endothelial cells. *Prostaglandins* 43:121–31
49. Grosser N, Abate A, Oberle S, Vreman HJ, Dennery PA, et al. 2003. Heme oxygenase-1 induction may explain the antioxidant profile of aspirin. *Biochem. Biophys. Res. Commun.* 308:956–60
50. Grosser N, Hemmerle A, Berndt G, Erdmann K, Hinkelmann U, et al. 2004. The antioxidant defense protein heme oxygenase 1 is a novel target for statins in endothelial cells. *Free Rad. Biol. Med.* 37: 2064–71
51. Zhang B, Tanaka J, Yang L, Yang L, Sakanaka M, et al. 2004. Protective effect of vitamin E against focal brain ischemia and neuronal death through induction of target genes of hypoxia-inducible factor-1. *Neuroscience* 126:433–40
52. Zhuang H, Kim YS, Koehler RC, Dore S. 2003. Potential mechanism by which resveratrol, a red wine constituent, protects neurons. *Ann. NY Acad. Sci.* 993: 276–86
53. Balogun E, Hoque M, Gong P, Killeen E, Green CJ, et al. 2003. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. *Biochem. J.* 371:887–95
54. Peyton KJ, Reyna SV, Chapman GB, Ensenat D, Liu XM, et al. 2002. Heme oxygenase-1-derived carbon monoxide is an autocrine inhibitor of vascular smooth muscle cell growth. *Blood* 99:4443–48
55. Yang L, Quan S, Nasjletti A, Laniado-Schwartzman M, Abraham NG. 2004. Heme oxygenase-1 gene expression modulates angiotensin II-induced increase in blood pressure. *Hypertension* 43:1221–26
56. Roberts GP, Youn H, Kerby RL. 2004. CO-sensing mechanisms. *Microbiol. Mol. Biol. Rev.* 68:453–73
57. Stevenson TH, Gutierrez AF, Alderton WK, Lian L, Scrutton NS. 2001. Kinetics of CO binding to the haem domain of murine inducible nitric oxide synthase: differential effects of haem domain ligands. *Biochem. J.* 358:201–8
58. Ryter SW, Otterbein LE. 2004. Carbon monoxide in biology and medicine. *Bioessays* 26:270–80
59. Uchida T, Sato E, Sato A, Sagami I, Shimizu T, Kitagawa T. 2005. CO-dependent activity-controlling mechanism of heme-containing CO-sensor protein, neuronal PAS domain protein 2. *J. Biol. Chem.* 280:21358–68
60. Dioum EM, Rutter J, Tuckerman JR, Gonzalez G, Gilles-Gonzalez MA, McKnight SL. 2002. NPAS2: a gas-responsive transcription factor. *Science* 298:2385–87
61. Collier J, Vallance P. 1989. Second messenger role for NO widens to nervous and immune systems. *Trends Pharmacol. Sci.* 10:427–31
62. Kamisaki Y, Saheki S, Nakane M, Palmieri JA, Kuno T, et al. 1986. Soluble guanylate cyclase from rat lung exists as a heterodimer. *J. Biol. Chem.* 261:7236–41
63. Zabel U, Kleinschnitz C, Oh P, Nedvetsky P, Smolenski A, et al. 2002. Calcium-dependent membrane association sensitizes soluble guanylyl cyclase to nitric oxide. *Nat. Cell Biol.* 4:307–11
64. Friebe A, Mullershausen F, Smolenski A, Walter U, Schultz G, Koesling D. 1998.

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
by STEWARD OBSERVATORY on 02/24/06. For personal use only.

YC-1 potentiates nitric oxide- and carbon monoxide-induced cyclic GMP effects in human platelets. *Mol. Pharmacol.* 54:962–67

65. Zhao Y, Brandish PE, Ballou DP, Marletta MA. 1999. A molecular basis for nitric oxide sensing by soluble guanylate cyclase. *Proc. Natl. Acad. Sci. USA* 96:14753–58
66. Carr HS, Tran D, Reynolds MF, Burstyn JN, Spiro TG. 2002. Activation of soluble guanylyl cyclase by four-coordinate metalloporphyrins: evidence for a role for porphyrin conformation. *Biochemistry* 41:10149–57
67. Vogel KM, Hu S, Spiro TG, Dierks EA, Yu AE, Burstyn JN. 1999. Variable forms of soluble guanylyl cyclase: protein-ligand interactions and the issue of activation by carbon monoxide. *J. Biol. Inorg. Chem.* 4:804–13
68. Utz J, Ullrich V. 1991. Carbon monoxide relaxes ilial smooth muscle through activation of guanylate cyclase. *Biochem. Pharmacol.* 41:1195–201
69. Ramos KS, Lin H, McGrath JJ. 1989. Modulation of cyclic guanosine monophosphate levels in cultured aortic smooth muscle cells by carbon monoxide. *Biochem. Pharmacol.* 38:1368–70
70. Cardell LO, Ueki IF, Stjarne P, Agusti C, Takeyama K, et al. 1998. Bronchodilatation *in vivo* by carbon monoxide, a cyclic GMP related messenger. *Br. J. Pharmacol.* 124:1065–68
71. Friebe A, Wedel B, Harteneck C, Foerster J, Schultz G, Koesling D. 1997. Functions of conserved cysteines of soluble guanylyl cyclase. *Biochemistry* 36:1194–98
72. Martin E, Czarnecki K, Jayaraman V, Murad F, Kincaid J. 2005. Resonance Raman and infrared spectroscopic studies of high-output forms of human soluble guanylyl cyclase. *J. Am. Chem. Soc.* 127:4625–31
73. Kharitonov VG, Sharma VS, Magde D, Koesling D. 1999. Kinetics and equilibria of soluble guanylate cyclase ligation by CO: effect of YC-1. *Biochemistry* 38:10699–706
74. Vincent SR, Das S, Maines MD. 1994. Brain heme oxygenase isoenzymes and nitric oxide synthase are co-localized in select neurons. *Neuroscience* 63:223–31
75. Yamanaka M, Yamabe K, Saitoh Y, Katoh-Semba R, Semba R. 1996. Immunohistochemical localization of heme oxygenase-2 in the rat cerebellum. *Neurosci. Res.* 24:403–7
76. Wang R, Wu L. 1997. The chemical modification of KCa channels by carbon monoxide in vascular smooth muscle cells. *J. Biol. Chem.* 272:8222–26
77. Liu H, Mount DB, Nasjletti A, Wang W. 1999. Carbon monoxide stimulates the apical 70-pS K+ channel of the rat thick ascending limb. *J. Clin. Invest.* 103:963–70
78. Kaasik K, Lee CC. 2004. Reciprocal regulation of haem biosynthesis and the circadian clock in mammals. *Nature* 430:467–71
79. Ben-Shlomo R, Akhtar RA, Collins BH, Judah DJ, Davies R, Kyriacou CP. 1995. Light pulse-induced heme and iron-associated transcripts in mouse brain: a microarray analysis. *Chronobiol. Int.* 22:455–71
80. Schibler U, Sassone-Corsi P. 2002. A web of circadian pacemakers. *Cell* 111:919–22
81. Storch KF, Lipan O, Leykin I, Viswanathan N, Davis FC, et al. 2002. Extensive and divergent circadian gene expression in liver and heart. *Nature* 417:78–83
82. Boehning D, Snyder SH. 2002. Circadian rhythms. Carbon monoxide and clocks. *Science* 298:2339–40
83. Zhou YD, Barnard M, Tian H, Li X, Ring HZ, et al. 1997. Molecular characterization of two mammalian bHLH-PAS domain proteins selectively expressed in the central nervous system. *Proc. Natl. Acad. Sci. USA* 94:713–18
84. Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, et al. 1994. Mutagenesis and mapping of a mouse gene,

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
by STEWARD OBSERVATORY on 02/24/06. For personal use only.

Clock, essential for circadian behavior. *Science* 264:719–25

85. King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, et al. 1997. Positional cloning of the mouse circadian clock gene. *Cell* 89:641–53
86. Rutter J, Reick M, Wu LC, McKnight SL. 2001. Regulation of Clock and NPAS2 DNA binding by the redox state of NAD cofactors. *Science* 293:510–14
87. Artinian LR, Ding JM, Gillette MU. 2001. Carbon monoxide and nitric oxide: interacting messengers in muscarinic signaling to the brain's circadian clock. *Exp. Neurol.* 171:293–300
88. Ewing JF, Maines MD. 1991. Rapid induction of heme oxygenase 1 mRNA and protein by hyperthermia in rat brain: heme oxygenase 2 is not a heat shock protein. *Proc. Natl. Acad. Sci. USA* 88:5364–68
89. Ryter SW, Morse D, Choi AM. 2004. Carbon monoxide: to boldly go where NO has gone before. *Sci. STKE* 230:RE6
90. Zhang X, Shan P, Otterbein LE, Alam J, Flavell RA, et al. 2003. Carbon monoxide inhibition of apoptosis during ischemia-reperfusion lung injury is dependent on the p38 mitogen-activated protein kinase pathway and involves caspase 3. *J. Biol. Chem.* 278:1248–58
91. Zhang X, Shan P, Alam J, Davis RJ, Flavell RA, Lee PJ. 2003. Carbon monoxide modulates Fas/Fas ligand, caspases, and Bcl-2 family proteins via the p38alpha mitogen-activated protein kinase pathway during ischemia-reperfusion lung injury. *J. Biol. Chem.* 278:22061–70
92. Zhang X, Shan P, Alam J, Fu XY, Lee PJ. 2005. Carbon monoxide differentially modulates STAT1 and STAT3 and inhibits apoptosis via a phosphadidylinositol 3-kinase/Akt and p38 kinase-dependent STAT3 pathway during anoxia-reoxygenation injury. *J. Biol. Chem.* 280: 8714–21
93. Han J, Lee JD, Tobias PS, Ulevitch RJ. 1993. Endotoxin induces rapid protein tyrosine phosphorylation in 70Z/3 cells expressing CD14. *J. Biol. Chem.* 268:25009–14
94. Han J, Lee JD, Bibbs L, Ulevitch RJ. 1994. A MAP kinase targeted by endotoxin and hyperosmolarity in mammalian cells. *Science* 265:808–11
95. Lee JC, Laydon JT, McDonnell PC, Gallagher TF, Kumar S, et al. 1994. A protein kinase involved in the regulation of inflammatory cytokine biosynthesis. *Nature* 372:739–46
96. Jiang Y, Chen C, Li Z, Guo W, Gegner JA, et al. 1996. Characterization of the structure and function of a new mitogen-activated protein kinase (p38beta). *J. Biol. Chem.* 271:17920–26
97. Lechner C, Zahalka MA, Giot JF, Moller NP, Ullrich A. 1996. ERK6, a mitogen-activated protein kinase involved in C2C12 myoblast differentiation. *Proc. Natl. Acad. Sci. USA* 93:4355–59
98. Li Z, Jiang Y, Ulevitch RJ, Han J. 1996. The primary structure of p38 gamma: a new member of p38 group of MAP kinases. *Biochem. Biophys. Res. Commun.* 228:334–40
99. Jiang Y, Gram H, Zhao M, New L, Gu J, et al. 1997. Characterization of the structure and function of the fourth member of p38 group mitogen-activated protein kinases, p38delta. *J. Biol. Chem.* 272:30122–28
100. Kumar S, McDonnell PC, Gum RJ, Hand AT, Lee JC, Young PR. 1997. Novel homologues of CSBP/p38 MAP kinase: activation, substrate specificity and sensitivity to inhibition by pyridinyl imidazoles. *Biochem. Biophys. Res. Commun.* 235:533–38
101. Hanks SK, Hunter T. 1995. Protein kinases 6. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification. *FASEB J.* 9:576–96
102. Rouse J, Cohen P, Trigon S, Morange M, Alonso-Llamazares A, et al. 1994. A novel kinase cascade triggered by stress

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
by STEWARD OBSERVATORY on 02/24/06. For personal use only.

and heat shock that stimulates MAPKAP kinase-2 and phosphorylation of the small heat shock proteins. *Cell* 78:1027–37

103. Nebreda AR, Porras A. 2000. p38 MAP kinases: beyond the stress response. *Trend Biochem. Sci.* 25:257–60
104. Sweeney G, Somwar R, Ramlal T, Volchuk A, Ueyama A, Klip A. 1999. An inhibitor of p38 mitogen-activated protein kinase prevents insulin-stimulated glucose transport but not glucose transporter translocation in 3T3-L1 adipocytes and L6 myotubes. *J. Biol. Chem.* 274:10071–78
105. Heidenreich KA, Kummer JL. 1996. Inhibition of p38 mitogen-activated protein kinase by insulin in cultured fetal neurons. *J. Biol. Chem.* 271:9891–94
106. Zarubin T, Han J. 2005. Activation and signaling of the p38 MAP kinase pathway. *Cell Res.* 15:11–18
107. Kummer JL, Rao PK, Heidenreich KA. 1997. Apoptosis induced by withdrawal of trophic factors is mediated by p38 mitogen-activated protein kinase. *J. Biol. Chem.* 272:20490–94
108. Song R, Mahidhara RS, Zhou Z, Hoffman RA, Seol DW, et al. 2004. Carbon monoxide inhibits T lymphocyte proliferation via caspase-dependent pathway. *J. Immunol.* 172:1220–26
109. Pae HO, Oh GS, Choi BM, Chae SC, Kim YM, et al. 2004. Carbon monoxide produced by heme oxygenase-1 suppresses T cell proliferation via inhibition of IL-2 production. *J. Immunol.* 172:4744–51
110. Kume M, Yamamoto Y, Saad S, Gomi T, Kimoto S, et al. 1996. Ischemic preconditioning of the liver in rats: implications of heat shock protein induction to increase tolerance of ischemia-reperfusion injury. *J. Lab. Clin. Med.* 128:251–58
111. Van Molle W, Wielockx B, Mahieu T, Takada M, Taniguchi T, et al. 2002. HSP70 protects against TNF-induced lethal inflammatory shock. *Immunity* 16: 685–95
112. Ravagnan L, Gurbuxani S, Susin SA, Maisse C, Daugas E, et al. 2001. Heat-shock protein 70 antagonizes apoptosis-inducing factor. *Nat. Cell Biol.* 3:839–43
113. Trost SU, Omens JH, Karlon WJ, Meyer M, Mestril R, et al. 1998. Protection against myocardial dysfunction after a brief ischemic period in transgenic mice expressing inducible heat shock protein 70. *J. Clin. Invest.* 101:855–62
114. Meldrum KK, Burnett AL, Meng X, Misseri R, Shaw MBK, et al. 2003. Liposomal delivery of heat shock protein 72 into renal tubular cells blocks nuclear factor-κB activation, tumor necrosis factor-α production, and subsequent ischemia-induced apoptosis. *Circ. Res.* 92:293–99
115. Wong HR, Ryan M, Wispe JR. 1997. The heat shock response inhibits inducible nitric oxide synthase gene expression by blocking I-κB degradation and NF-κB nuclear translocation. *Biochem. Biophys. Res. Commun.* 231:257–63
116. Amersi F, Shen XD, Anselmo D, Melinek J, Iyer S, et al. 2002. *Ex vivo* exposure to carbon monoxide prevents hepatic ischemia/reperfusion injury through p38 MAP kinase pathway. *Hepatology* 35:815–23
117. Yee AS, Paulson EK, McDevitt MA, Rieger-Christ K, Summerhayes I, et al. 2004. The HBP1 transcriptional repressor and the p38 MAP kinase: unlikely partners in G1 regulation and tumor suppression. *Gene* 336:1–13
118. Bulavin DV, Phillips C, Nannenga B, Timofeev O, Donehower LA, et al. 2004. Inactivation of the Wip1 phosphatase inhibits mammary tumorigenesis through p38 MAPK-mediated activation of the p16(Ink4a)-p19(Arf) pathway. *Nat. Genet.* 36:343–50
119. Bulavin DV, Demidov ON, Saito S, Kauraniemi P, Phillips C, et al. 2002. Amplification of PPM1D in human tumors abrogates p53 tumor-suppressor activity. *Nat Genet.* 31:210–15
120. Takenaka K, Moriguchi T, Nishida E. 1998. Activation of the protein kinase p38

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
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in the spindle assembly checkpoint and mitotic arrest. *Science* 280:599–602

121. Molnar A, Theodoras AM, Zon LI, Kyriakis JM. 1997. Cdc42Hs, but not Rac1, inhibits serum-stimulated cell cycle progression at G1/S through a mechanism requiring p38/RK. *J. Biol. Chem.* 272:13229–35
122. Bulavin DV, Higashimoto Y, Popoff IJ, Gaarde WA, Basrur V, et al. 2001. Initiation of a G2/M checkpoint after ultraviolet radiation requires p38 kinase. *Nature* 411:102–7
123. Faust D, Dolado I, Cuadrado A, Oesch F, Weiss C, et al. 2005. p38alpha MAPK is required for contact inhibition. *Oncogene*. In press
124. Lee PJ, Alam J, Wiegand GW, Choi AM. 1996. Overexpression of heme oxygenase-1 in human pulmonary epithelial cells results in cell growth arrest and increased resistance to hyperoxia. *Proc. Natl. Acad. Sci. USA* 93:10393–98
125. Timofeev O, Lee TY, Bulavin DV. 2005. A subtle change in p38 MAPK activity is sufficient to suppress in vivo tumorigenesis. *Cell Cycle* 4:118–20
126. Haq R, Brenton JD, Takahashi M, Finan D, Finkielsztein A, et al. 2002. Constitutive p38HOG mitogen-activated protein kinase activation induces permanent cell cycle arrest and senescence. *Cancer Res.* 62:5076–82
127. Volonte D, Zhang K, Lisanti MP, Galbiati F. 2002. Expression of caveolin-1 induces premature cellular senescence in primary cultures of murine fibroblasts. *Mol. Biol. Cell.* 13:2502–17
128. Brancho D, Tanaka N, Jaeschke A, Ventura JJ, Kelkar N, et al. 2003. Mechanism of p38 MAP kinase activation in vivo. *Genes Dev.* 17:1969–78
129. Park WY, Park JS, Cho KA, Kim DI, Ko YG, et al. 2000. Up-regulation of caveolin attenuates epidermal growth factor signaling in senescent cells. *J. Biol. Chem.* 275:20847–52
130. Exner M, Minar E, Wagner O, Schillinger M. 2004. The role of heme oxygenase-1 promoter polymorphisms in human disease. *Free Radic. Biol. Med.* 37:1097–104
131. Novotny L, Vitek L. 2003. Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies. *Exp. Biol. Med.* 228:568–71
132. Nakao A, Murase N, Ho C, Toyogawa H, Billiar TR, et al. 2005. Biliverdin administration prevents the formation of intimal hyperplasia induced by vascular injury. *Circulation* 112:587–91
133. Ollinger R, Bilban M, Erat A, Froio A, McDaid J, et al. 2005. Bilirubin: a natural inhibitor of vascular smooth muscle cell proliferation. *Circulation* 112:1030–39
134. Melichar VO, Behr-Roussel D, Zabel U, Uttenthal LO, Rodrigo J, et al. 2004. Reduced cGMP signaling associated with neointimal proliferation and vascular dysfunction in late-stage atherosclerosis. *Proc. Natl. Acad. Sci. USA* 101:16671–76
135. Chen S, Kapturczak MH, Wasserfall C, Glushakova OY, Campbell-Thompson M, et al. 2005. Interleukin 10 attenuates neointimal proliferation and inflammation in aortic allografts by a heme oxygenase-dependent pathway. *Proc. Natl. Acad. Sci. USA* 102:7251–56
136. Burke SE, Lubbers NL, Chen YW, Hsieh GC, Mollison KW, et al. 1999. Neointimal formation after balloon-induced vascular injury in Yucatan minipigs is reduced by oral rapamycin. *J. Cardiovasc. Pharmacol.* 33:829–35
137. Shibata R, Kai H, Seki Y, Kusaba K, Takemiya K, et al. 2003. Rho-kinase inhibition reduces neointima formation after vascular injury by enhancing Bax expression and apoptosis. *J. Cardiovasc. Pharmacol.* 42(Suppl. 1):S43–47
138. Ivy DD, McMurtry IF, Colvin K, Imamura M, Oka M, et al. 2005. Development of occlusive neointimal lesions in distal pulmonary arteries of endothelin B receptor-deficient rats: a new model of severe

pulmonary arterial hypertension. *Circulation* 111:2988–96
139. Choi MH, Lee IK, Kim GW, Kim BU, Han YH, et al. 2005. Regulation of PDGF signalling and vascular remodelling by peroxiredoxin II. *Nature* 435:347–53
140. Lijnen HR. 2003–2004. Metalloproteinases in development and progression of vascular disease. *Pathophysiol. Haemost. Thromb.* 33:275–81
141. Ramirez Correa GA, Zacchigna S, Arsic N, Zentilin L, Salvi A, et al. 2004. Potent inhibition of arterial intimal hyperplasia by TIMP1 gene transfer using AAV vectors. *Mol. Ther.* 9:876–84
142. Hassan GS, Jasmin JF, Schubert W, Frank PG, Lisanti MP. 2004. Caveolin-1 deficiency stimulates neointima formation during vascular injury. *Biochemistry* 43:8312–21
143. Bergdahl A, Sward K. 2004. Caveolae-associated signaling in smooth muscle. *Can. J. Physiol. Pharmacol.* 82:289–99
144. Navarro A, Anand-Apte B, Parat M-O. 2004. A role of caveolae in cell migration. *FASEB J.* 18:1801–11
145. Morse D, Pischke SE, Zhou Z, Davis RJ, Flavell RA, et al. 2003. Suppression of inflammatory cytokine production by carbon monoxide involves the JNK pathway and AP-1. *J. Biol. Chem.* 278:36993–98
146. Wagener FA, Volk HD, Willis D, Abraham NG, Soares MP, et al. 2003. Different faces of the heme-heme oxygenase system in inflammation. *Pharmacol. Rev.* 55:551–71
147. Brouard S, Otterbein LE, Anrather, Tobiasch E, Bach FH, et al. 2000. Carbon monoxide generated by heme oxygenase 1 suppresses endothelial cell apoptosis. *J. Exp. Med.* 192:1015–26
148. Brouard S, Berberat PO, Tobiasch E, Seldon MP, Bach FH, Soares MP. 2002. Heme oxygenase-1-derived carbon monoxide requires the activation of transcription factor NF-κB to protect endothelial cells from tumor necrosis factor-α-mediated apoptosis. *J. Biol. Chem.* 277:17950–61
149. Petrache I, Otterbein LE, Alam J, Wiegand GW, Choi AM. 2000. Heme oxygenase-1 inhibits TNF-alpha-induced apoptosis in cultured fibroblasts. *Am. J. Physiol. Lung Cell Mol. Physiol.* 278:L312–19
150. Zuckerbraun BS, Billiar TR, Otterbein SL, Kim PK, Liu F. 2003. Carbon monoxide protects against liver failure through nitric oxide-induced heme oxygenase-1. *J. Exp. Med.* 198:1707–16
151. Pileggi A, Cattan P, Berney T, Molano RD, Vizzardelli C, et al. 2001. HO-1 upregulation protects the pancreatic cell line betaTC3 from cytokines and Fas-induced apoptosis. *Transplant. Proc.* 33:266–67
152. Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. 1999. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. *Immunity* 10:387–98
153. Ichijo H, Nishida E, Irie K, ten Dijke P, Saitoh M, et al. 1997. Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. *Science* 275:90–94
154. Ge B, Gram H, Di Padova F, Huang B, New L, et al. 2002. MAPKK-independent activation of p38alpha mediated by TAB1-dependent autophosphorylation of p38alpha. *Science* 295:1291–94
155. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. 1995. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor α-chains (CD25): Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J. Immunol.* 155:1151–64
156. Piccirillo CA, Shevach EM. 2004. Naturally-occurring CD4+CD25+ immunoregulatory T cells: central players in the arena of peripheral tolerance. *Semin. Immunol.* 16:81–88

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157. Takahashi T, Kuniyasu Y, Toda M, Sakaguchi N, Itoh M, et al. 1998. Immunologic self-tolerance maintained by CD25+CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state. *Int. Immunol.* 10:1969–80
158. Walker MR, Kasprowicz DJ, Gersuk VH, Benard A, Van Landeghen M, et al. 2003. Induction of FoxP3 and acquisition of T regulatory activity by stimulated human CD4+CD25- T cells. *J. Clin. Invest.* 112:1437–43
159. Choi BM, Pae HO, Jeong YR, Kim YM, Chung HT. 2005. Critical role of heme oxygenase-1 in Foxp3-mediated immune suppression. *Biochem. Biophys. Res. Commun.* 327:1066–71
160. Bettelli E, Dastrange M, Oukka M. 2005. Foxp3 interacts with nuclear factor of activated T cells and NF-kB to repress cytokine gene expression and effector functions of T helper cells. *Proc. Natl. Acad. Sci. USA* 102:5138–43
161. Fontenot JD, Gavin MA, Rudensky AY. 2003. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nat. Immunol.* 4:330–36
162. Wildin RS, Ramsdell F, Peake J, Faravelli F, Casanova JL, et al. 2001. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat. Genet.* 27:18–20
163. Ke B, Shen XD, Zhai Y, Gao F, Busuttil RW, et al. 2002. Heme oxygenase 1 mediates the immunomodulatory and antiapoptotic effects of interleukin 13 gene therapy in vivo and in vitro. *Hum. Gene Ther.* 13:1845–57
164. Katori M, Busuttil RW, Kupiec-Weglinski JW. 2002. Heme oxygenase-1 system in organ transplantation. *Transplantation* 74:905–12
165. McDaid J, Yamashita K, Chora A, Ollinger R, Strom TB, et al. 2005. Heme oxygenase-1 modulates the allo-immune response by promoting activation-induced cell death of T cells. *FASEB J.* 19:458–60
166. Pae HO, Oh GS, Choi BM, Chae SC, Chung HT. 2003. Differential expressions of heme oxygenase-1 gene in CD25− and CD25+ subsets of human CD4+ T cells. *Biochem. Biophys. Res. Commun.* 306:701–5
167. Thornton AM, Donovan EE, Piccirillo CA, Shevach EM. 2004. Cutting edge: IL-2 is critically required for the in vitro activation of CD4+CD25+ T cell suppressor function. *J. Immunol.* 172:6519–23
168. Browning DD, McShane MP, Marty C, Ye RD. 2000. Nitric oxide activation of p38 mitogen-activated protein kinase in 293T fibroblasts requires cGMP-dependent protein kinase. *J. Biol. Chem.* 275:2811–16
169. Chiche JD, Schlutsmeyer SM, Bloch DB, de la Monte SM, Roberts JD Jr, et al. 1998. Adenovirus-mediated gene transfer of cGMP-dependent protein kinase increases the sensitivity of cultured vascular smooth muscle cells to the antiproliferative and pro-apoptotic effects of nitric oxide/cGMP. *J. Biol. Chem.* 273:34263–71
170. Williams SE, Wootton P, Mason HS, Bould J, Iles DE, et al. 2004. Hemoxygenase-2 is an oxygen sensor for a calcium-sensitive potassium channel. *Science* 306:2093–97
171. Jaggar JH, Leffler CW, Cheranov SY, Tcheranova D, Shuyu E, Cheng X. 2002. Carbon monoxide dilates cerebral arterioles by enhancing the coupling of Ca2+ sparks to Ca2+-activated K+ channels. *Circ. Res.* 91:610–17
172. Dubuis E, Potier M, Wang R, Vandier C. 2005. Continuous inhalation of carbon monoxide attenuates hypoxic pulmonary hypertension development presumably through activation of BKCa channels. *Cardiovasc. Res.* 65:751–61
173. Golub T, Wacha S, Caroni P. 2004. Spatial and temporal control of signaling through

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
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lipid rafts. *Curr. Opin. Neurobiol.* 14:542–50

174. Li H, Brodsky S, Basco M, Romanov V, De Angelis DA, Goligorsky MS. 2001. Nitric oxide attenuates signal transduction: possible role in dissociating caveolin-1 scaffold. *Circ. Res.* 88:229–36
175. Feron O, Kelly RA. 2001. The caveolar paradox. Suppressing, inducing, and terminating eNOS signaling. *Circ. Res.* 88:129–31
176. Pelkmans L, Fava E, Grabner H, Hannus M, Habermann B, et al. 2005. Genome-wide analysis of human kinases in clathrin- and caveolae/raft-mediated endocytosis. *Nature* 436:78–86
177. Caselli A, Taddei ML, Manao G, Camici G, Ramponi G. 2001. Tyrosine-phosphorylated caveolin is a physiological substrate of the low M(r) protein-tyrosine phosphatase. *J. Biol. Chem.* 276:18849–54
178. Vargas MR, Pehar M, Cassina P, Martinez-Palma L, Thompson JA, et al. 2005. Fibroblast growth factor-1 induces heme oxygenase-1 via nuclear factor erythroid 2-related factor 2 (Nrf2) in spinal cord astrocytes: consequences for motor neuron survival. *J. Biol. Chem.* 280:25571–79
179. Tacchini L, De Ponti C, Matteucci E, Follis R, Desiderio MA. 2004. Hepatocyte growth factor-activated NF-kappaB regulates HIF-1 activity and ODC expression, implicated in survival, differently in different carcinoma cell lines. *Carcinogenesis* 25:2089–100
180. Fernandez M, Bonkovsky HL. 2003. Vascular endothelial growth factor increases heme oxygenase-1 protein expression in the chick embryo chorioallantoic membrane. *Br. J. Pharmacol.* 139:634–40
181. Liu H, Nowak R, Chao W, Bloch KD. 2003. Nerve growth factor induces anti-apoptotic heme oxygenase-1 in rat pheochromocytoma PC12 cells. *J. Neurochem.* 86:1553–63
182. Salinas M, Diaz R, Abraham NG, Ruiz de Galarreta CM, Cuadrado A. 2003. Nerve growth factor protects against 6-hydroxydopamine-induced oxidative stress by increasing expression of heme oxygenase-1 in a phosphatidylinositol 3-kinase-dependent manner. *J. Biol. Chem.* 278:13898–904
183. Ning W, Song R, Li C, Park E, Mohsenin A, 2002. TGF-beta1 stimulates HO-1 via the p38 mitogen-activated protein kinase in A549 pulmonary epithelial cells. *Am. J. Physiol.* 283:L1094–102
184. Braun S, Hanselmann C, Gassmann MG, auf dem Keller U, Born-Berclaz C, et al. 2002. Nrf2 transcription factor, a novel target of keratinocyte growth factor action which regulates gene expression and inflammation in the healing skin wound. *Mol. Cell Biol.* 22:5492–505
185. Gould SE, Day M, Jones SS, Dorai H. 2002. BMP-7 regulates chemokine, cytokine, and hemodynamic gene expression in proximal tubule cells. *Kidney Int.* 61:51–60
186. Durante W, Peyton KJ, Schafer AI. 1999. Platelet-derived growth factor stimulates heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle cells. *Arterioscler. Thromb. Vasc. Biol.* 19:2666–72
187. Deshane J, Wright M, Agarwal A. 2005. Heme oxygenase-1 expression in disease states. *Acta. Biochim. Pol*. 52:273–84
188. Lu A, Ran RQ, Clark J, Reilly M, Nee A, Sharp FR. 2002. 17-beta-estradiol induces heat shock proteins in brain arteries and potentiates ischemic heat shock protein induction in glia and neurons. *J. Cereb. Blood Flow Metab.* 22:183–95
189. Malaguarnera L, Imbesi RM, Scuto A, D'Amico F, Licata F, et al. 2004. Prolactin increases HO-1 expression and induces VEGF production in human macrophages. *J. Cell Biochem.* 93:197–206
190. Lam CW, Getting SJ, Perretti M. 2005. In vitro and in vivo induction of heme oxygenase 1 in mouse macrophages

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following melanocortin receptor activation. *J. Immunol.* 174:2297–304

191. Pomeraniec Y, Grion N, Gadda L, Pannunzio V, Podesta EJ, Cymeryng CB. 2004. Adrenocorticotropin induces heme oxygenase-1 expression in adrenal cells. *J. Endocrinol.* 180:113–24
192. Kiemer AK, Bildner N, Weber NC, Vollmar AM. 2003. Characterization of heme oxygenase 1 (heat shock protein 32) induction by atrial natriuretic peptide in human endothelial cells. *Endocrinology* 144:802–12
193. Martinez-Cruz F, Espinar A, Pozo D, Osuna C, Guerrero JM. 2002. Melatonin prevents focal rat cerebellum injury as assessed by induction of heat shock protein (HO-1) following subarachnoid injections of lysed blood. *Neurosci. Lett.* 331:208–10
194. Haugen EN, Croatt AJ, Nath KA. 2000. Angiotensin II induces renal oxidant stress in vivo and heme oxygenase-1 in vivo and in vitro. *Kidney Int.* 58:144–52
195. Acevedo CH, Ahmed A. 1998. Heme-oxygenase-1 inhibits human myometrial contractility via carbon monoxide and is upregulated by progesterone during pregnancy. *J. Clin. Invest.* 101:949–55
196. Raju VS, McCoubrey WK Jr, Maines MD. 1997. Regulation of heme oxygenase-2 by glucocorticoids in neonatal rat brain: characterization of a functional glucocorticoid response element. *Biochim. Biophys. Acta* 1351:89–104
197. Kutty RK, Maines MD. 1989. Selective induction of heme oxygenase-1 isozyme in rat testis by human chorionic gonadotropin. *Arch. Biochem. Biophys.* 268:100–7
198. Kim EH, Kim DH, Na HK, Surh YJ. 2004. Effects of cyclopentenone prostaglandins on the expression of heme oxygenase-1 in MCF-7 cells. *Ann. NY Acad. Sci.* 1030:493–500
199. Haloui M, Meilhac O, Jandrot-Perrus M, Michel JB. 2003. Atorvastatin limits the pro-inflammatory response of rat aortic smooth muscle cells to thrombin. *Eur. J. Pharmacol.* 474:175–84
200. Maines MD, Kappas A. 1976. Selenium regulation of hepatic heme metabolism: induction of delta-aminolevulinate synthase and heme oxygenase. *Proc. Natl. Acad. Sci. USA* 73:4428–31
201. Satoh T, Ishige K, Sagara Y. 2004. Protective effects on neuronal cells of mouse afforded by ebselen against oxidative stress at multiple steps. *Neurosci. Lett.* 371:1–5
202. Deng YM, Wu BJ, Witting PK, Stocker R. 2004. Probucol protects against smooth muscle cell proliferation by upregulating heme oxygenase-1. *Circulation* 110:1855–60
203. Choi BM, Kim YM, Jeong YR, Pae HO, Song CE, et al. 2004. Induction of heme oxygenase-1 is involved in antiproliferative effects of paclitaxel on rat vascular smooth muscle cells. *Biochem. Biophys. Res. Commun.* 321:132–37
204. Knowles HJ, Tian YM, Mole DR, Harris AL. 2004. Novel mechanism of action for hydralazine: induction of hypoxia-inducible factor-1alpha, vascular endothelial growth factor, and angiogenesis by inhibition of prolyl hydroxylases. *Circ. Res.* 95:162–69
205. Liu XM, Peyton KJ, Ensenat D, Wang H, Schafer AI, et al. 2005. Endoplasmic reticulum stress stimulates heme oxygenase-1 gene expression in vascular smooth muscle. Role in cell survival. *J. Biol. Chem.* 280:872–77
206. Alam J. 1994. Multiple elements within the 5′ distal enhancer of the mouse heme oxygenase-1 gene mediate induction by heavy metals. *J Biol Chem.* 269:25049–56
207. Ishikawa K, Navab M, Leitinger N, Fogelman AM, Lusis AJ. 1997. Induction of heme oxygenase-1 inhibits the monocyte transmigration induced by mildly oxidized LDL. *J. Clin. Invest.* 100:1209–16
208. Ishii T, Itoh K, Ruiz E, Leake DS, Unoki H, et al. 2004. Role of Nrf2 in the regulation of CD36 and stress protein

expression in murine macrophages: activation by oxidatively modified LDL and 4-hydroxynonenal. *Circ. Res.* 94:609–16

209. Kobayashi M, Yamamoto M. 2005. Molecular mechanisms activation of the Nrf2-Keap1 pathway of antioxidant gene regulation. *Antioxid. Redox Signal.* 7:385–95
210. Foresti R, Clark JE, Green CJ, Motterlini R. 1997. Thiol compounds interact with nitric oxide in regulating heme oxygenase-1 induction in endothelial cells. Involvement of superoxide and peroxynitrite anions. *J. Biol. Chem.* 272:18411–17
211. Iles KE, Dickinson DA, Wigley AF, Welty NE, Blank V, Forman HJ. 2005. HNE increases HO-1 through activation of the ERK pathway in pulmonary epithelial cells. *Free Radic. Biol. Med.* 39:355–64
212. Kim do K, Kim JS, Kim JE, Kim SJ, Lee JS, et al. 2005. Heme oxygenase-1 induction by dieldrin in dopaminergic cells. *Neuroreport* 16:509–12
213. Muller T, Gebel S. 1994. Heme oxygenase expression in Swiss 3T3 cells following exposure to aqueous cigarette smoke fractions. *Carcinogenesis* 15:67–72
214. Liu LG, Yan H, Zhang W, Yao P, Zhang XP, et al. 2004. Induction of heme oxygenase-1 in human hepatocytes to protect them from ethanol-induced cytotoxicity. *Biomed. Environ. Sci.* 17:315–26
215. Liby K, Hock T, Yore MM, Suh N, Place AE, et al. 2005. The synthetic triterpenoids, CDDO and CDDO-imidazolide, are potent inducers of heme oxygenase-1 and Nrf2/ARE signaling. *Cancer Res.* 65:4789–98
216. Chow JM, Shen SC, Huan SK, Lin HY, Chen YC. 2005. Quercetin, but not rutin and quercitrin, prevention of H2O2-induced apoptosis via anti-oxidant activity and heme oxygenase 1 gene expression in macrophages. *Biochem. Pharmacol.* 69:1839–51
217. Zurich MG, Lengacher S, Braissant O, Monnet-Tschudi F, Pellerin L, Honegger P. 2005. Unusual astrocyte reactivity caused by the food mycotoxin ochratoxin A in aggregating rat brain cell cultures. *Neuroscience* 134:771–82
218. Sultana R, Ravagna A, Mohmmad-Abdul H, Calabrese V, Butterfield DA. 2005. Ferulic acid ethyl ester protects neurons against amyloid beta- peptide(1–42)-induced oxidative stress and neurotoxicity: relationship to antioxidant activity. *J. Neurochem.* 92:749–58
219. Nakamura Y, Yoshida C, Murakami A, Ohigashi H, Osawa T, Uchida K. 2004. Zerumbone, a tropical ginger sesquiterpene, activates phase II drug metabolizing enzymes. *FEBS Lett.* 572:245–50
220. Rieder CR, Williams AC, Ramsden DB. 2004. Selegiline increases heme oxygenase-1 expression and the cytotoxicity produced by dopamine treatment of neuroblastoma SK-N-SH cells. *Braz. J. Med. Biol. Res.* 37:1055–62
221. Tron K, Novosyadlyy R, Dudas J, Samoylenko A, Kietzmann T, Ramadori G. 2005. Upregulation of heme oxygenase-1 gene by turpentine oil-induced localized inflammation: involvement of interleukin-6. *Lab. Invest.* 85:376–87
222. Kweon MH, Jung MJ, Sung HC. 2004. Cytoprotective effects of heme oxygenase-1 induction by 3-O-caffeoyl-1-methylquinic acid. *Free. Radic. Biol. Med.* 36:40–52
223. Gong P, Hu B, Cederbaum AI. 2004. Diallyl sulfide induces heme oxygenase-1 through MAPK pathway. *Arch. Biochem. Biophys.* 432:252–60
224. Foresti R, Hoque M, Monti D, Green CJ, Motterlini R. 2005. Differential activation of heme oxygenase-1 by chalcones and rosolic acid in endothelial cells. *J. Pharmacol. Exp. Ther.* 312:686–93
225. Schmidt R, Hoetzel A, Baechle T, Loop T, Humar M, et al. 2004. Isoflurane pretreatment lowers portal venous resistance by increasing hepatic heme oxygenase activity in the rat liver in vivo. *J. Hepatol.* 41:706–13

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226. Olszanecki R, Marcinkiewicz J. 2004. Taurine chloramine and taurine bromamine induce heme oxygenase-1 in resting and LPS-stimulated J774.2 macrophages. *Amino Acids* 27:29–35
227. Cavin C, Holzhaeuser D, Scharf G, Constable A, Huber WW, Schilter B. 2002. Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem. Toxicol.* 40:1155–63
228. Haridas V, Hanausek M, Nishimura G, Soehnge H, Gaikwad A, et al. 2004. Triterpenoid electrophiles (avicins) activate the innate stress response by redox regulation of a gene battery. *J. Clin. Invest.* 113:65–73
229. Juan SH, Cheng TH, Lin HC, Chu YL, Lee WS. 2005. Mechanism of concentration-dependent induction of heme oxygenase-1 by resveratrol in human aortic smooth muscle cells. *Biochem. Pharmacol.* 69:41–48
230. Attuwaybi B, Kozar RA, Gates KS, Moore-Olufemi S, Sato N, et al. 2004. Hypertonic saline prevents inflammation, injury, and impaired intestinal transit after gut ischemia/reperfusion by inducing heme oxygenase 1 enzyme. *J. Trauma.* 56:749–58
231. Takeda K, Lin J, Okubo S, Akazawa-Kudoh S, Kajinami K, et al. 2004. Transient glucose deprivation causes upregulation of heme oxygenase-1 and cyclooxygenase-2 expression in cardiac fibroblasts. *J. Mol. Cell Cardiol.* 36:821–30
232. Christou H, Bailey N, Kluger MS, Mitsialis SA, Kourembanas S. 2005. Extracellular acidosis induces heme oxygenase-1 expression in vascular smooth muscle cells. *Am. J. Physiol. Heart Circ. Physiol.* 288:H2647–52
233. Durante W, Kroll MH, Christodoulides N, Peyton KJ, Schafer AI. 1997. Nitric oxide induces heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle cells. *Circ. Res.* 80:557–64
234. Marquis JC, Demple B. 1998. Complex genetic response of human cells to sublethal levels of pure nitric oxide. *Cancer Res.* 58:3435–40
235. Foresti R, Sarathchandra P, Clark JE, Green CJ, Motterlini R. 1999. Peroxynitrite induces haem oxygenase-1 in vascular endothelial cells: a link to apoptosis. *Biochem. J.* 339:729–36
236. Naughton P, Foresti R, Bains SK, Hoque M, Green CJ, Motterlini R. 2002. Induction of heme oxygenase 1 by nitrosative stress. A role for nitroxyl anion. *J. Biol. Chem.* 277:40666–74
237. Naughton P, Hoque M, Green CJ, Foresti R, Motterlini R. 2002. Interaction of heme with nitroxyl or nitric oxide amplifies heme oxygenase-1 induction: involvement of the transcription factor Nrf2. *Cell. Mol. Biol.* 48:885–94
238. Choi BM, Pae HO, Chung HT. 2003. Nitric oxide priming protects nitric oxide-mediated apoptosis via heme oxygenase-1 induction. *Free Radic. Biol. Med.* 34:1136–45
239. Hartsfield CL, Alam J, Cook JL, Choi AM. 1997. Regulation of heme oxygenase-1 gene expression in vascular smooth muscle cells by nitric oxide. *Am. J. Physiol. Lung Cell Mol. Physiol.* 273:L980–88
240. Motterlini R, Foresti R, Intaglietta M, Winslow RM. 1996. NO-mediated activation of heme oxygenase: endogenous cytoprotection against oxidative stress to endothelium. *Am. J. Physiol. Heart Circ. Physiol.* 270:H107–14
241. Yee EL, Pitt BR, Billiar TR, Kim YM. 1996. Effect of nitric oxide on heme metabolism in pulmonary artery endothelial cells. *Am. J. Physiol. Lung Cell Mol. Physiol.* 271:L512–18
242. Pae HO, Choi BM, Oh GS, Lee MS, Ryu DG, et al. 2004. Roles of heme oxygenase-1 in the antiproliferative and antiapoptotic effects of nitric oxide on Jurkat T cells. *Mol. Pharmacol.* 66:122–28
243. Malaguarnera L, Imbesi R, Di Rosa

M, Scuto A, Castrogiovanni P, et al. 2005. Action of prolactin, IFN-γ, TNF-α and LPS on heme oxygenase-1 expression and VEGF release in human monocytes/macrophages. *Int. Immunopharmacol.* 5:1458–69

244. Chen XL, Varner SE, Rao AS, Grey JY, Thomas S, et al. 2003. Laminar flow induction of antioxidant response element-mediated genes in endothelial cells. A novel anti-inflammatory mechanism. *J. Biol. Chem.* 278:703–11
245. Wagner CT, Durante W, Christodoulides N, Hellums JD, Schafer AI. 1997. Hemodynamic forces induce the expression of heme oxygenase in cultured vascular smooth muscle cells. *J. Clin. Invest.* 100:589–96
246. Berger SP, Hunger M, Yard BA, Schnuelle P, Van Der Woude FJ. 2000. Dopamine induces the expression of heme oxygenase-1 by human endothelial cells in vitro. *Kidney Int.* 58:2314–19
247. Chang YC, Lai CC, Lin LF, Ni WF, Tsai CH. 2005. The up-regulation of heme oxygenase-1 expression in human gingival fibroblasts stimulated with nicotine. *J. Periodontal Res.* 40:252–57
248. Ham D, Schipper HM. 2000. Heme oxygenase-1 induction and mitochondrial iron sequestration in astroglia exposed to amyloid peptides. *Cell Mol. Biol.* 46:587–96
249. Chopra VS, Chalifour LE, Schipper HM. 1995. Differential effects of cysteamine on heat shock protein induction and cytoplasmic granulation in astrocytes and glioma cells. *Brain Res. Mol. Brain Res.* 31:173–84
250. Vile GF, Tyrrell RM. 1993. Oxidative stress resulting from ultraviolet-A irradiation of human skin fibroblasts leads to a heme oxygenase-dependent increase in ferritin. *J. Biol. Chem.* 268:14678–81
251. Galbraith RA, Drummond GS, Krey L, Kappas A. 1987. Relationship of suppression of the androgenic axis by cobalt-protoporphyrin to its effects on weight loss and hepatic heme oxygenase induction. *Pharmacology* 34:241–49
252. Wu WT, Chi KH, Ho FM, Tsao WC, Lin WW. 2004. Proteasome inhibitors up-regulate haem oxygenase-1 gene expression: requirement of p38 MAPK (mitogen-activated protein kinase) activation but not of NF-kappaB (nuclear factor kappaB) inhibition. *Biochem. J.* 379:587–93
253. Couet J, Sargiacomo M, Lisanti MP. 1997. Interaction of a receptor tyrosine kinase, EGF-R, with caveolins. Caveolin binding negatively regulates tyrosine and serine/threonine kinase activities. *J. Biol. Chem.* 272:30429–38
254. Cho CH, Lee CS, Chang M, Jang IH, Kim SJ, et al. 2004. Localization of VEGFR-2 and PLD2 in endothelial caveolae is involved in VEGF-induced phosphorylation of MEK and ERK. *Am. J. Physiol. Heart Circ. Physiol.* 286(5):H1881–88
255. Razani B, Zhang XL, Bitzer M, von Gersdorff G, Bottinger EP, Lisanti MP. 2001. Caveolin-1 regulates transforming growth factor (TGF)-beta/SMAD signaling through an interaction with the TGF-beta type I receptor. *J. Biol. Chem.* 276: 6727–38
256. Smith RM, Harada S, Smith JA, Zhang S, Jarett L. 1998. Insulin-induced protein tyrosine phosphorylation cascade and signalling molecules are localized in a caveolin-enriched cell membrane domain. *Cell Signal.* 10:355–62
257. Liu P, Ying Y, Ko YG, Anderson RG. 1996. Localization of platelet-derived growth factor-stimulated phosphorylation cascade to caveolae. *J. Biol. Chem.* 271: 10299–303
258. Bilderback TR, Gazula VR, Lisanti MP, Dobrowsky RT. 1999. Caveolin interacts with Trk A and p75(NTR) and regulates neurotrophin signaling pathways. *J. Biol. Chem.* 274:257–63
259. Ishizaka N, Griendling KK, Lassegue B, Alexander RW. 1998. Angiotensin II type

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1 receptor: relationship with caveolae and caveolin after initial agonist stimulation. *Hypertension* 32:459–66

260. Ko YG, Lee JS, Kang YS, Ahn JH, Seo JS. 1999. TNF-alpha-mediated apoptosis is initiated in caveolae-like domains. *J. Immunol.* 162:7217–23
261. Guignot J, Bernet-Camard MF, Pous C, Plancon L, Le Bouguenec C, Servin AL. 2001. Polarized entry of uropathogenic Afa/Dr diffusely adhering *Escherichia coli* strain IH11128 into human epithelial cells: evidence for alpha5beta1 integrin recognition and subsequent internalization through a pathway involving caveolae and dynamic unstable microtubules. *Infect. Immun.* 69:1856–68
262. Gingras D, Gauthier F, Lamy S, Desrosiers RR, Beliveau R. 1998. Localization of RhoA GTPase to endothelial caveolae-enriched membrane domains. *Biochem. Biophys. Res. Commun.* 247: 888–93
263. Michaely PA, Mineo C, Ying YS, Anderson RG. 1999. Polarized distribution of endogenous Rac1 and RhoA at the cell surface. *J. Biol. Chem.* 274:21430–36
264. Chun M, Liyanage UK, Lisanti MP, Lodish HF. 1994. Signal transduction of a G protein-coupled receptor in caveolae: colocalization of endothelin and its receptor with caveolin. *Proc. Natl. Acad. Sci. USA* 91:11728–32
265. Annabi B, Lachambre M, Bousquet-Gagnon N, Page M, Gingras D, Beliveau R. 2001. Localization of membrane-type 1 matrix metalloproteinase in caveolae membrane domains. *Biochem. J.* 353: 547–53
266. Puyraimond A, Fridman R, Lemesle M, Arbeille B, Menashi S. 2001. MMP-2 colocalizes with caveolae on the surface of endothelial cells. *Exp. Cell Res.* 262:28–36
267. Schwab W, Gavlik JM, Beichler T, Funk RH, Albrecht S, et al. 2001. Expression of the urokinase-type plasminogen activator receptor in human articular chondrocytes: association with caveolin and beta 1-integrin. *Histochem. Cell Biol.* 115:317–23
268. Carlin SM, Resink TJ, Tamm M, Roth M. 2005. Urokinase signal transduction and its role in cell migration. *FASEB J.* 19:195–202
269. Razani B, Rubin CS, Lisanti MP. 1999. Regulation of cAMP-mediated signal transduction via interaction of caveolins with the catalytic subunit of protein kinase A. *J. Biol. Chem.* 274:26353–60
270. Tang ZL, Scherer PE, Lisanti MP. 1994. The primary sequence of murine caveolin reveals a conserved consensus site for phosphorylation by protein kinase C. *Gene* 147:299–300
271. Ju H, Venema VJ, Liang H, Harris MB, Zou R, Venema RC. 2000. Bradykinin activates the Janus-activated kinase/signal transducers and activators of transcription (JAK/STAT) pathway in vascular endothelial cells: localization of JAK/STAT signalling proteins in plasmalemmal caveolae. *Biochem. J.* 351:257–64
272. Rothberg KG, Heuser JE, Donzell WC, Ying YS, Glenney JR, Anderson RG. 1992. Caveolin, a protein component of caveolae membrane coats. *Cell* 68:673–82
273. Bickel PE, Scherer PE, Schnitzer JE, Oh P, Lisanti MP, Lodish HF. 1997. Flotillin and epidermal surface antigen define a new family of caveolae-associated integral membrane proteins. *J. Biol. Chem.* 272:13793–802
274. Salzer U, Prohaska R. Stomatin 2002. Flotillin-1 and flotillin-2 are major integral proteins of erythrocyte lipid rafts. *Blood* 2001 97:1141–43
275. Pelkmans L, Puntener D, Helenius A. 2002. Local actin polymerization and dynamin recruitment in SV40-induced internalization of caveolae. *Science* 296:535–39
276. Kanzaki M, Pessin JE. 2002. Caveolin-associated filamentous actin (Cav-actin) defines a novel F-actin structure in

Annu. Rev. Pharmacol. Toxicol. 2006.46:411-449. Downloaded from arjournals.annualreviews.org
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adipocytes. *J. Biol. Chem.* 277:25867–69

277. Volonte D, Galbiati F, Pestell RG, Lisanti MP. 2001. Cellular stress induces the tyrosine phosphorylation of caveolin-1 (Tyr(14)) via activation of p38 mitogen-activated protein kinase and c-Src kinase. Evidence for caveolae, the actin cytoskeleton, and focal adhesions as mechanical sensors of osmotic stress. *J. Biol. Chem.* 276:8094–103
278. Takenouchi T, Miyashita N, Ozutsumi K, Rose MT, Aso H. 2004. Role of caveolin-1 and cytoskeletal proteins, actin and vimentin, in adipogenesis of bovine intramuscular preadipocyte cells. *Cell Biol. Int.* 28:615–23
279. Yao Q, Chen J, Cao H, Orth JD, McCaffery JM, et al. 2005. Caveolin-1 interacts directly with dynamin-2. *J. Mol. Biol.* 348:491–501
280. Dessy C, Kelly RA, Balligand JL, Feron O. 2000. Dynamin mediates caveolar sequestration of muscarinic cholinergic receptors and alteration in NO signaling. *EMBO J.* 19:4272–80
281. Oh P, McIntosh DP, Schnitzer JE. 1998. Dynamin at the neck of caveolae mediates their budding to form transport vesicles by GTP-driven fission from the plasma membrane of endothelium. *J. Cell Biol.* 141:101–14
282. Fujimoto T. 1993. Calcium pump of the plasma membrane is localized in caveolae. *J. Cell Biol.* 120:1147–57
283. Fujimoto T, Miyawaki A, Mikoshiba K. 1995. Inositol 1,4,5-trisphosphate receptor-like protein in plasmalemmal caveolae is linked to actin filaments. *J. Cell Sci.* 108:7–15
284. Murakami M, Nakatani Y, Kuwata H, Kudo I. 2000. Cellular components that functionally interact with signaling phospholipase A(2)s. *Biochim. Biophys. Acta* 1488159–66
285. Kim HP, Lee JY, Jeong JK, Bae SW, Lee HK, Jo I. 1999. Nongenomic stimulation of nitric oxide release by estrogen is mediated by estrogen receptor alpha localized in caveolae. *Biochem. Biophys. Res. Commun.* 263:257–62
286. McDonald KK, Zharikov S, Block ER, Kilberg MS. 1997. A caveolar complex between the cationic amino acid transporter 1 and endothelial nitric-oxide synthase may explain the "arginine paradox." *J. Biol. Chem.* 272:31213–16
287. Shaul PW, Smart EJ, Robinson LJ, German Z, Yuhanna IS, et al. 1996. Acylation targets endothelial nitric-oxide synthase to plasmalemmal caveolae. *J. Biol. Chem.* 271:6518–22
288. Garcia-Cardena G, Oh P, Liu J, Schnitzer JE, Sessa WC. 1996. Targeting of nitric oxide synthase to endothelial cell caveolae via palmitoylation: implications for nitric oxide signaling. *Proc. Natl. Acad. Sci. USA* 93:6448–53
289. Teubl M, Groschner K, Kohlwein SD, Mayer B, Schmidt K. 1999. Na(+)/Ca(2+) exchange facilitates Ca(2+)-dependent activation of endothelial nitric-oxide synthase. *J. Biol. Chem.* 274: 29529–35
290. de Weerd WF, Leeb-Lundberg LM. 1997. Bradykinin sequesters B2 bradykinin receptors and the receptor-coupled Galpha subunits Galphaq and Galphai in caveolae in DDT1 MF-2 smooth muscle cells. *J. Biol. Chem.* 272:17858–66
291. Jung NH, Kim HP, Kim BR, Cha SH, Kim GA, et al. 2003. Evidence for heme oxygenase-1 association with caveolin-1 and -2 in mouse mesangial cells. *IUBMB Life* 55:525–32
292. Kim HP, Wang X, Galbiati F, Ryter SW, Choi AM. 2004. Caveolae compartmentalization of heme oxygenase-1 in endothelial cells. *FASEB J.* 18:1080–89
293. Mueller A, Kelly E, Strange PG. 2002. Pathways for internalization and recycling of the chemokine receptor CCR5. *Blood* 99:785–91
294. Soong G, Reddy B, Sokol S, Adamo R, Prince A. 2004. TLR2 is mobilized into an apical lipid raft receptor complex to

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signal infection in airway epithelial cells. *J. Clin. Invest.* 113:1482–89

295. Flemming JA, Perkins KH, Luus L, Ferguson AR, Corley RB. 2004. Disruption of membrane cholesterol stimulates MyD88-dependent NF-kappaB activation in immature B cells. *Cell Immunol.* 229:68–77
296. Dai Q, Zhang J, Pruett SB. 2005. Ethanol alters cellular activation and CD14 partitioning in lipid rafts. *Biochem. Biophys. Res. Commun.* 332:37–42
297. Brainard AM, Miller AJ, Martens JR, England SK. 2005. Maxi-K channels localize to caveolae in human myometrium: a role for an actin-channel-caveolin complex in the regulation of myometrial smooth muscle K+ current. *Am. J. Physiol. Cell Physiol.* 289:C49–57
298. Wang XL, Ye D, Peterson TE, Cao S, Shah VH, et al. 2005. Caveolae targeting and regulation of large conductance Ca(2+)-activated K+ channels in vascular endothelial cells. *J. Biol. Chem.* 280: 11656–64
299. Bergdahl A, Gomez MF, Dreja K, Xu SZ, Adner M, et al. 2003. Cholesterol depletion impairs vascular reactivity to endothelin-1 by reducing store-operated Ca2+ entry dependent on TRPC1. *Circ. Res.* 93:839–47
300. Schnitzer JE, Oh P, Jacobson BS, Dvorak AM. 1995. Caveolae from luminal plasmalemma of rat lung endothelium: microdomains enriched in caveolin, Ca(2+)-ATPase, and inositol trisphosphate receptor. *Proc. Natl. Acad. Sci. USA* 92:1759–63
301. Huang C, Hepler JR, Chen LT, Gilman AG, Anderson RG, Mumby SM. 1997. Organization of G proteins and adenylyl cyclase at the plasma membrane. *Mol. Biol. Cell* 8:2365–78
302. Kang YH, West WL, George M. 1983. Ultracytochemical localization of guanylate cyclase in the oviduct of estrogen-stimulated rat. *Anat. Rec.* 205:251–62
303. Liu L, Mohammadi K, Aynafshar B, Wang H, Li D, et al. 2003. Role of caveolae in signal-transducing function of cardiac Na+/K+-ATPase. *Am. J. Physiol. Cell Physiol.* 284:C1550–60
304. Scherer PE, Lisanti MP, Baldini G, Sargiacomo M, Mastick CC, Lodish HF. 1994. Induction of caveolin during adipogenesis and association of GLUT4 with caveolin-rich vesicles. *J. Cell Biol.* 127:1233–43
305. Acevedo L, Yu J, Erdjument-Bromage H, Miao RQ, Kim JE, et al. 2004. A new role for Nogo as a regulator of vascular remodeling. *Nat. Med.* 10:382–88
306. Spisni E, Griffoni C, Santi S, Riccio M, Marulli R, et al. 2001. Colocalization prostacyclin (PGI2) synthase–caveolin-1 in endothelial cells and new roles for PGI2 in angiogenesis. *Exp. Cell Res.* 266:31–43
307. Sargiacomo M, Sudol M, Tang Z, Lisanti MP. 1993. Signal transducing molecules and glycosyl-phosphatidylinositol-linked proteins form a caveolin-rich insoluble complex in MDCK cells. *J. Cell Biol.* 122:789–807
308. Song KS, Li S, Okamoto T, Quilliam LA, Sargiacomo M, Lisanti MP. 1996. Co-purification and direct interaction of Ras with caveolin, an integral membrane protein of caveolae microdomains. Detergent-free purification of caveolae microdomains. *J. Biol. Chem.* 271:9690–97
309. Dorahy DJ, Lincz LF, Meldrum CJ, Burns GF. 1996. Biochemical isolation of a membrane microdomain from resting platelets highly enriched in the plasma membrane glycoprotein CD36. *Biochem. J.* 319:67–72

Annual Review of Pharmacology and Toxicology
Volume 46, 2006

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