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Cell Cycle and Apoptosis: Common Pathways to Life and Death

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Abstract Programmed cell death, or apoptosis, is a highly regulated process used to eliminate unwanted or damaged cells from multicellular organisms. The morphology of cells undergoing apoptosis is similar to cells undergoing both normal mitosis and an aberrant form of mitosis called mitotic catastrophe. During each of these processes, cells release substrate attachments, lose cell volume, condense their chromatin, and disassemble the nuclear lamina. The morphological similarities among cells undergoing these processes suggest that the underlying biochemical changes also may be related. The susceptibility of cells to apoptosis frequently depends on the differentiation state of the cell. Additionally, cell cycle checkpoints appear to link the cell cycle to apoptosis. Deregulation of the cell cycle components has been shown to induce mitotic catastrophe and also may be involved in triggering apoptosis. Some apoptotic cells express abnormal levels of cell cycle proteins and often contain active Cdc2, the primary kinase active during mitosis. Although cell cycle components may not be involved in all forms of apoptosis, in many instances cell proliferation and cell death may share common pathways.

Key words: mitosis, mitotic catastrophe, apoptosis, cell cycle components, Cdc2

The ability of an organism to maintain cellular homeostasis is critically dependent upon a balance of cell proliferation, differentiation, and death. All somatic cells proliferate using the common process of mitosis. Control of cell division has been extensively studied, and much is known about the biochemical signals associated with cell cycle progression and mitosis. Programmed cell death, or apoptosis, also appears to be a ubiquitous process in multicellular organisms. This mechanism allows an organism to eliminate unwanted or defective cells by an orderly process of cellular disintegration without inducing an inflammatory response [reviewed in Schwartzman and Cidlowski, 1993]. Apoptosis plays a role in a variety of physiological processes such as differentiation during embryogenesis, establishment of immune self-tolerance, and killing of cells by cytotoxic immune cells. This process of cell suicide can be induced in many different cell types in response to a variety of stimuli including DNA damage, growth factor withdrawal, Ca^{+2} influx, and viral infection. Different cell types display similar morphologies upon induction of apoptosis [Wyllie et al., 1980]. These similarities suggest that, although many signals appear cell-type specific, it is likely that all signals converge to a final common pathway. Our understanding of the biochemical pathways associated with these morphological changes, however, is rudimentary. Ucker [1991] has proposed that apoptosis is a type of abortive mitosis. Others have suggested that apoptosis results from incompatible signals for proliferation and cell cycle arrest [Yonish-Rouach et al., 1993]. In this article, we examine the relationship between the cell cycle and cell death and speculate about critical steps that may be common to the apoptotic, mitotic, and mitotic catastrophe pathways.

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MORPHOLOGICAL CHANGES DURING MITOSIS, MITOTIC CATASTROPHE, AND APOPTOSIS

Cells undergoing mitosis, mitotic catastrophe, and apoptosis share a number of morphological and biochemical features (Table I). Mitosis is

characterized by chromatin condensation, spindle formation, and rearrangement of the actin cytoskeleton [Murray and Hunt, 1993]. Cells undergoing mitosis release substrate attachments, become more rounded, and shrink. In most multicellular organisms mitosis is characterized by the breakdown of the nuclear envelope. During nuclear envelope dissolution, the intermediate filament cytoskeleton underlying the nuclear membrane disassembles and the nuclear envelope breaks into small vesicles. After the mitotic spindle forms, the chromosomes condense, align themselves on the spindle, and are transported to opposite poles of the dividing cell [Murray and Hunt, 1993]. Upon successful completion of mitosis, the nucleus reassembles and the actin cytoskeleton becomes reorganized.

When the orderly progression of the cell cycle is disrupted, an abnormal mitosis, called mitotic catastrophe, occurs. This aberrant process takes place when cell cycle components are overexpressed or sustain mutations [Russel and Nurse, 1987; Heald et al., 1993]. Cells undergoing mitotic catastrophe will bypass normal mitotic checkpoints that ensure one part of the cycle is complete before the next phase can occur and enter mitosis before DNA replication is complete [Russel and Nurse, 1987]. These cells display many of the morphological changes seen in cells undergoing normal mitosis. Baby hamster kidney (BHK) cells undergoing mitotic catastrophe detach from the substrate and round up in a manner similar to mitotic cells [Heald et al., 1993]. Additionally, cell volume is reduced, the cell condenses and aggregates its chromatin, the nuclear lamins disassemble, and the nuclear envelope breaks down. Although the mitotic spindle forms, chromosomes fail to orient properly. By contrast to mitotic cells, these cells contain fragmented and "pulverized" DNA due to incomplete chromosome replication [Heald et al., 1993].

TABLE I. Morphological and Biochemical Similarities Among Apoptosis, Mitosis, and Mitotic Catastrophe*

Morphological similarities	Biochemical similarities
Rounding of cell	Expression of cell cycle genes
Release of substrate attachments	Activation of Cdc2
Reduction in cell volume	Phosphorylation of lamins
Chromatin condensation	
Lamin disassembly	

*See text for references.

Surprisingly, cells undergoing apoptosis also share some of the morphological features typically associated with mitosis [Ucker, 1991] and mitotic catastrophe (Table I). Comparison of mitotic and apoptotic phenotypes, therefore, may provide useful insights into the biochemical mechanisms and regulation of both processes. Apoptotic cells, like mitotic cells, are characterized by their lack of adhesion, rounded morphology, and reduced cell volume [Wyllie et al., 1980]. Both mitotic and apoptotic cells also condense their chromatin and disassemble the nuclear lamina [Lazebnik et al., 1993]. Although apoptotic cells display many mitotic characteristics, there are also several distinct differences (Table II). Unlike mitotic cells, apoptotic cells do not assemble a mitotic spindle, they display rapid cytoplasmic blebbing, and in most cases they cleave their DNA into approximately 200 bp fragments [Wyllie et al., 1980]. In the final stages of apoptosis, cells are broken into multiple apoptotic bodies and are phagocytized by neighboring cells or nearby macrophages. Thus, although apoptosis and mitosis display similar morphologies, the end result of each process is strikingly different.

BIOCHEMICAL PATHWAYS OF MITOSIS, MITOTIC CATASTROPHE, AND APOPTOSIS

Because mitosis, mitotic catastrophe, and apoptosis share similar morphologies, it is likely that some of the biochemical changes that occur during each process may also be similar. Apoptosis and mitosis can be triggered by ligand binding to cell-specific receptors. The biochemical changes resulting from mitogen binding cause the dramatic restructuring of cellular architecture during mitosis. These morphological changes are induced by activation of cyclin-dependent kinases (Cdks) [Murray and Hunt, 1993]. The enzymatic activity of this family of serine/threonine-specific kinases is tightly controlled by both activating and inhibitory phosphorylation of the kinases and their association with a family of regulatory subunits called cyclins. When Cdks are associated with cyclin alone, the kinases are in an active form. Upon binding of these complexes to inhibitory proteins, such as p21, p16, and CAP20, the Cdk-cyclin complexes become inactive [Xiong et al., 1993; Ser-

TABLE II. Morphological and Biochemical Differences Among Apoptosis, Mitosis, and Mitotic Catastrophe*

Apoptosis	Mitosis	Mitotic catastrophe
Results in death	Results in cell division	Results in death
Activation of protease(s) and nuclease(s)	Formation of cleavage furrow	Chromosomes not oriented properly on spindle
Cytoplasmic blebbing	Reformation of nucleus	Incomplete DNA replication
Activation of transglutaminase	Separation of chromosomes into daughter cells	
Fragmentation of nucleus		
Fragmentation of cell		
Uptake of apoptotic cells by phagocytosis		

*See text for references.

rano et al., 1993; Gu et al., 1993]. Association with regulatory proteins as well as phosphorylation of these kinases appear to serve as cell cycle checkpoints to ensure that Cdks are active only at the appropriate time in the cell cycle. During mitosis, cyclins bind to Cdc2 (a Cdk) and are transported into the nucleus. Cdc2-dependent phosphorylation of both nuclear and cytoplasmic proteins, such as histones, lamins, and microtubule-binding proteins, appears to modulate reorganization of cellular machinery during mitosis.

Mitotic catastrophe occurs when cell cycle components are mutated or overexpressed. In yeast, for example, the kinase, Wee1, has been shown to inhibit mitosis by suppressing the activity of Cdc2 [Russel and Nurse, 1987; Lundgren et al., 1991], and when the gene encoding Wee1 sustains mutations cells undergo mitotic catastrophe. BHK cells can be induced to undergo mitotic catastrophe when cotransfected with the cell cycle gene, cdc2 in association with either cyclin A or cyclin B1 [Heald et al., 1993]. Deregulation of these cell cycle components leads to hyperactivation of Cdc2 at an inappropriate time during the cell cycle, and this kinase activity probably results in morphological changes associated with mitotic catastrophe. Furthermore, Wee1 blocks mitotic catastrophe induced by deregulated expression of Cdc2 and cyclins in BHK cells [Heald et al., 1993]. Thus, deregulation of Cdk activity can have lethal consequences.

In addition to regulating cell proliferation, the highly conserved and ubiquitously expressed cell cycle proteins may also play a pivotal role in apoptosis. Although progression through the cell cycle is not required for apoptosis, the propensity of cells to undergo programmed cell death is frequently dependent on their state of differentiation. For example, quiescent NIH BALB/c 3T3 cells are more resistant to cytotoxic T lymphocyte–induced apoptosis than are proliferating cells [Nishioka and Welsh, 1994]. Some cells undergo apoptosis upon receiving conflicting signals for cell cycle progression and arrest. Cells proliferating due to constitutive expression of the protooncogene, c-*myc*, undergo apoptosis upon withdrawal of growth factors (Evans et al., 1992; Shi et al., 1992). Apoptosis often is accompanied by growth arrest and, unlike mitotic catastrophe, can occur during any phase of the cell cycle (Fig. 1). Furthermore, sensitivity of proliferating cells to some death stimuli is frequently dependent on the phase of the cell cycle. For example, HL 60 cells in S phase will undergo apoptosis when treated with topoisomerase inhibitors, whereas hypothermia induces programmed cell death in these cells when in G1, and gamma radiation initiates apoptosis in cells at the G2/M phase interface [Solary et al., 1994]. Interestingly, other death stimuli, such as cycloheximide, induce death equally in cells in all phases of the cell cycle. Blocking cell cycle progression also can induce apoptosis. Inhibition of the immature B-cell lymphoma cell line, WEHI-231, in each phase of the cell cycle results in induction of apoptosis [Jones and LaFrenz, 1992]. Thus, cell cycle checkpoints appear to link the cell cycle to cell death.

Checkpoint proteins have been shown to be involved in the apoptotic response. p53, proposed to act at the G1 checkpoint, can inhibit cell cycle progression in response to DNA damage [Kastan et al., 1992; Kuerbitz et al., 1992]. Loss of p53 results in resistance to some, but not all, apoptotic triggers in certain cell types [Lowe et al., 1993; Clarke et al., 1993], and transfection of p53 into cell lines lacking this protein can induce cell death [Yonish-Rouach et al., 1991]. Thus, cell cycle checkpoints may act as a toggle switch between proliferation and death by sensing deregulation of the cell cycle. Alternatively,

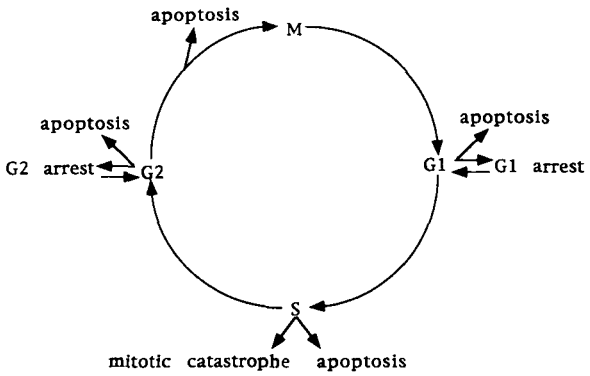

Fig. 1. Options in the cell cycle.

cell cycle deregulation may be part of the common pathway of apoptosis, and checkpoints may be actively bypassed after the cell is committed to die.

Evidence supporting involvement of deregulation of the cell cycle with induction of apoptosis comes from analysis of cell cycle proteins in apoptotic cells. A variety of cell types triggered by different death signals to undergo apoptosis have been shown to express cell cycle genes. For example, expression of cyclin D1, a regulator of the G1 phase of the cell cycle, increases tenfold in noncycling neurons undergoing apoptosis [Freeman et al., 1994]. When the early T-cell line, AGF, is triggered to undergo programmed cell death by incubation with thymidine, the expression of c-*myc*, cdc2, PCNA, and cyclin A increases [Gazitt and Erdos, 1994]. Expression and activation of cell cycle components in apoptotic cells is conceptually pleasing because of the similar phenotypes between mitotic and apoptotic cells. Although no uniform group of cell cycle genes is induced in all apoptotic cells, it is possible that different apoptosis-inducing agents can aberrantly activate different portions of the cell cycle pathway.

Cdk activation is a likely pathway to be induced in apoptosis because these kinases are thought to generate the morphological changes associated with mitosis and therefore may also be required to produce apoptosis-associated morphology. Some circumstances may exist in which Cdks do not play a role in apoptosis. For example, Cdc2 is not active in quiescient thymocytes induced to undergo apoptosis. However, other Cdks were not examined in this model system [Norbury et al., 1994]. In other systems, however, Cdc2 activity has been demonstrated. YAC1 lymphoma cells undergoing NK-induced apoptosis display Cdc2 kinase activity upon induction of apoptosis [Shi et al., 1994]. Additionally, Shi et al. [1994] have identified a murine mammary carcinoma cell line that is resistant to NK-induced apoptosis and contains dysfunctional Cdc2. HeLa cells show activation of cyclin A–dependent kinases during apoptosis [Meikrantz et al., 1994]. Thus, both apoptosis and mitotic catastrophe may be induced by deregulation of cell cycle components. Premature entry into mitosis results in mitotic catastrophe and death in yeast and BHK cells [Russel and Nurse, 1987; Heald et al., 1993]. Cells may have adapted this response to inappropriate mitosis to actively induce an apoptotic form of cell death. For example, Cdk activation induced by inappropriately bypassing mitotic checkpoints may result in death to the cell in a manner similar to that seen in mitotic catastrophe. Alternatively, Cdk-dependent phosphorylation may result in cell death by activating other apoptotic proteins such as nucleases or may alter nuclear envelope structure to allow damaging agents into the nucleus.

APOPTOTIC INHIBITION AND THE CELL CYCLE

If cell cycle components play an essential role in apoptosis, inhibitors of this process may protect cells from death by acting upon cell cycle proteins. Apoptosis is inhibited by overexpression of the B-cell lymphoma/leukemia 2 (*bcl*-2) gene in a number of different cell types [reviewed in Reed, 1992]. First identified as a cellular protooncogene involved in the formation of B-cell lymphomas, *bcl*-2 encodes a 25–26 kD protein that contains a membrane anchoring sequence at the C-terminus. This membrane protein appears to reside in the nuclear envelope, endoplasmic reticulum, and mitochondrial membrane. Although the manner by which Bcl-2 inhibits apoptosis has not been determined, several mechanisms of action have been proposed [Reed, 1992]. Bcl-2 could inhibit death by controlling Ca^{+2} release from stores in the mitochondria and endoplasmic reticulum. Ca^{+2} has been shown to be required by nucleases and proteases that are thought to play a role in cellular destruction during apoptosis [Hughes and Cidlowski, 1994; Squier et al., 1994]. Bcl-2 could also block accumulation of lipid peroxides and control cellular redox reactions which may activate apoptosis. Bcl-2 may regulate nuclear transport [Reed, 1992; Meikrantz et al., 1994].

Cells overexpressing Bcl-2 contain reduced amount of Cdc2 in the nucleus [Meikrantz et al., 1994]. HeLa cells triggered to undergo apoptosis by the kinase inhibitor staurosporine show increased cyclin A–dependent kinase activity, and, although Bcl-2 does not suppress the activity of this kinase, it restricts access of Cdc2 to the nucleus [Meikrantz et al., 1994]. Thus, Bcl-2 may block apoptosis by preventing transport of this kinase into the nucleus. This proposed mechanism is very similar to that proposed for inhibition of mitotic catastrophe by the mitotic inhibitor, Wee1. Deregulation of the cell cycle by transfection of cyclin and cdc2 induces mitotic catastrophe in BHK cells. If these cells are also transfected with wee1, however, they do not undergo mitotic catastrophe [Heald et al., 1993]. Nuclear Cdc2 activity in these cells is low even though kinase activity is elevated in the cytoplasm. Wee1 is localized to the nucleus in these cells and is thought to block mitotic catastrophe by inhibiting Cdc2 activity in the nucleus, thereby preventing early entry into mitosis.

The adenovirus E1B 19 K protein inhibits apoptosis induced by E1A expression [White et al., 1992]. Both adenovirus E1A and E1B 19 K proteins are required for transformation of rodent cells. E1A alone induces apoptosis of the host cell in a p53-dependent manner. Thus, E1B suppresses the cell death pathway that is activated by E1A, thereby enhancing the transforming activity of E1A. When E1B is replaced with Bcl-2, E1A-induced apoptosis is also inhibited, indicating that Bcl-2 and E1B 19K protein are functionally interchangeable at least in these transformation assays. Furthermore, E1B 19 K protein shares limited amino acid homology with Bcl-2 [White, 1993] and is localized to the nuclear envelope [White et al., 1984], suggesting that these inhibitors of apoptosis may have a similar biochemical function.

CONCLUSIONS AND PERSPECTIVES

Cells undergoing mitosis, mitotic catastrophe, and apoptosis have strikingly similar morphologies, suggesting that these processes share overlapping biochemical pathways (Fig. 2). Although circumstances may exist in which cell cycle components do not participate in programmed cell death [Norbury et al., 1994], apoptosis and cell cycle progression appear intrinsically linked in many cases. For example, cells progressing through the cell cycle appear more susceptible to apoptosis than quiescent cells. Cell cycle checkpoints appear to play a role in some apoptotic pathways. Additionally apoptotic cells often contain abnormal levels of cell cycle components, and both apoptosis and mitotic catastrophe may be induced by deregulation of cell cycle genes. Thus, the same cell cycle components could be used to regulate both proliferation and death. Although mitotic catastrophe and apoptosis share numerous characteristics, these processes differ in that apoptosis is a highly regulated process and mitotic catastrophe appears more of an accidental death. Thus, viewing apoptosis as simply an aberration of the cell cycle is probably too simplistic. Apoptotic cells may utilize the same cell cycle components in a unique manner to induce a tightly controlled cell death. It is unclear whether apoptosis is a direct consequence of alterations in the roles of cell cycle components, as appears to be the case in mitotic catastrophe, or if cell cycle checkpoints are used as sensory devices to induce a lethal pathway. In either case, linking the cell cycle to death should facilitate removal of cells defective for cell cycle regulation. Thus, investigators need to use caution when studying apoptosis in transformed cell lines that, by their nature, are defective in cell cycle regulation because apoptotic pathways may also be altered.

Because of the importance of apoptosis in cancer, AIDS, and other diseases, the relationship between the cell cycle and cell death needs to be investigated further. To test the hypothesis that Cdks may be part of the apoptotic pathway, these enzymes need to be assayed in

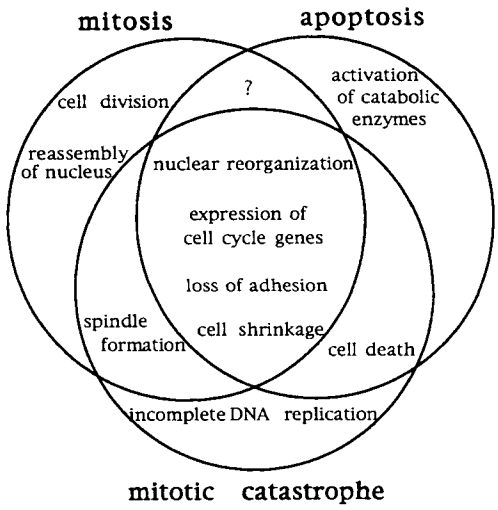

Fig. 2. Common pathways among mitosis, mitotic catastrophe, and apoptosis (see text for references).

apoptotic cells treated with different death stimuli. If Cdk activity is detected in all cells undergoing apoptosis, these kinases may be part of the common pathway of apoptosis as well as mitosis. Studies using cell lines that contain mutant Cdks may shed light on the role of these enzymes in apoptosis. Furthermore, cells that lack cell cycle checkpoints should be tested for their sensitivity to death triggers that affect cells at specific phases of the cell cycle. Analyses of the relationship between the cell cycle and apoptosis should provide powerful insights into the highly conserved mechanisms of cellular homeostasis.

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