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Review

Programs for Cell Death

Apoptosis is Only One Way to Go

Michael Blank

Yosef Shiloh*

The David and Inez Myers Laboratory for Genetic Research; Department of Human Molecular Genetics and Biochemistry; Sackler School of Medicine; Tel Aviv University; Tel Aviv, Israel

*Correspondence to: Yosef Shiloh; The David and Inez Myers Laboratory for Genetic Research; Department of Human Molecular Genetics and Biochemistry; Sackler School of Medicine; Tel Aviv University; Tel Aviv 69978, Israel; Tel.: 972.3.6409760; Fax: 972.3.6407471; Email: yossih@post.tau.ac.il

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ABSTRACT

Cell death programs are major players in tissue homeostasis, development and cellular stress responses. A prominent cause of malignant transformation is the cumulative genetic alterations in pathways that regulate cellular growth and death. The processes that govern cell death following genotoxic stress are a major focus of basic research and are also very relevant to translational research in clinical oncology: understanding cell death following cancer therapy is essential for designing new treatment modalities. Cell death is usually, and sometimes automatically, linked with one of its major programs, apoptosis. Recent advances have led, however, to the emergence of additional, non-apoptotic cell death pathways, each with its triggers and readouts. Genotoxic stress appears to induce several cell death pathways, only part of which fall within the classical definition of apoptosis. Accordingly, solid tumor cells that are refractive to apoptosis were shown to die via non-apoptotic mechanisms. Recently we demonstrated that mitotic cell death induced by DNA damage in cells with defective G_2/M checkpoint is mechanistically distinct from apoptosis. This review outlines recent advances in the understanding of molecular networks operative in apoptotic and non-apoptotic cell death mechanisms and their cross-talks.

INTRODUCTION

Cell death is essential for embryonic development and maintenance of tissue homeostasis in multicellular organisms. Defects in cell death pathways lead to different pathological states as well as to cell immortalization and tumorigenesis.

It has long been evident that cell death is a carefully programmed process. Much of the attention in the cell death field has been drawn in recent years to a major cell death pathway - apoptosis, which is often synonymous with cell death. The elucidation of additional programmed cell death pathways is gradually changing this notion. According to a recent classification, eight different types of cell death were delineated,[1] and some researchers describe as many as 11 pathways of cell death in mammals, 10 of which appear to be programmed.[2] These pathways can be broadly divided into two main groups: apoptotic and non-apoptotic.

Apoptotic cell death includes, in addition to classic apoptosis, apoptosis induced by loss of attachment to the substrate or to other cells (anoikis).[3] Anoikis overlaps with apoptotis in molecular terms, but is classified as a separate entity because of its specific form of induction.[1] Non-apoptotic death includes autophagic cell death, necrosis (oncosis), mitotic cell death (MCD, often referred to as mitotic catastrophe), and caspases-independent cell death (CICD) preceded/triggered by mitochondrial outer membrane permeabilization (MOMP) (referred to hereafter as CICD). Although CICD shares features with classical apoptosis (e.g., MOMP induction, diffusion of some proteins from the intermembrane space of the mitochondria and the ensuing DNA fragmentation), it does not involve activation of the caspase cascade with subsequent cleavage of the plethora of defined intracellular caspase substrates, and is therefore classified as a non-apoptotic form of death.[4]

APOPTOSIS VERSUS CICD

We discuss these two types of cell death together because both apoptosis and CICD share a prominent feature - permeabilization of the outer mitochondrial membrane and the release into the cytosol of numerous proteins that trigger implementation of death programs.

Apoptosis, also referred to as type I programmed cell death, is the most well-defined type of cell death pathway, both morphologically and biochemically. It is characterized by membrane blebbing, cytoplasmic shrinkage and reduction of cellular volume (pyknosis), condensation of the chromatin, and fragmentation of the nucleus (karyorrhexis), all of which ultimately lead to formation of apoptotic bodies, a prominent morphological feature of apoptotic cell death.[1,5,6] The morphological appearance of apoptosis depends on the type of cell, the type and strength of the trigger that induced it, and whether it is in the early or late stage.

Apoptosis is governed by several genes, some of which are mutated or dysfunctionally regulated in various of human tumors.[7-9] Biochemically, apoptosis is defined as a form of programmed cell death executed by a family of zymogenic proteases known as caspases that dismantle the cell in an orderly fashion by cleaving an array of intracellular substrates. Activation of the caspases cascade in a chain reaction-like fashion and subsequent cleavage of its downstream targets are therefore considered the biochemical hallmark of apoptotic cell death.

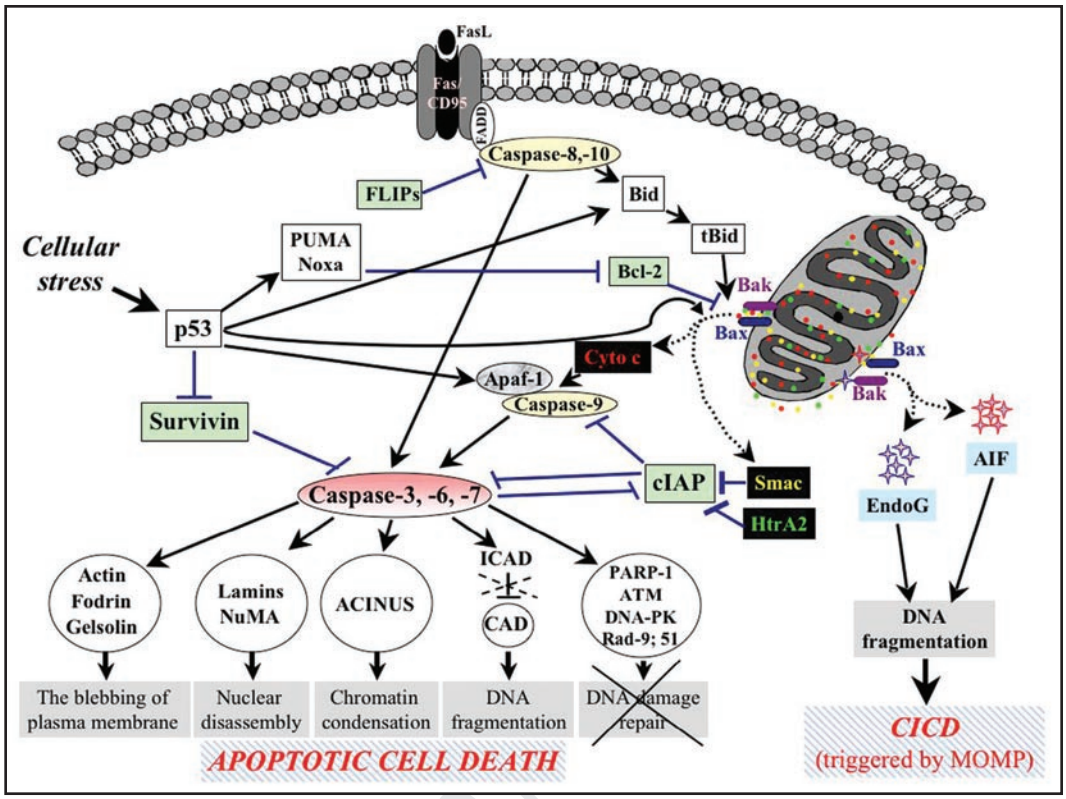

Figure 1. Schematic representation of mechanisms that govern extrinsic and intrinsic apoptotic pathways and CICD. The common denominator in both cell death processes is permeabilization of the outer mitochondrial membrane and the release into the cytosol of proteins that trigger death programs. Initiator and effector caspases appear in yellow and red circles, respectively. Inhibitors of apoptosis are in green boxes.

Two major apoptotic pathways have been described in eukaryotic cells: extrinsic and intrinsic (Fig. 1). The extrinsic signaling pathway involves the binding of extracellular ligands (e.g., FasL) to cell surface receptors (e.g., Fas/CD95), resulting in the recruitment of cytosolic adaptor proteins [e.g., FADD (Fas-associated death domain)], activation of initiator caspases (e.g., caspase-8), and subsequent activation of the downstream effector caspases (caspases-3, -6 and -7).[10] The latter may also be achieved in the extrinsic pathway through induction of MOMP (e.g., via the truncated form of the BH3-only Bid protein Ref. 11,12), with subsequent formation of the apoptosome (a complex between cytochrome c/Apaf-1/procaspase-9 complex).[13,14] It is noteworthy that although MOMP is not required for the development the extrinsic apoptosis pathway, it significantly amplifies the signal received by the cell from its death receptor on the cytosolic membrane.

In certain types of cells, particularly neurons, apoptosis can also be induced by ligand withdrawal and inhibited upon binding of receptor-specific ligands. These receptors have been referred to as dependence receptors because of their ability to promote programmed cell death without ligands.[15,16] Among them are: deleted in colorectal cancer (DCC) receptor, uncoordinated gene 5H1-3 (UNC5H1-3) receptor, rearranged during transfection (RET) receptor, the Patched receptor, p75 neutrophin receptor, $\alpha_v\beta_3$ integrin receptor, and the androgen receptor.[17] In the absence of ligand, most dependence receptors undergo proteolytic processing that generates pro-apoptotic peptides, which directly or indirectly lead to caspase activation and apoptosis.[17] Interestingly, UNC-5H and p75 receptors contain a death domain, similar to Fas and TNF receptors, although the mechanism of p75 cytotoxicity appears to differ from that of Fas-mediated cell killing.[18]

The intrinsic (or mitochondrial) pathway integrates signals generated by a variety of stressors that converge on the mitochondria, including DNA damage, cytoskeletal damage, endoplasmic reticulum stress, loss of adhesion, growth factor withdrawal, macromolecular synthesis inhibition, and others. These apoptotic stimuli evoke MOMP, possibly by the formation of membrane-spanning pores through which the intermembrane space proteins are released into the cytosol. Cytochrome c, a component of the electron transport chain, is the most famous among them. It serves as a cofactor for Apaf-1 to trigger the formation of the apoptosome and subsequent activation of the initiator and executioner caspases, usually caspase-9 and -3, respectively.[19-21]

The p53 tumor suppressor serves as a positive regulator of both extrinsic and intrinsic pathways.[22] It can transactivate genes encoding pro-apoptotic Bcl-2 family members such as Bax[23] and several BH3-only members (e.g., Puma, Noxa, Bid),[24-26] the disruptor of mitochondrial function p53AIP,[27] the apoptosome component Apaf-1,[28] effector caspases (e.g., caspase-6),[29] PIDD (p53-induced protein with death domain),[30] Fas/CD95 receptor,[31] the death receptor DR5,[32] and the gene encoding the FAS ligand TNFSF6.[33] On the other hand, p53 acts as a transrepressor of genes encoding anti-apoptotic proteins (e.g., survivin).[34] It also exhibits its pro-apoptotic functions through transcription-independent mechanisms:

upon apoptotic stimuli p53 was reported to rapidly translocate to the mitochondria where it can initiates MOMP by a dual action: via neutralizing anti-apoptotic proteins (e.g., Bcl-xL) and activating of the pro-apoptotic Bcl-2 protein MOMP regulators Bax or Bak.[35,36]

The induction of MOMP leads to the cytosolic release not only of cytochrome c, but of other essential pro-apoptotic molecules as well, such as Smac (second mitochondrial activator of caspases)/Diablo (direct IAP binding protein with low pH) and Omi/HtrA2 (high temperature requirement factor), which can significantly enhance apoptotic execution through inactivation of a variety of cellular inhibitors of apoptosis (IAPs).[37,38] XIAP (X chromosome-linked inhibitor of apoptosis) protein is thought to be the most efficient of the currently known IAPs. It binds to active forms of caspase-3, -7 and -9 and directly inhibits their enzymatic activities.[7,39,40] The binding of Smac/Diablo and/or Omi/HtrA2 to the XIAP protein countermands its caspase-inhibitory activities, thereby promoting the activation of caspases and the progression of apoptosis (Fig. 1). Overexpression of Smac/Diablo or Omi/HtrA2 in cells has been shown to markedly increase their sensitivity to apoptosis induction by DNA damage and other signals.[37,41] It is noteworthy that pro-apoptotic Omi/HtrA2 has been implicated also in CICD, apparently due to its serine-protease activity, but the mechanisms underlying this phenomenon are poorly understood.[7,42]

MOMP has been referred to as "the point of no return" because it is responsible for engaging the apoptotic cascade in numerous cell death pathways,[19,43] but recent studies have questioned this view (see below). Once MOMP has occurred, the cytosolic machinery responds by activating caspases, or, if this pathway is inhibited, by CICD. The latter may involve loss of mitochondrial function, and release of mitochondrial intermembrane space proteins such as apoptosis-inducing factor (AIF) and endonuclease G.[42,44] Although CICD, like apoptosis, involves MOMP, this process cannot be referred to as apoptotic cell death since it lacks caspases activation and cleavage of their intracellular substrates - one of the major hallmarks of apoptotic machinery (Fig. 1).

Caspase substrates point to major processes and downstream players are involved in the apoptotic process. Notable caspase substrates are:

(A) Actin and actin-binding proteins gelsolin and fodrin—cytoskeleton proteins, whose caspase-mediated degradation contributes to the blebbing of the plasma membrane.[45,46]

(B) Lamins (Lamin A/C and Lamin B—peripheral nuclear lamina) and nuclear mitotic apparatus protein NuMA (nuclear matrix protein), which are responsible for maintenance of nuclear integrity and whose cleavage by caspases underlies nuclear fragmentation in apoptotic cells.[47-49]

(C) ACINUS (apoptotic chromatin condensation inducer in the nucleus), which functions as a "pure" regulator of apoptosis-related chromatin condensation because it lacks the DNAse activities exhibited by other cellular factors that can induce chromatin condensation via DNA fragmentation.[50,51] ACINUS has been shown to be a direct substrate for cleavage of activated caspase-3.[50]

(D) ICAD (inhibitor of caspase-activated DNAse), also known as DFF45 (DNA fragmentation factor with molecular weight of 45 kDa), whose caspase-dependent cleavage releases active CAD (caspase-activated DNAse; DFF40). The cleaved CAD/DFF40 then translocates into the nucleus and induces DNA fragmentation, initially as ~50-kb fragments (a size consistent with chromatin loop domains), followed by oligonucleosomal DNA cleavage (also called DNA laddering).[52] The DNA fragmentation is readily detected as "ladder" in horizontal agarose gel electrophoresis[53] as well as sub-G_1 peaks in FACS analyses of cell stained with propidium-iodide.[4] Although DNA fragmentation and sub-G_1 FACS analysis are both widely used for apoptosis detection, the demonstration of DNA fragmentation alone without the additional biochemical apoptosis-associated events (e.g., activation of caspases and cleavage of caspases substrates) is not sufficient to define cell death as apoptotic. Evidence is mounting that DNA fragmentation may also occur in other forms of cell death, for example in CICD where the both AIF[54] and endonuclease G[55] cleave DNA in CAD-independent manner.[42,56]

Other important intracellular caspase substrates are central players in the cellular DNA damage response, whose cleavage disrupts the cell's ability to activate this response and contributes to an irreversibility of apoptosis. Among these substrates are the ataxia-telangiectasia mutated (ATM) protein kinase,[57] the chief transducer of the cellular response to DNA double strand breaks (DSBs);[58-60] the catalytic subunit of the DNA-dependent protein kinase (DNA-PK),[61] a major player in the nonhomologous end-joining pathway of DSB repair;[62] the recombinase Rad51 and the Rad9 protein,[63] which are involved in the homologous recombination pathway of DSB repair[64] and many aspects of maintaining genome integrity,[65] respectively; and poly(ADP-ribose)polymerase-1 (PARP-1),[66] which regulates many cellular functions by synthesizing and attaching poly(ADP-ribose) chains to key players in these processes.[67] Importantly, intact PARP-1 and its enzymatic activities are essential for the induction of CICD, which involves the release of AIF from the mitochondria.[68-70] It has been shown that PARP-1-mediated synthesis of poly(ADP-ribose) is absolutely required for AIF to translocate from the mitochondria to the nucleus, where it induces large-scale DNA fragmentation that leads to chromatin condensation at the nuclear periphery in a process called chromatinolysis.[69,71] Endonuclease G is proposed to be released simultaneously from mitochondria and to take part in this process with AIF. As caspases are not involved in this process, it leaves PARP-1 intact to be activated by the fragmented DNA, which causes massive poly(ADP-ribose) synthesis, NAD+ and ATP depletion, ultimately resulting in cell death.[67,68]

In addition to the proteins involved in the DNA damage response, caspases also cleave and inactivate other substrates crucial for cell division and survival including MEKK-1, PKC-σ, PAK2, Akt-1 and Raf-1.[7,72] The effector caspases also inactivate several suicide cell death antagonists - antiapoptotic molecules such as Bcl-2,[73] Bcl-xL[74] and XIAP,[75] whose cleavage provides significant support for apoptosis implementation in the cells. However, caspases can drive apoptosis not only by inactivation of antiapoptotic molecules but also via caspase-mediated activation of proapoptotic regulators such as Bid.[11,12]

Recent studies indicate that in the presence of certain cellular settings, MOMP does not necessarily result in cell death. Several proteins in addition to XIAP have been shown to bind to the various apoptosome components and inhibit its formation and activity. The list of currently known IAPs includes Aven,[76] Hsp70,[77] Hsp90,[78] APIP,[79] TUCAN,[80] HBXIP,[81] Hsp27.[82] TUCAN and HBXIP, bind to caspase-9 and inhibit its activation by preventing its interaction with Apaf-1.[80,81] Hsp27 appears to inhibit apoptosome formation through a unique mechanism involving binding to cytosolic cytochrome c, preventing its interaction with Apaf-1 and subsequently inhibiting the activation of caspase-9.[82]

Another prominent molecule that significantly affects the development of the apoptotic response in cells is survivin.[83] This protein together with aurora-B kinase, the inner centromere protein

(INCENP) and the telophase disk antigen TD-60, makes up the chromosomal passenger complex—a mitotic regulatory complex that orchestrates chromosome alignment, histone modification, and cytokinesis.[84] Survivin was assigned to the IAP protein family because it contains a BIR domain (baculoviral inhibitor of apoptosis protein repeats) and effectively inhibits apoptosis via binding and inactivation of caspase-3 and -7, similarly to other IAPs (Fig. 1). Survivin is selectively expressed in the most common human neoplasms and appears to be involved in resistance of tumor cells to some anticancer agents and ionizing radiation (IR). It therefore represents one of the most attractive targets for anticancer interventions.[85]

These data suggest that while MOMP is an essential step in triggering the apoptotic execution program, it does not represent a strict "point of no return". The events followed by induction of MOMP can be efficiently inhibited by a plethora of intracellular apoptosis inhibitory molecules. The stage at which the effector caspases execute the cleavage of their substrates, especially those essential for maintaining cellular homeostasis (e.g., PARP-1 and others), appears a more apt "point of no return" in apoptotic cell death.

In addition to the classical apoptotic inhibitors described above, most cells, predominantly those in the immune system, express caspase-8 decoys called FLIPs (FLICE inhibitory proteins).[86] c-FLIP via DED (death effector domain)-DED interactions binds with high affinity to DISC (death-inducing signaling complex formed by the binding to CD95 of adapter molecule FADD, and the death protease caspase-8 (FLICE)). Binding c-FLIP to DISC prevents both activation of caspase-8 (and possibly caspase-10) and transduction of the pro-apoptotic signal from death receptors.[87] c-FLIPs exist in two forms: short c-$FLIP_S$ and long c-$FLIP_L$. Both of these c-FLIP splice variants bind to FADD within the DISC and inhibit caspase 8 activation.[88] Interestingly, under certain experimental conditions c-$FLIP_L$ can facilitate rather than inhibits the activation of caspase-8, probably by assisting the dimerization of procaspase-8 in the DISC.[89] In addition, the DED-containing molecule BAR (bifunctional apoptosis regulator) competes with FADD for binding to procaspase-8 and -10, thereby preventing FAS-mediated apoptosis.[90] Importantly, the BAR protein can also inhibit the intrinsic mitochondrial pathway by interacting with and enhancing the anti-apoptotic activity of the Bcl-2 and Bcl-xL proteins, opposing Bax-mediated cell death.[90,91]

As in many other signaling networks, important relays in cell death pathways are protein kinases and their substrates. The death-associated protein kinases (DAP kinases) are emerging players in that regard.[92,93] The prototype member of this kinase family is DAP kinase 1 (DAPk); the five known members share a similar catalytic domain. These kinases are activated during apoptosis triggered by death receptors, cytokines, matrix detachment and oncogene-induced hyperproliferation, and also play a role in non-apoptotic, autophagic cell death (see below). Among the documented substrates of these kinases are the p53 ubiquitin ligase Mdm2, histones, α- and β-tubulin, and myosin II regulatory light chain, pointing to a role of these kinases in various components of the apoptotic process.[92]

Overall, the genetic and functional alterations that pro-and anti-apoptotic regulators undergo in cells during tumorigenesis significantly impede the effective execution of an apoptotic program even when these cells are exposed to appropriate stimuli. While IR and anti-tumoral drugs have been valued mainly for their capacity to induce apoptosis in tumor cells, it is now evident that apoptosis is not the primary mechanism of cell death in solid tumors[4,9,94] and other non-apoptotic pathways of tumor death may be effective in combating cancer. Indeed, the fraction of tumor cells that undergo non-apoptotic death are significantly increased if apoptosis-related mechanisms are inhibited.[94]

NON-APOPTOTIC CELL DEATH

In addition to CICD, several other apparently independent mechanisms of non-apoptotic cell death have been identified, including necrosis, autophagic cell death and MCD. Senescence will also be discussed here as it is considered a tumor-suppressor mechanism whose defects contribute to tumorigenesis.

Senescence. Originally defined as a series of cellular changes associated with aging, senescence now refers more commonly to a signal transduction program leading to irreversible arrest.[95] Senescent cells maintain the integrity of their plasma membranes but undergo permanent growth arrest and lose their clonogenicity, giving them the attribute "living cell death".

Two types of senescence—"replicative" and "accelerated"—have been described. Replicative senescence results from a gradual shortening of telomeres during cell division, which signals a cascade of events leading to permanent growth arrest. Telomere shortening can be reversed by the ribonucleoprotein telomerase, and telomerase activation has been shown to be one of the major mechanisms through which "immortal" tumor cells overcome the barrier of replicative senescence.[96,97]

Accelerated senescence was described in cells following DNA damage, in cells with oncogenic mutations in genes encoding the proteins Ras, Raf or MKK6, and in cells treated with agents that induce telomere shortening.[4] Senescent cells cannot divide even if stimulated by mitogens, but remain metabolically and synthetically active. The induction of senescence is usually accompanied by distinct changes in cellular morphology, notably the appearance of enlarged and flattened cells with increased granularity.[95,98]

Biochemically, senescence is accompanied by changes in metabolism and the induction of senescence-associated β-galactosidase (SA-β-gal) activity that appears to reflect increased lysosomal mass of senescent cells.[99] At the genetic level, alterations in chromatin structures and gene-expression patterns have been observed.

A senescence program is thought to be initiated by p53's downstream transcriptional target $p21^{waf\text{-}1}$, as well as by activation of another tumor suppressor gene, Rb (retinoblastoma protein).[95,100] One of the prominent proteins that stimulate p53 activities under the conditions of replicative and RAS-induced accelerated senescence is promyelocytic leukemia (PML) tumor suppressor, which regulates p53 acetylation, thereby promoting its activation.[101,102] After onset of senescence, the cellular levels of these senescence-initiator proteins decrease and another CDK (cyclin-dependent kinase) inhibitor, $p16^{INK4A}$, becomes constitutively up-regulated, suggesting the role of p16 in the maintenance of growth arrest in senescent cells.[103,104] Other CDK inhibitors such as $p27^{Kip1}$ and $p15^{INK4B}$ were also shown to play a role in senescence.[105,106] Interestingly, despite their senescent phenotype, some types of cells may probably recover from growth arrest, reenter the cell cycle, replicate their DNA, and die at the advanced stages of cell cycle.[107]

While evidence is mounting that senescence is up-regulated by tumor-suppressor genes like those encoding the p16 and p53 proteins as well as p53's transcriptional target *TP21* (encoding p21), there are other indications that treatment-induced senescence in tumor cells might occur in the absence of these proteins.[95] In particular, p16-deficient tumor cell lines such as HT1080 and HCT116 show a

strong senescence response both in vitro and in vivo.[107] Furthermore, the inhibition or knockout of p53 or p21 in these types of cells did not fully abolish drug- or radiation-induced senescence, as determined by positive cell staining for SA-β-gal,[108] and moderate doses of doxorubicin induced senescent phenotype in p53-null cells (e.g., Saos-2 cells), in cells bearing mutant p53 (e.g., SW480 and U251 cells), and in HeLa and Hep-2 cell lines, all of which have compromised p53 due to the presence of HPV-E6.[108] These data suggest that in addition to p53, p21 and p16, other proteins are apparently involved and mediate damage-induced senescence of tumor cells.

It is also noteworthy that while senescent cells do not divide but remain metabolically active, they can produce numerous secreted factors with diverse paracrine activities. In addition to those that inhibit tumor growth (e.g., BTG1 and BTG2, Maspin, MIC-1 and others), senescent tumor cells might also generate factors that stimulate tumor growth (e.g., extracellular matrix component Cyr61 and prosaposin, TGF-α, galectin) and potentially contribute to metastatic cell proliferation.[95]

Thus, successful tumor treatment based on senescence-induced strategy must take into account multiple tumor-suppressing and tumor-promoting activities in the cells. Comprehensive analysis of tumor cell senescence may offer a plausible approach to the development of novel cancer therapeutic strategies.

Autophagic cell death. Autophagy is based on evolutionary conserved, genetically controlled turnover of cellular constituents that occurs in all eukaryotic cells.[109] This process is activated in response to nutrient starvation, during differentiation, and following developmental triggers. It is an adaptive process responding to metabolic stress that results in degradation of intracellular proteins and organelles. In addition, autophagy can also be activated by hypoxic conditions and high temperatures.[110] Defective autophagy underlies number of pathological conditions including vacuolar myopathies, neurodegenerative diseases, liver diseases, and some forms of cancer.[109]

Autophagy is a major mechanism by which long-lived proteins and organelle components are directed to and degraded within lysosomes. It is defined morphologically by the appearance of numerous cytosolic vacuole-like structures (autophagic vesicles), or autophagosomes, which are formed by the assembly and expansion of double-layered, membrane-bound structures of unknown origin around whole organelles and isolated proteins. The origins of autophagosomes are difficult to determine because they contain a mixture of markers from the ER, endosomes and lysosomes. The autophagosome encapsulates cytosolic materials and subsequently docks and fuses with lysosomes or other vacuoles, resulting in the degradation of the autophagosomal contents.[111]

Under normal physiological conditions, autophagy occurs at basal levels in most tissues, contributing to the routine turnover of cytoplasmic components and promoting cell adaptation and survival during stress, such as starvation. Excess autophagy, on the other hand, leads to cell death—autophagic cell death—often referred to as "type II programmed cell death". Defects in the autophagic cell death program can lead to cancer, stimulate tumor growth and synergize with defective apoptosis to promote tumorigenesis.[112]

At the molecular level, autophagy is mediated by a set of evolutionary conserved, autophagy-related genes (referred to as *ATG*) originally discovered in budding yeast. The autophagy protein Beclin-1 is a mammalian ortholog of yeast Atg6. In a complex with class III phosphoinositide-3-kinase (PI3-K), Beclin-1 is responsible for autophagosome formation.[113] This autophagy-mediated complex was recently demonstrated to undergo activation by the protein product of UVRAG (UV irradiation resistance-associated gene).[114] Importantly, Beclin-1 has been suggested to be a haplosufficient tumor suppressor gene. Beclin-$1^{+/-}$ mice suffer from a high incidence of spontaneous tumors,[115,116] and Beclin-1 was found to be monoallelically deleted in a high percentage of sporadic human breast, ovarian and prostate carcinomas.[117]

Other positive (p53, phosphatase and tensin homolog [PTEN] and death-associated protein kinase DAPk) and negative (class I PI3-K, Akt and mammalian target of rapamycin [mTOR]) regulators of autophagy have been described.[111] The Ser/Thr kinase mTOR integrates signals from growth factors and nutrients to regulate cell size, division, and metabolism through control of protein synthesis.[118] It has also been shown to be essential for the expansion of the preautophagosomal compartment (execution step) as well as for autophagosome maturation after sequestration.[119] mTOR controls autophagy through the phosphorylations of mRNA translation regulators such as 4E-BP1 (4E-binding protein-1), S6K (p70 S6 kinase) and eEF-2K (eukaryotic translation elongation factor 2 kinase).[120]

The proposed mechanisms by which autophagy may suppress tumorigenesis include: (a) the degradation of specific organelles and long-lived proteins essential for cell growth regulation; (b) the removal of damaged organelles that generate reactive oxygen species and increase genotoxic stress; and (c) the induction of autophagic cell death.[121]

Autophagic cell death is thought to represent an alternative pathway to cell death when apoptosis is impeded, but there are indications that autophagic cell death and apoptosis are not mutually exclusive death pathways, and can cross-talk with each other. Subcellular organelles such as mitochondria, ER and lysosomes appear to play central roles in integration of apoptosis and autophagic cell death.[111] The following findings support the existence of communication between autophagic cell death and apoptosis: (a) apoptosis-regulating molecules such as Bcl-2, Bcl-xL, Bax and Bak were implicated in the regulation of autophagy, both independently and through interaction with Beclin-1;[121,122] (b) the lysosomal protease cathepsin B was shown to contribute to apoptosis in TNF-α treated hepatocytes by promoting mitochondrial release of cytochrome c and activation of the pro-apoptotic BH3-only family member Bid;[123,124] (c) phosphorylation of p70S6K and Akt by PDK-1 (class I PI3-K) inhibited both autophagy and apoptosis;[125] (d) mTOR is involved in many cellular processes besides autophagy, including apoptosis;[126] (e) some of the endonucleases that take a part in apoptosis-associated DNA fragmentation may originate in lysosomes;[127] (f) the apoptosis-inducing ligand TRAIL also mediates autophagy in mammary acini;[128] (g) the death-associated protein kinases DAPk and DPR-1 can induce as apoptotic blebbing as well as autophagic vacuole formation.[92,93,121,129]

The detection of autophagy relies mainly on morphological investigations aimed on the detection of autophagic vesicles. Those include transmission electron microscopy, immunoelectronmicroscopy, and fluorescent labeling of autophagosome marker proteins such as Atg5, microtubule-associated protein 1 light chain 3 (LC3; Atg8), Atg7, LAMP1 and LAMP2 (lysosome-associated membrane proteins) in combination with fluorescent and non-fluorescent dyes specific for acidic compartments and lysosomes such as acridine orange, monodansyl cadaverive and lysotrackers. Other approaches developed for the monitoring of autophagy include flow cytometric analysis of acridine orange uptake, measurement of cytosolic lactate

dehydrogenase activity in purified membrane fractions, determination of the degradation rate of radiolabeled long-lived proteins, and biochemical resolution of LC3 cleavage and lipidation to form LC3-II.[111]

Similar molecular mechanisms (involving the same set of the proteins, e.g., Atg5, Atg6, and Atg7) have been shown to underlie both autophagic cell death and autophagy associated with cell survival: how these two opposite outcomes are regulated remains unresolved. A clue came recently from the study of S. Shimizu et al,[122] who showed that in autophagic cell death the expression levels of Atg5 and Atg6 were significant elevated as compared to survival-associated autophagy. How these observations help distinguish between the two outcomes of autophagy requires further study. The death associated protein kinases (e.g., DAPk) have been suggested to be other "molecular switchers" in shifting from autophagy associated with cell survival to autophagic cell death.[92,93,130]

Whether autophagy serves as a dominant survival or death pathway for cancer cells remains controversial. Inhibitors of autophagy have been reported to both increase and decrease cell death following treatment with anticancer drugs.[131] It appears that the outcome of the cellular response varies with the type of insult or cellular stress as well as the particular cellular settings.

Necrosis. This form of cells death is usually a consequence of pathophysiological conditions such as infection, inflammation or ischemia. The prominent features are cellular energy depletion (ATP depletion therefore precludes ATP-dependent cell death such as apoptosis), damage to membrane lipids with cell membrane swelling and rupture, loss of function of homeostatic ion pumps/channels, and activation of non-apoptotic proteases. Although necrosis has been deemed to be a passive process, some recent findings suggest it could be a regulated process.[112,132,133]

One example of "programmed necrosis" is Ca^{2+}-mediated necrosis. The suggested mechanism is that the increase in the concentration of intracellular Ca^{2+}, due either to the excess entry of extracellular Ca^{2+} or its release from ER, can induce activation of Ca^{2+}-dependent proteases such as calpains. This subsequently lead to the cleavage of the plasma membrane Ca^{2+} exchanger (required for extrusion of Ca^{2}+ from the cells), and to sustained high levels of Ca^{2+} within the cell.[134] The prolonged retention of Ca^{2+} in cytosol triggers mitochondrial Ca^{2+} overload, leading to depolarization of the mitochondrial inner membrane. This leads to the loss of protein gradient and shutdown of ATP production, resulting in the depletion of intracellular ATP. Finally, depletion of ATP impedes the function of membrane transporters, destroying electrochemical gradient and culminating in necrotic cell death.[135,136]

Another proposed mechanism relates to hyperactivation of PARP-1 following DNA damage with alkylating agents. The hyperactivation of PARP has been shown to deplete cytosolic NAD, thereby inhibiting glycolysis and hence depleting the cellular ATP pool. As in Ca^{2+}-mediated necrosis, this culminates in loss of cellular function and necrotic cell death. This mechanism may lead to tumor-selective cell death because highly proliferating tumor cells are dependent on cellular NAD to generate energy through aerobic glycolysis.[137]

Still more evidence that necrosis may be genetically programmed and triggered by the inability to adapt to metabolic stress comes from the work of Degenhardt et al.[112] They showed that inactivation of apoptosis combined with activation of the PI3-kinase/AKT pathway results in inhibition of autophagy-mediated survival and induction of necrosis under conditions of starvation, demonstrating a level of genetic control governing the propensity for necrosis.

Overall, these findings suggest that necrosis may be genetically controlled and functionally interact with other types of programmed cell death.

Mitotic cell death (MCD). MCD, often referred to as mitotic catastrophe, is an outcome of aberrant mitosis that results in the formation of cells with two or more micronuclei. This is a major form of tumor cell death after treatments with IR or certain chemotherapeutic agents.[94,138,139] MCD is a poorly defined type of programmed cell death that develops within a few days of genotoxic insult (delayed type of cell death).[140-142] It prevails in cells with impaired G_1, G_2, prophase and mitotic spindle checkpoint functions.[94,143,144] Of these, the p53-mediated arm of the G_2/M checkpoint was shown to play an essential role in preventing MCD in DNA damaged cells.[144,145]

Two main mechanisms have been proposed for MCD. The first one is based on aberrant duplication of centrosomes that leads to multipolar mitosis and subsequent formation of micronuclei.[146] However, extra centrosomes do not always lead to multipolarity and MCD. Certain cell types suppress multipolarity and form a bipolar spindle during mitosis even though the centrosomes are amplified.[147] Furthermore, some centrosomal defects induce centrosomal amplification without multipolarity.[148] Recently, it was shown that spindle multipolarity can be effectively prevented in cells with supernumerary centrosomes by a centrosomal clustering mechanism.[149] They found that microtubule motor cytoplasmic dynein plays a critical role in this coalescing machinery, and that in some tumor cells overexpression of the spindle protein NuMA interfered with dynein localization, thereby promoting multipolarity.

The second proposed mechanism of MCD relates mainly to cells in which DNA was damaged (Fig. 2). MCD in such cells results from unscheduled activation of Cdk1 and the entry into premature mitosis of cells with unrepaired DNA damage. These cells fail to produce proper chromatin compaction and chromosome alignment, and, thanks to compromised spindle checkpoint functions and spindle multipolarity, also fail at proper chromosome segregation in anaphase. This process finally leads to generation of polynucleated cells, which arise through the formation of nuclear envelopes around clusters of chromosomes or chromosome fragments during a catastrophic mitosis.[94,143]

Multimicronucleation is most notable after severe DNA damage that causes the fragmentation of chromosomes into pieces. The vast majority of such cells is non-viable or become non-viable shortly after the catastrophic mitosis. However, some of them (~5–10%) might undergo interphase restitution and enter into endoreduplication cycles in which they try to repair the DNA damage, apparently via homologous recombination.[150] Conceivably, most of these cells will eventually die, but some in which DNA repair processes (at least in the genes essential for maintenance of cell viability) were successfully completed could survive and bear progenitors with increased genomic instability, thereby increasing tumor aneuploidity and rendering them even more insensitive to anticancer treatments.[151-153] Indeed, there is documentation of endopolyploid giant cells after genotoxic stress in tumors as a result of mitotic catastrophe.[154,155] From this standpoint, incomplete death of cells following mitotic catastrophe could represent a mechanism for survival and potentiate tumorigenesis. However, since a large number of tumor cells exhibit compromised cell cycle checkpoint functions and have profound defects in apoptosis execution machinery, they may be particularly susceptible to death via MCD. The complete understanding of the molecular pathways underlying MCD is thus important for designing cancer therapeutic regimens.

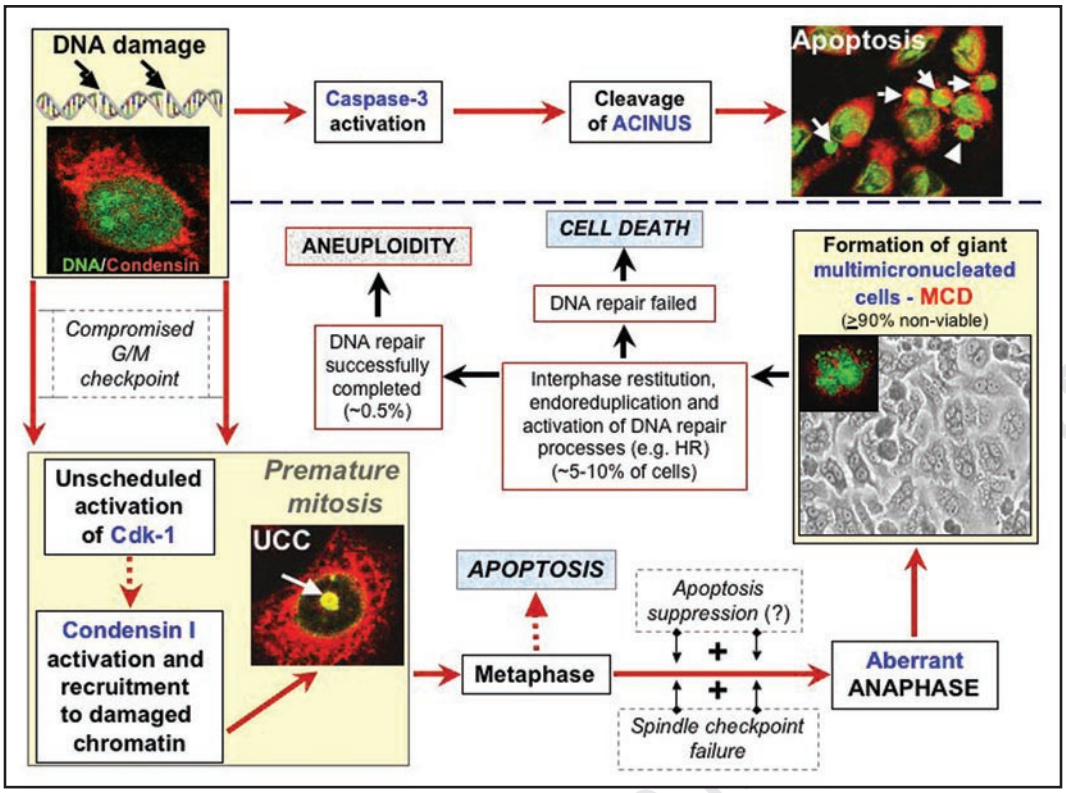

Figure 2. Current view of molecular mechanisms leading to MCD following extensive DNA damage. In cells with defective G_2/M checkpoint such damage leads to entry of cells with unrepaired DNA into premature mitosis with unscheduled Cdk-1 activation, condensin I activation and its recruitment to damaged chromatin, and formation of unaligned, hypercondensed chromatin aggregates representing UCC (note differences in morphological appearance and condensin distribution between UCC and apoptotic chromatin condensation). Some of these cells may activate apoptosis during mitosis. Concomitant suppression of apoptosis and compromised spindle checkpoint function may allow the cells to proceed through aberrant anaphase to telophase without cytokinesis, resulting in multimicronucleated cells, most of which become non-viable. Some of the polynucleated cells may survive, however, via interphase restitution and endocycling with activation of DNA repair processes. Such cells may enter a second mitosis, giving rise to progenitors with significantly increased aneuploidy. DNA-green; condensin-red.

As mentioned above, one of the early steps in MCD is cell entry into premature mitosis before DNA repair processes have been completed. One of the prominent morphological hallmarks of premature mitosis is induction of uneven chromatin condensation (UCC),[94,143,144] a process whose mechanism is elusive. In a recent study we provided some of the missing links between DNA damage and the development of such chromatin abnormalities during MCD.[142] We showed that the development of UCC following severe DNA damage engaged some of the proteins involved in chromatin packaging during normal mitosis,[156] but not the acinus-mediated mechanism that operates in apoptotic chromatin condensation.[51] Condensin recruitment was a common denominator of mitotic chromatin condensation and UCC, but UCC involved activated condensin I and not condensin II, thereby differing from mitosis that entails recruitment of both condensins to chromatin.[157,158] Condensin recruitment is important not only for the establishment of fully condensed chromosomes, but also for their proper chromosome alignment and subsequent segregation (because condensins take a part in assembly and orientation of centromere structures[157,158]); thus, the exclusive targeting of condensin I to damaged chromatin apparently lead to formation of unaligned, hypercondensed chromatin aggregates typical of UCC with subsequent aberrant mitosis and generation of multimicronucleated cells—the hallmark of MCD (Fig. 2).

We found no evidence of the involvement of apoptotic execution machinery in either early or late development events of the UCC-MCD pathway. However, in some experimental models, MCD may exhibit features typical of apoptosis or even of senescence,[159-161] but only apoptosis and senescence and not MCD are promoted by p53.[94] It is noteworthy that in our panel of several human cell lines with compromised p53, an impaired p53-mediated G_2/M checkpoint was found to be an important but not a sole requirement for the activation of UCC-MCD pathway following extensive DNA damage.[142] It is now clear that the outcome of the cellular response varies depending on the nature of cells, the type of insult trigger, and its extent.

In addition to p53, the other important regulators of cell transition through transient G_2 arrest via premature mitosis and aberrant anaphase towards formation of multimicronucleated cells have been identified. The updated list for the most important ones includes:

(A) proteins involved in sustaining and recovering of DNA-damage induced G_2 checkpoint such as ATR, Chk1, BRCA-1, the Polo-like kinase, Wee1, $p21^{waf1}$ and 14-3-3-σ, Cdc25 phosphatase family proteins (especially Cdc25A), the Aurora A kinase, cyclin-dependent activating kinase,[94,144,145,153,162-165] and probably cyclin G_1.[166] These molecules directly as well as indirectly regulate G_2-to-M mitotic progression via activation (or inhibition) of Cdk1, master regulator of mitotic events. Importantly, the emerging data indicate that ATR rather than ATM is the major player in the DNA

damage-induced G_2 checkpoint.[167-169] In our recent study there was also no significant impact of ATM on UCC-MCD development.[142] These observations draw a line between DSB-induced processes that are under ATM jurisdiction (e.g., cellular rescue and apoptosis) and those that are not (MCD).

(B) Decatenation checkpoint regulators such as topoisomerase II and its upstream DNA-damage induced regulators such as ATR and BRCA1, which delay cell entry into mitosis until chromosomes have been disentangled through the action of topoisomerase II.[170,171]

(C) Mitotic spindle checkpoint proteins, especially Mad2 and BubR1, which significantly affect MCD in DNA-damaged cells.[143,172]

Many of these molecules are under extensive investigation as potential targets for anticancer therapy.[132,173] One approach to target tumor cell to die via MCD is direct inhibition of the G_2 checkpoint in conjunction with DNA damage. Indeed, some chemical compounds capable of abrogating residual G_2/M checkpoint, thereby sensitizing tumor cell to DNA damage, have been developed (e.g., UCN-01 (7-hydroxystaurosporine)) and are now undergoing preclinical and clinical trials.[132]

In closing. Understanding the molecular networks underlying tumorigenesis and cellular escape from programmed cell death (spontaneous or induced) is prerequisite to the development of new approaches to effective cancer treatment. The design of such approaches will have to take into account that targeting a specific cell death-related molecules or pathway could, under certain circumstances, produce undesirable results, such as the survival and propagation of cancer cells with increased insensitivity to treatment. The outcome of cellular response will vary with the type of tumor, the nature of the cell-death trigger, and myriad other factors specific to the given patient, such as hormonal status.

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