NEW CONCEPTS IN GASTROENTEROLOGY

Dying a Thousand Deaths: Redundant Pathways From Different Organelles to Apoptosis and Necrosis

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Cell death is an essential event in normal life and development, as well as in the pathophysiological processes that lead to disease. Although the literature on cell death has grown enormously in size and complexity, a pattern has emerged that each of several distinct organelles (plasma membrane, mitochondrion, nucleus, endoplasmic reticulum, lysosome) gives rise to signals that induce cell death. Most often these signals converge on mitochondria to initiate a common pathway to either caspase-dependent apoptosis or ATP depletion-dependent necrosis. This brief overview emphasizes the multiple and often redundant pathways between different organelles that lead ultimately to a cell's demise.

Cell death is a prominent and essential event in both normal life of organisms and pathophysiological processes that lead to disease. In development, programmed cell death, or apoptosis, occurs to sculpt and remodel organs and body parts, as in creating clefts in limb buds to form fingers and toes.[1] In more mature organisms, immune surveillance induces apoptosis in transforming preneoplastic cells and in virally infected cells.[2] Apoptosis also often accounts for reversion of hypertrophy to atrophy.[3] In the gastrointestinal tract, where renewal of epithelial cells can occur every few days, programmed death of old and presumably worn out cells exactly matches their replacement by mitotic proliferation.[4] Although rarer, necrotic cell death, also called oncosis or oncotic necrosis,[5] also occurs physiologically, as in the shedding of the uterine decidua in human menses. The literature on cell death, especially apoptosis, has grown enormously in size and complexity, but a pattern emerges that each of several distinct organelles gives rise to signals leading to cell killing. Moreover, most often these signals converge on the mitochondrion as an initiator of both apoptotic and necrotic cell death. This brief overview emphasize the multiple and often redundant pathways between different organelles that lead ultimately to a cell's demise.

Modes of Cell Death: Necrosis and Apoptosis

Cell death, both necrotic and apoptotic, is frequently a dominant feature of disease. In liver, particularly, disease processes cause hepatocellular death with replacement of hepatocytes by scar tissue.[6] Prevention of cell death is thus often an important therapeutic goal. Conversely in cancer chemotherapy, cell death is the objective. Likewise, a promising therapy in hepatic fibrosis is induction of apoptosis in collagen-producing stellate cells of the liver.[7]

Abbreviations used in this paper: Akt, proto-oncogene product of the viral oncogene v-akt; AIF, apoptosis inducing factor; Apaf-1, apoptotic protease activating factor-1; ATF6, activating transcription factor 6; Bad, heterodimeric partner for Bcl-xL and Bcl-2; Bak, Bcl2 homologous antagonist/killer; Bax, conserved homolog that heterodimerizes with Bcl2; Bcl2, B cell lymphoma-2; BclxL, Bcl extra long; Bid, novel BH3 domain-only death agonist; BH3, Bcl2 homology domain 3; caspase, cysteine-aspartate protease; CHOP, C/EBP homologous protein; DISC, death-inducing signaling complex; DR4/5, death receptor 4/5; Drp-1, dynamin-like protein type 1; eIF-2α, eukaryotic initiation factor-2α; ER, endoplasmic reticulum; FADD, Fas-associated protein with death domain; GRP78, glucose-regulated protein-78; GRP94, glucose-regulated protein-94; HtrA2/Omi, high temperature requirement A2; IKK, IκB kinase; IGF, insulin-like growth factor; iNOS, inducible nitric oxide synthase; IRE1, type 1 ER transmembrane protein kinase; IκB, inhibitor of κB; IAP-1, inhibitor of apoptosis protein-1; IAP-2, inhibitor of apoptosis protein-2; JNK, cJUN NH_2-terminal kinase; Mcl-1, myeloid cell leukemia sequence 1; MPT, mitochondrial permeability transition; NFκB, nuclear factor κB; p21, 21 kDa promoter; p53, 53 kDa promoter; PARP, polyadenosine ribose polymerase; PERK, PKR like ER kinase; PI3 kinase, phosphoinositide 3-kinase; PIP3, phosphatidylinositol trisphosphate; PKR, RNA-activated protein kinase; PUMA, p53 up-regulated modulator of apoptosis; Smac, second mitochondria-derived activator of caspases; tBid, truncated Bid; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α; TNFR1, TNF receptor 1; TRADD, TNF receptor-associated death domain protein; TRAF2, TNFR-associated factor 2; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; UPR, unfolded protein response; VDAC, voltage dependent anion channel; XBP1, X-box-binding protein 1; XIAP, X-linked inhibitor of apoptosis protein.

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Necrotic Cell Death

The features of necrotic and apoptotic cell death are well described and reviewed elsewhere.[1,5,8,9] The penultimate event in necrotic cell death is abrupt loss of the plasma membrane permeability barrier caused literally by plasma membrane rupture.[10,11] As a consequence, cells release enzymes like ALT and LDH, lose metabolic intermediates such as those that reduce tetrazolium dyes, and take up supravital dyes like trypan blue and propidium iodide as markers of cell death. For reversible stresses like anoxia, cells can be rescued up to the point of plasma membrane rupture, but not afterwards.[11] Usually necrosis is the consequence of metabolic disruption and ATP depletion, which produces inhibition of plasmalemmal Na,K ion pumps. Thus, cellular swelling often precedes onset of necrotic cell death.[5]

Apoptosis

Whereas necrotic cell death occurs abruptly by ATP depletion-dependent plasma membrane rupture, apoptosis is an ATP-requiring process without a clearly distinguished point of no return. Moreover, apoptosis unlike necrosis may take hours to go to completion. Nonetheless, the two modes of cell death are not necessarily independent phenomenon, but can be intertwined. For example, ATP depletion in cells undergoing apoptosis leads to necrosis, whereas ATP replenishment to prevent necrosis can induce apoptosis instead.[12–16] Indeed, necrosis and apoptosis can represent different outcomes of identical pathways committing cells to death, a process of 'necrapoptosis.'[17]

In most instances of apoptosis, activation of caspase 3, one of a family of caspases (cysteine-aspartate proteases[1]) involved in apoptosis, begins execution of the final and committed phase of apoptotic cell death, which is characterized by chromatin condensation, internucleosomal DNA degradation, cell shrinkage, formation of numerous small surface blebs (zeiosis), and phosphatidyl serine externalization on the plasma membrane. Pathways leading to caspase 3 activation and apoptosis seem only to become more complex, and it is no exaggeration to say that cells can die a thousand deaths. A pattern emerges, however, that each major cellular structure can originate its own set of unique signals to induce apoptosis. These signals are often associated with specific damage or perturbation to the organelle involved. In this way, cells choose death by apoptosis rather than life with the consequences of organelle damage.

Plasma Membrane

The plasma membrane is the recipient of a broad range of receptor-mediated signals. Prototypic proapoptotic signaling occurs from binding of death ligands (eg, TNFα, Fas ligand, TRAIL) to their corresponding death receptors (TNFR1, Fas, DR4/5).[18,19] In the simplest form of signaling (Type 1, Figure 1), ligand binding leads to receptor trimerization, association of adapter proteins (TRADD, FADD) and activation of caspase 8, an initiator caspase. Activated caspase 8 then proteolytically activates caspase 3 and apoptosis ensues. Similar signaling occurs after association of Fas ligand with Fas and TRAIL with DR4/5.

Various events in the plasma membrane modulate death receptor signaling. The degree of expression of receptor genes is, of course, an important determinant of a cell's sensitivity to death receptor ligands. Additionally, certain stimuli, such as hydrophobic bile acids, recruit death receptors like Fas to the cell surface, presumably by exocytosis of endomembranes.[20] Death receptors so recruited may self-activate even in the absence of ligand. A variety of receptors localize to lipid rafts containing relatively stiff membrane lipids like cholesterol and sphingomyelin, the latter concentrated in the outer leaflet of the bilayer. With death receptor activation, sphingomyelin hydrolysis to ceramide occurs in these rafts, usually via acid sphingomyelinase, an enzyme that may also incorporate into the plasma membrane through fusion of endomembrane vesicles. Ceramide so formed then self-associates through hydrogen bonding to promote raft coalescence and formation of molecular platforms that cluster signal transducers, including activated receptors, adaptor proteins, and caspase 8—the so-called death-inducing signaling complex (DISC).[18] Sphingomyelinase and exogenous ceramide are apoptogenic in many cells, and the rearrangement of lipid rafts into much larger platforms may be an important costimulatory factor in death receptor-mediated apoptosis.[21] Glycosphingolipids, such as ganglioside GD3, also integrate into signaling platforms to promote apoptosis.[22]

Mitochondria

Cytochrome c Release

The discovery in 1996 that cytochrome c promotes caspase 3 activation in extracts of cytosol solidified growing evidence of involvement of mitochondria in apoptotic signaling.[23] In so-called Type 2 signaling, activated caspase 8 cleaves the cytosolic protein Bid to a truncated active fragment, tBid, that translocates to mitochondria and induces cytochrome c release.[19,24–26] tBid

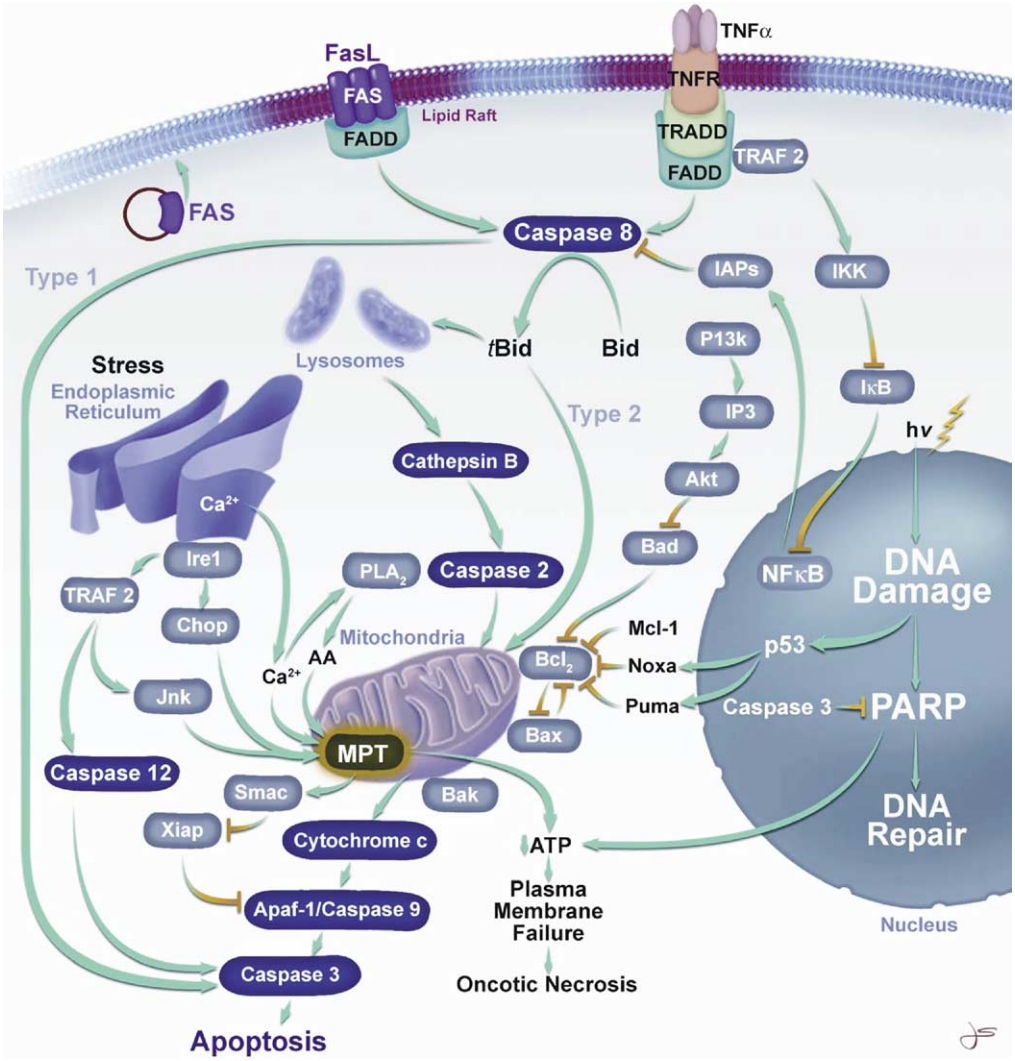

Figure 1. Scheme of apoptotic signaling from the plasma membrane, mitochondria, nucleus, endoplasmic reticulum, and lysosomes.

is a BH3 only proapoptotic Bcl2 family member that interacts with either Bak or Bax, 2 other proapoptotic Bcl2 family members, to induce cytochrome c release.[27] In hepatocytes exposed to TNFα, Fas ligation, or TGFβ, Type 2 signaling leads to opening of nonspecific mitochondrial permeability transition (MPT) pores in the inner membrane conducting all solutes up to 1500 Da.[28–31] This drastic alteration to mitochondrial permeability causes mitochondrial depolarization, uncoupling of oxidative phosphorylation and large amplitude mitochondrial swelling. Swelling, in turn, leads to rupture of the outer membrane and leakage of cytochrome c into the cytosol. Cytochrome c induces Apaf-1 and procaspase 9 to assemble into haptomeric apoptosomes and an ATP (or dATP)-dependent cascade of caspase 9 and caspase 3 activation.[32,33] Because the MPT represents such a severe perturbation of mitochondrial function, onset of the MPT virtually assures cell death, but the mode of cell death depends on other factors. If onset of the MPT is rapid and synchronous in all of a cell's mitochondria, as occurs with stresses like ischemia/reperfusion, Ca^{2+} overload, various hepatotoxicants and exposure to reactive oxygen species, then a precipitous fall of ATP (and dATP) occurs that actually inhibits caspase 9/3 activation. When this occurs, cell death has a necrotic pattern. By contrast, if onset of the MPT is slower and less synchronous or when alternative sources of ATP formation (eg, glycolysis) are present, then necrosis is prevented and caspase activation leading to apoptosis occurs instead.[9,15–17,34,35]

Studies of mitochondrial involvement in apoptosis range a gamut of cell types from developing worms and frog eggs to undifferentiated tumor cells and differentiated mammalian cells like hepatocytes, enterocytes, and myocytes. Although various cell types are described as having Type 1 or Type 2 signaling, in reality both

pathways often co-exist, one simply producing faster signaling that the other.[29] In many models of Type 2 signaling, cytochrome c release appears to occur via formation of specific pores in the mitochondrial outer membrane rather than via the MPT. Except for the important requirement for either Bak or Bax, the molecular composition and properties of the putative cytochrome c release channels remain poorly understood.[27] In HeLa cells (a cell line derived from an atypical cervical adenocarcinoma), cytochrome c release from mitochondria activates caspase 3, which then acts retrogradely to cause mitochondrial depolarization and inhibition of NADH-linked respiration.[36,37] By contrast in primary hepatocytes, mitochondrial inner membrane permeabilization (the MPT) with depolarization occurs prior to cytochrome c release and caspase 3 activation.[28,29,31] In hepatocytes, caspase 3 inhibition does not prevent mitochondrial depolarization after death receptor signaling, whereas specific inhibition of the MPT prevents depolarization, cytochrome c release, caspase 3 activation, and apoptosis.

An argument against involvement of the MPT in many forms of apoptosis is the assertion that cell killing occurs without mitochondrial swelling, but careful electron microscopy shows that mitochondrial swelling with outer membrane rupture occurs in virtually all of a broad range of apoptotic models.[38] A role of physical disruption of the outer membrane in cytochrome c release is also consistent with the empirical observation that Bcl-2 family proteins make the outer membrane permeable to solutes up to at least two million Da molecular mass.[39] One recent proposal is that the cytochrome c release channel is not a protein at all but is made up of lipid ceramide barrel structures in the bilayer that grow progressively in size after pro-apoptotic signaling,[40,41] whereas other work implicates ganglioside GD3 in onset of mitochondrial permeabilization.[22] Another proposal attempts to reconcile the roles of inner and outer membrane permeabilization in cytochrome c release.[42] Outer membrane permeabilization is proposed to occur first, but even after opening of cytochrome c release channels in the outer membrane, much cytochrome c is retained in the mitochondrial cristae due to the narrow necks of these tubular invaginations of the inner membrane.[43] When the MPT occurs, the inner membrane undergoes a configurational change much like that studied extensively in the 1960s and 1970s.[44,45] Such remodeling seems due to leakage from the matrix space of adenine nucleotides and other metabolites after MPT pore opening.[46–48] As a consequence, the narrow necks connecting the cristae to the mitochondrial surface open up to allow intracristal cytochrome c release. Although this model has received much attention, the idea that cytochrome c goes rapidly through putative 3 nm release channels in the outer membrane but not through the ~30 nm openings of cristae in the inner membrane seems implausible. Clearly, future investigations are needed to determine whether cytochrome c release actually occurs via one mechanism or by a variety of different mechanisms. The latter would certainly be consistent with the redundancy of apoptotic signaling in many other respects. Such redundancy of signaling and multiplicity of mechanisms requires that apoptotic signaling be characterized in each individual cell type of interest.

Regulation of Mitochondrial Signaling

Numerous mechanisms tightly regulate apoptotic signaling. Expression levels of procaspases, Apaf-1, and other proteins vary from cell to cell, and some terminally differentiated cells, such as neurons, do not respond to microinjected cytochrome c with caspase activation and apoptosis.[49] Expression of anti-apoptotic Bcl2 family members, like Bcl2, Bcl-xL, and Mcl-1, is another important mechanism frequently used by cancer cells to block apoptosis.[50,51] These antiapoptotic Bcl2 family members purportedly make heterodimers with proapoptotic family members like Bax and Bak, but the real specifics of the interaction and how such interactions neutralize the cytochrome c-releasing properties of Bax and Bak is not well understood. The voltage-dependent anion channel (VDAC) in the outer membrane is proposed to be an important anchoring point for Bax and other proteins regulating cytochrome c release.[52,53] A functional complex of Bad (a proapoptotic Bcl2 family member regulated by phosphorylation), protein phosphatase-1, glucokinase, and other proteins has also been proposed to exist in isolated liver mitochondria and be important for integrating pathways of glucose metabolism and apoptosis,[54] although other reports indicate that no detectable glucokinase is associated with mitochondria isolated from mice and rats.[55,56]

Inhibitor of apoptosis proteins (IAPs) provide another brake on apoptotic signaling by inhibiting caspases, including IAP-1, IAP-2, and XIAP.[57,58] Some IAPs inhibit signaling upstream of mitochondria at caspase 8, whereas others like XIAP inhibit caspase 9/3 activation after cytochrome c release. Additional proteins suppress IAP activity, providing an "inhibitor of the inhibitor" effect that promotes apoptosis. In particular, mitochondria contain Smac, a mitochondrial intermembrane protein that is released with cytochrome c after apoptotic signaling.[57,59,60] Smac inhibits XIAP and thus promotes apoptotic signaling after mitochondrial signaling. Thus, the XIAP to Smac ratio is an important determinant of

whether caspase 3 activation occurs after cytochrome c release. During ischemia to hepatocytes, XIAP but not Smac decreases in hepatocytes, which makes the cells more vulnerable to apoptosis after reperfusion.[61] Along with cytochrome c and Smac, other proapoptotic proteins released from mitochondria during apoptotic signaling through mitochondria include AIF (a flavoprotein oxidoreductase that promotes chromatin condensation and DNA degradation), endonuclease G (an enzyme that degrades DNA), and HtrA2/Omi (a serine protease that inhibits and degrades IAPs).[57,62–66]

Mitochondrial fragmentation is often prominent in apoptosis. Drp-1, a large GTPase mechanoenzyme, mediates mitochondrial fission. Drp-1 also forms complexes with BAX and other proapoptotic Bcl2 family members to promote outer membrane permeabilization and cytochrome c release during apoptosis.[67] Drp-1 overexpression promotes apoptosis, whereas Drp-1 mutants inhibit it. Thus, fusion-fission events in mitochondria may also sensitize the organelles to pro-apoptotic signaling.

Survival Pathways

Death receptors also stimulate antiapoptotic NFκB signaling through the adapter protein, TRAF2, and IKK.[19,68] IKK phosphorylates IκB, an endogenous inhibitor of NFκB activation, leading to proteosomal IκB degradation. Degradation relieves inhibition of NFκB and allows NFκB to translocate to the nucleus and activate gene expression. These genes include IAPs, BclxL, inducible nitric oxide synthase (iNOS) and other survival factors.[69,70] Nitric oxide from iNOS leads to inhibitory S-nitrosylation of caspases and cGMP-dependent suppression of the MPT.[71,72] In many models, activation of NFκB suppresses apoptosis after death receptor ligation. Apoptosis then only occurs when NFκB signaling is blocked, as with proteosomal inhibition, protein synthesis inhibition or overexpression of a nondegradable IκB superreppressor.[19,28,69] In liver in vivo, induction of apoptosis with TNFα requires co-treatment with galactosamine, which depletes dUTP and thus blocks protein synthesis.[73,74] Simultaneous stimulation of potent pro- and anti-apoptotic pathways by death receptor ligands accounts, in part, for their pleiotropic effects and the consternation of investigators.

Another source of antiapoptotic signaling is the PI3 kinase/Akt pathway.[75,76] Binding of insulin, IGF, and various other growth factors to their corresponding receptors activates PI3 kinase, causing formation of PIP3 and then activation of Akt/protein kinase B, a serine/threonine protein kinase. One consequence is the phosphorylation and inactivation of the proapoptotic Bcl2 family member, Bad, but several other antiapoptotic targets of PI3 kinase/Akt signaling exist. In many cell lines, withdrawal of serum or specific growth factors induces apoptosis due to suppression of the PI3 kinase/Akt survival pathway.

Nucleus

Death receptors initiate what is called the extrinsic pathway of apoptosis. In the intrinsic pathway, signaling begins in the nucleus. The prototypic initiating event is UV or gamma irradiation causing DNA damage. DNA damage leads to activation of p53, a nuclear transcription factor, with transactivation of genes for apoptosis and/or cell-cycle arrest, especially the proapoptotic Bcl2 family members PUMA, NOXA, and Bax for apoptosis and p21 for cell cycle arrest.[77,78] PUMA, NOXA, and Bax translocate to mitochondria to interact with antiapoptotic Bcl2 proteins to induce cytochrome c release by the same mechanisms discussed above for the extrinsic pathway.[79–81] Additionally, p53 itself translocates to mitochondria and may interact with Bcl2 family members to induce apoptosis.[82,83] Many tumors, especially those from the gastrointestinal tract, have loss of function mutations for p53.

DNA damage also activates PARP, a DNA repair enzyme. With moderate activation, PARP helps mend the broken DNA, but with strong activation PARP causes formation of polyadenosine-ribose polymers that deplete cellular NAD and ultimately exhaust cellular ATP. ATP depletion then leads to necrotic cell death. However, if p53-dependent apoptotic signaling occurs more quickly, activated caspase 3 proteolytically degrades and inactivates PARP. Thus, irradiation can lead to either PARP activation and ATP depletion-dependent necrosis or PARP degradation during caspase-dependent apoptosis.[84,85]

Endoplasmic Reticulum

The endoplasmic reticulum (ER) is another organelle that is a source of proapoptotic signals. Main functions of the ER include protein synthesis and storage of a rapidly mobilized pool of calcium. Oxidative stress and other perturbations can inhibit ER calcium pumps and activate calcium release pathways with the consequence that calcium dumps into the cytosol from the ER to be taken up by mitochondria.[86,87] Such uptake may induce a Ca^{2+}-dependent MPT. ER calcium release also activates phospholipase A2 and the formation of arachidonic acid, another promoter of the MPT.[88]

Additionally, ER calcium depletion perturbs the proper folding of newly formed proteins in the lumen of ER cisternae, which causes "ER stress" and the unfolded

protein response (UPR).[89–91] Inhibitors of glycosylation, various toxicants, and synthesis of mutant proteins can also cause ER stress. Calcium-binding chaperones in the ER, such as GRP78 and GRP94, mediate the detection of unfolded and misfolded proteins. These chaperones help fold nascent unfolded proteins into a proper mature protein conformation. In the absence of unfolded/misfolded proteins, GRP78 associates with and inhibits specific sensors of ER stress. During ER stress, GRP78 translocates from the sensors to unfolded/misfolded proteins to cause sensor activation by disinhibition. The 3 principal sensors are PKR (and PERK), IRE1, and ATF6. PKR and PERK are protein kinases that promote phosphorylation of eukaryotic initiation factor-2a (eIF-2α), which suppresses ER protein synthesis, decreases delivery of newly formed protein to the ER lumen and attenuates the unfolding stress.[92] Ire1 is a membrane-spanning receptor protein kinase and riboendonuclease that initiates splicing of a preformed mRNA, XBP1, into an activated transcription factor.[93] ATF6 is another transcription factor that is transported to the Golgi after ER stress.[94] Proteases in the Golgi process ATF6 to an amino-terminal fragment that is released and taken up into the nucleus. Together Ire1 and ATF6 act to increase expression of GRP78 and other proteins that increase protein-folding capacity in the ER to alleviate the unfolding stress.

If the UPR persists, Ire1- and ATF6-dependent expression of CHOP and continued activation of Ire1 initiate apoptotic signaling. Activated IRE1 associates with TRAF2 to activate caspase 12 and JNK.[95,96] Caspase 12 activates caspase 3, whereas JNK together with CHOP activates the mitochondrial pathway. Additionally, ER stress itself leads Ca^{2+} release, which also promotes mitochondrial signaling. Larger proteins, such as GRP78, can also be released after ER stress.[90] Remarkably, the same Bcl-2 family members that associate with mitochondria and regulate mitochondrial signaling of apoptosis, including Bcl-2, Bcl-xL, Bax, and Bak, also associate with the ER. Available evidence suggests that pro-apoptotic Bcl-2 family members like Bax and Bak act to increase the size of the ER calcium store, thus increasing the proapoptotic potential of ER calcium release.[97] An interrelation also exists between ATP and ER stress, since chaperones require ATP to induce proper protein folding.[98] Thus, perturbations that decrease ATP can augment ER stress.

Lysosomes

Lysosomes and the associated process of autophagy (self-digestion) represent another source of pro-apoptotic signaling. So-called autophagic cell death has long been recognized by pathologists and is characterized by an abundance of autophagic vacuoles in dying cells.[99] Autophagic cell death is especially prominent in involuting tissues. In autophagy, elements of smooth ER surround and then sequester portions of cytoplasm to form a double membrane autophagosome, which then fuses with lysosomes (or late endosomes) to form an autolysosome.[100] In this way, cellular constituents are removed and digested, an appropriate action for any tissue undergoing involution. Although once thought to be random, increasing evidence suggests that autophagy is relatively selective for specific organelles, especially if they are damaged.[101,102] For example, stresses inducing the MPT may help signal autophagy of mitochondria.[103]

Controversy remains as to whether autophagy promotes or prevents cell death.[104,105] Some evidence suggests that autophagy promotes cell death, because deletion of certain autophagy genes decreases apoptosis. Other data supports the conclusion that autophagy prevents cell death, since disruption of autophagic processing and/or lysosomal function promotes caspase-dependent cell death.[104–106] In the latter circumstance, enzymes may leak from lysosomes/autolysosomes, such as cathepsins and other hydrolases, that initiate mitochondrial permeabilization and caspase activation. Lysosomal permeabilization appears also to augment death receptor-mediated apoptosis. In particular, cathepsin B is released from lysosomes (or related structures such as late endosomes) during TNFα signaling and contributes to mitochondrial release of cytochrome c.[107,108] Lysosomal extracts also can cleave Bid to its active form, and another lysosomal protease, cathepsin D activates Bax.[109,110]

In the current issue of GASTROENTEROLOGY, these pathways are further clarified.[111] During TNFα signaling in hepatocytes, caspase 8-dependent Bid cleavage to tBid initiates lysosomal permeabilization. Consequent release of lysosomal cathepsin B then activates caspase 2 to cause mitochondrial permeabilization and cytochrome c release. Lysosomal permeabilization with release of cathepsin B is also implicated in lipotoxicity, namely apoptosis induced by steatosis or exposure to high amounts of free fatty acids.[112] Remarkably, Bax translocation to lysosomes occurs prior to lysosomal permeabilization. Thus, Bax translocation occurs in association with dysfunction and apoptotic signaling in 3 different organelles—mitochondria, endoplasmic reticulum, and lysosomes—and may be promoting a permeability transition in each.

Conclusion

In conclusion, damage and stress to different cellular structures elicit responses that activate cell death signaling. In most but not all cases, a common final pathway is via mitochondrial permeabilization with release of cytochrome c and other proapoptotic factors, leading to caspase activation and apoptosis. Alternatively, mitochondrial membrane dysfunction induced by the same stimuli can lead to ATP depletion and a necrotic mode of cell death. Such shared pathways leading to different modes of cell death constitute necrapoptosis. In general, however, apoptosis represents a better outcome for the organism since it promotes a more orderly resorption of dying cells, whereas necrotic cell death leads to proinflammatory release of cellular constituents into the extracellular space. For gastroenterological research, the question of which of these multiple and redundant pathways actually leads to cell death in a specific cell type can only be answered empirically. Given the abundance of different terminally differentiated cells in the GI tract, that leaves us lots to do.

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