Biochimica et Biophysica Acta 1813 (2011) 238–259

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Anti-apoptosis and cell survival: A review

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ARTICLE INFO

Article history:
Received 13 August 2010
Received in revised form 4 October 2010
Accepted 11 October 2010
Available online 20 October 2010

Keywords:
Cell death
Anti-death
Pre-condition
Stress response
Regulation of apoptosis
Survival

ABSTRACT

Type I programmed cell death (PCD) or apoptosis is critical for cellular self-destruction for a variety of processes such as development or the prevention of oncogenic transformation. Alternative forms, including type II (autophagy) and type III (necrotic) represent the other major types of PCD that also serve to trigger cell death. PCD must be tightly controlled since disregulated cell death is involved in the development of a large number of different pathologies. To counter the multitude of processes that are capable of triggering death, cells have devised a large number of cellular processes that serve to prevent inappropriate or premature PCD. These cell survival strategies involve a myriad of coordinated and systematic physiological and genetic changes that serve to ward off death. Here we will discuss the different strategies that are used to prevent cell death and focus on illustrating that although anti-apoptosis and cellular survival serve to counteract PCD, they are nevertheless mechanistically distinct from the processes that regulate cell death.

1. Introduction: an overview of programmed cell death (PCD)

Apoptotic cell death is a genetically programmed mechanism(s) that allows the cell to commit suicide [1–4]. Apoptosis is critically important for the survival of multicellular organisms by getting rid of damaged or infected cells that may interfere with normal function [5,6]. The extrinsic and intrinsic pathways represent the two major well-studied apoptotic processes [2,7]. The extrinsic pathway is mediated by a sub-group of Tumor Necrosis Factor receptors (TNFR) superfamily that includes TNFR, Fas and TRAIL. Activation of these so-called death receptors leads to the recruitment and activation of initiator caspases such as caspases 8 and 10 (Fig. 1). The process involves the formation and activation of complexes such as the death inducing signaling complex (DISC). This leads to the activation of an effector caspase, typically caspase 3. The active caspase 3 is responsible for the cleavage of a number of so-called death substrates that lead to the well-known characteristic hallmarks of an apoptotic cell including DNA fragmentation, nuclear fragmentation, membrane blebbing and other morphological and biochemical changes. More recent evidence suggests even greater complexity and diversity in the extrinsic pathways that also involves the cross-activation of other apoptotic pathways such as the intrinsic apoptotic as well as necrotic sub-pathways [2,8] (see also below).

The cell autonomous or intrinsic pathway is largely centered around and/or regulated by the mitochondria [9–11]. The most widely studied form of intrinsic apoptosis is initiated by the stress-mediated release of cytochrome c from the mitochondria that results in the formation of the apoptosome (Fig. 1). The apoptosome then activates initiator caspase, typically caspase 9, which leads to the activation of the executioner caspase 3. This leads to the same type of apoptotic response as observed for the extrinsic pathway. In response to apoptotic stimuli, pro-apoptotic members of the Bcl-2 protein family (Bax and Bak) become activated and act on the mitochondria to induce the release of cytochrome c. Other pro-apoptotic proteins are also released by the mitochondria including Smac/Diablo (Second Mitochondrial derived activator of Caspase/Direct IAP-Binding protein with a LOw pI), the serine protease Omi/HtrA2, endonuclease G (EndoG) and apoptosis inducing factor (AIF) [12–14]. These later examples as well as a number of others described later, clearly demonstrates the central role of the mitochondria in the highly regulated and complex process of many forms of programmed cell death (PCD) [9,11,15–17]. As mentioned above, activation of the mitochondrial pathway can also occur following the activation of the extrinsic pathway. This has been shown to occur via the caspase 8 cleavage of the pro-apoptotic Bcl-2 member Bid to its activated tBid form [10]. This relatively simple example of cross-talk between apparently distinct apoptotic pathways further serves to illustrate a common theme of the complex interrelationships that is now commonly observed in the different processes involved in regulating cell death (see also below) [8,13,17,18].

In addition to type I or apoptotic cell death, at least two other major forms of programmed cell death exist [2,4,19]. Autophagy has received considerable more attention in recent years because of the dual and somewhat contradictory roles it plays in mediating decisions between life and death. Autophagy is an important multifunctional process, which cells use to recycle cellular constituents, a process that

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doi:10.1016/j.bbamcr.2010.10.010

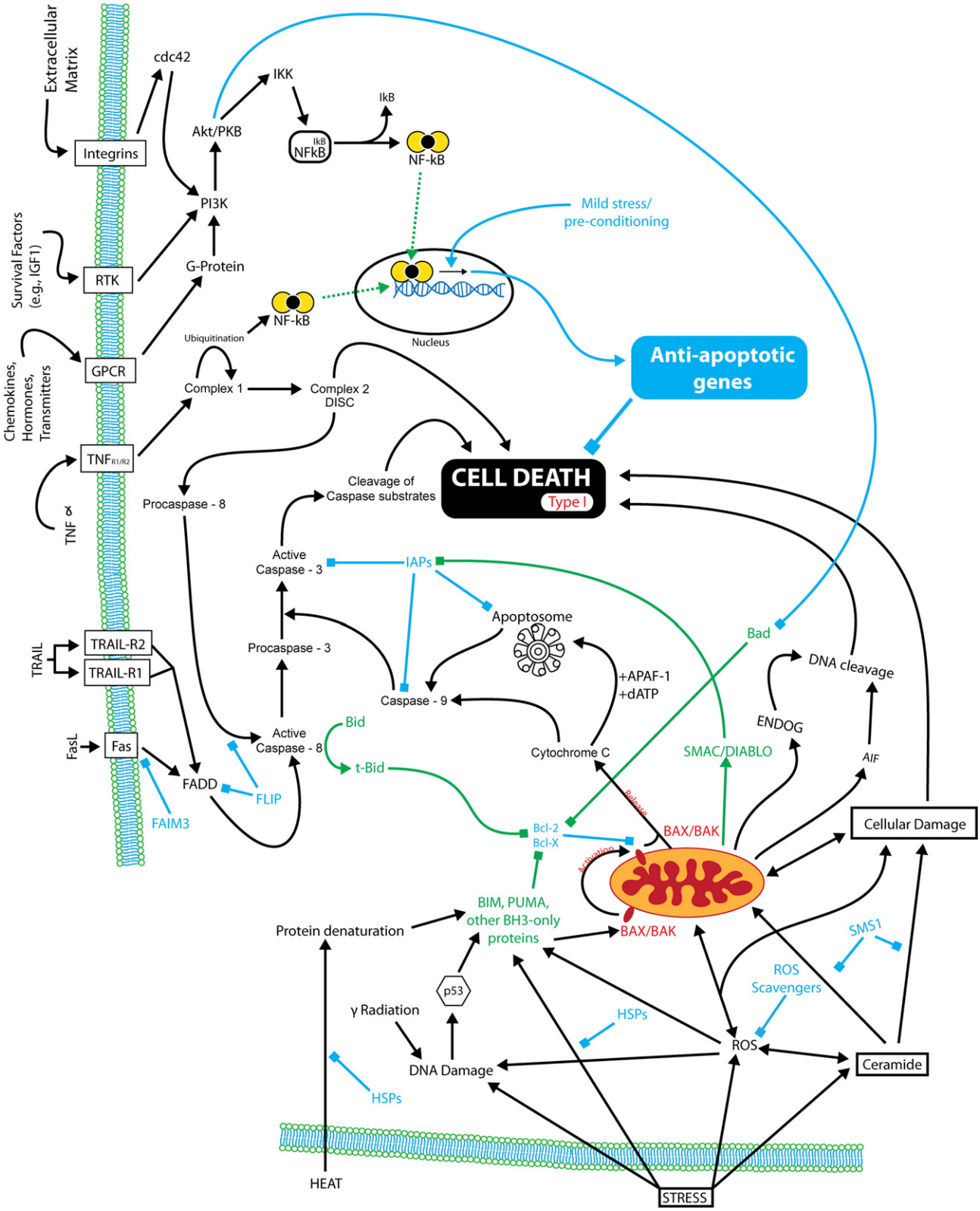

Fig. 1. Schematic representation of the cellular pathways of apoptosis or type II programmed cell death (PCD) with an emphasis on the mechanisms that promote survival. A variety of central players are illustrated including different membrane proteins imbedded into the cell membrane, the mitochondria is shown as a orange oval while an empty oval depicts the nucleus. Cell death and anti-apoptotic genes are respectively shown as black and blue boxes. There are two forms of type I PCD named intrinsic and extrinsic. The intrinsic form is triggered by a variety of stimuli including a number of stresses. The stresses lead to activation of Bax (via activation of Bcl-2 BH3 only proteins), the production of Reactive Oxygen Species (ROS) and ceramide that serve as second messengers that converge on the mitochondria. This leads to the release of apoptogenic factors including cytochrome c, endonuclease G (Endo G) and Apoptosis Inducing Factor (AIF). Cytochrome c combines with pro-caspase 9, APAF-1 and dATP to form the apoptosome that leads to cell death via the activation of a caspase cascade. Extrinsic apoptosis is also due to the activation of the same caspase cascade as the intrinsic form but in this case, it is activated by cytokine type receptors for TNF, TRAIL and FasL. Cross-talk between the extrinsic and intrinsic forms occurs via the extrinsic mediated activation of the BH3 only Bid protein into its tBid active form. A variety of proteins serve to antagonize type I PCD including Inhibitors of Apoptosis Proteins (IAPs), FLIPs, Faim3 and the anti-apoptotic Bcl-2 proteins of which Bcl-2 is the most common. The color blue is used to depict anti-apoptotic processes while squares at the end of lines indicate inhibition.

plays an important role in normal cellular homeostasis [20,21]. The ability to recycle old components into new building blocks makes autophagy essential for survival during starvation. Studies that are more recent have also shown that autophagy is activated by a multitude of stresses and it is critical for surviving these stresses. Autophagy is reported to be so powerful and ubiquitous that it is likely the most impressive weapon in the cell's anti-death arsenal [22]. Almost paradoxically, autophagy is also well known as type II PCD that may be described as a type of caspase independent cell death that is associated with the presence of autophagosomes [23–27].

Necrosis or type III cell death was originally thought to be the catastrophic form of death [25]. More recent evidence, including the fact that there are genetic inhibitors of some forms of necrosis, suggests that subforms of necrotic death may have a genetic component. For example, in addition to activating apoptosis, stimulation of TNF-α receptors can also lead to the induction of a programmed from of necrosis called necroptosis [28]. Receptor mediated activation of Receptor Interacting Protein 1 (RIP1) kinase and formation of a necroptosis inducing active complex consisting of RIP1 and RIP3 has been implicated. Thus it also functions as a form of PCD that occurs under certain pathological situations (i.e. in the heart or brain during ischemia) [29,30]. The lysosome itself may directly participate in type III PCD by releasing lysosomal components such as proteases that may themselves trigger cell death [31]. Other organelles like the endoplasmic reticulum (ER) may have more complex roles since it may be involved in triggering type III or type I PCD [32,33]. More specialized or alternative forms of cell death including anoikis (the PCD that occurs when cells lose anchorage, contact with their substratum or neighboring cells) and pyroptosis (infection mediated cell death) are also important under some conditions or in some cell types [34–37]. The diversity in the processes involved in inducing PCD belies the complexity and a large number of different proteins that can prevent the different "specialized" forms of apoptosis [38–41].

Although many excellent global reviews on cell death have been presented there have been comparatively very few attempts at providing a comprehensive review on the processes involved in promoting cell survival. Given the overwhelming evidence that anti-apoptosis is a global cellular process that is complimentary but distinct from apoptosis (think kinases versus phosphatases), we have attempted here to provide a global type framework for anti-apoptosis and cell survival processes. The topic is huge and we apologize for the omission of a large number of references that we could not include here due to space limitations. We refer the reader to a number of excellent reviews that provide more in depth analysis of some of the subtopics within the cell survival field [4,38,42–55].

2. Regulation of apoptosis

2.1. Induction of apoptosis

All metazoan as well as all protozoan cells examined have the ability to undergo apoptosis when conditions are appropriate [16,56–59]. The sacrifice of individual cells that are defective, damaged or otherwise a potential threat to the integrity of the whole organism, or to the colony in the case of protozoans, is thought to be an important survival mechanism. Apoptosis can be induced by a wide range of stimuli that are encountered during normal or pathophysiological processes [3,60]. For example death receptor agonists may be used by immune cells to trigger apoptosis in specific populations of defective cells. In contrast, increased neurohormonal stimulation including elevated levels of agonists for adrenergic and Angiotensin II (AngII) G-Protein Coupled Receptors (GPCR) that are observed in patients with chronic heart failure also trigger cell death in cardiac and skeletal muscle cells [61–63]. In addition to specific stimuli such as receptor agonists, other stimuli including a multitude of other extracellular and intracellular stresses that can serve to induce the intrinsic apoptotic pathway [3,57]. These include a large variety of different physico-chemical stresses such as chemotherapeutic agents (i.e. doxorubicin), alterations in temperature and osmolarity, DNA damaging agents, free radical generating compounds (i.e. H_20_2), removal of nutrients, oxygen or growth factors, pro-inflammatory cytokines as well as normal physiological processes such as aging and development [3,62,64–71]. Some of these as well as a number of other apoptotic stimuli are linked to specific diseases. The pathological stimuli include ischemia and subsequent reperfusion that is seen in heart attacks or stroke as well as other processes including the accumulation of misfolded ER proteins that is often seen and may be the basis for the cell death observed in neurological diseases such as Parkinson's [17,55,72].

The processes involved in initiating the intrinsic pro-apoptotic cascade in response to an appropriate stress is like many processes associated with PCD, very well studied but, still incompletely understood (Fig. 1). What appears to be clear, at least in some cases, is that the stress leads to activation of pro-apoptotic Bcl-2 members like Bax or Bak [10,73–75]. Active Bax is recruited to the mitochondria and forms pores that allow the release of pro-apoptogenic factors such as cytochrome c, which then leads to the formation of the apoptosome. This serves to initiate the intrinsic apoptotic signaling cascade that involves sequential activation of both initiator and effector caspases leading to cell death (Fig. 1). Reactive oxygen species (ROS) also represents a major player in this process [76,77]. It should be noted that the term ROS refers to a number of different physiologically relevant molecules including superoxide anions ($O^2{}_2$), hydrogen peroxide (H_2O_2), free hydroxyl radicals (OH), nitric oxide (NO) as well as some combinations of ROS (i.e., NO and $O^2{}_2$) can yield new species such as peroxynitite ($ONOO^-$) [4,78,79]. Different stimuli will lead to the production of different ROS species and in turn these will elicit different responses [80,81]. Its levels are increased in response to stress likely due to increases in mitochondrial damage. It appears to stimulate the apoptotic cascade by causing damage to many cellular components including proteins, lipids and the mitochondria itself which in turn likely facilitates the further release of apoptogenic factors [77,82]. Like ROS, the sphingolipid ceramide also plays a critical pro-apoptotic role. Although less is known regarding ceramide, likely due in part to the technical difficulties in monitoring the levels of sphingolipids, it is nevertheless quite clear that ceramide is a ubiquitous pro-apoptotic second messenger whose levels are elevated in response to multiple stresses [83–85]. Ceramide has been shown to activate a variety of intracellular targets but the mechanism by which it induces apoptosis is not well known [86].

It is quite clear from the above discussion that Bax, ROS and ceramide are important mediators of the cell death that is induced by a variety of different stresses (Fig. 2). Quite a bit is known regarding the regulation and the function of these factors. For example, the source of stress-mediated increases in ROS is likely the mitochondria or NADPH oxygenase [82]. Similarly, the stress-mediated activation of Sphingomyelinase (SMase) which serves to produce ceramide from sphingomyelin is likely the major source of the increase in ceramide during stresses [83]. Although numerous models have been developed, the activation of Bax by stress activated BH3 only Bcl-2 proteins, is the most likely scenario [74]. Ceramide, ROS and active Bax seem to behave independently of each other since increases in any of the three is sufficient to trigger cell death. However, they are also intimately linked such that increases in either one of the three leads to either increased levels of the other or an increase in their ability to function. Commonly proposed mechanisms of cross-talk between ROS and Bax mediated apoptosis involves the convergent activation of common pro-apoptotic proteins such as JNK kinase as well as the possibility that proteins such as Bcl-2 have dual functions as a Bax inhibitor as well as being able to mediate a small increase in the production of ROS

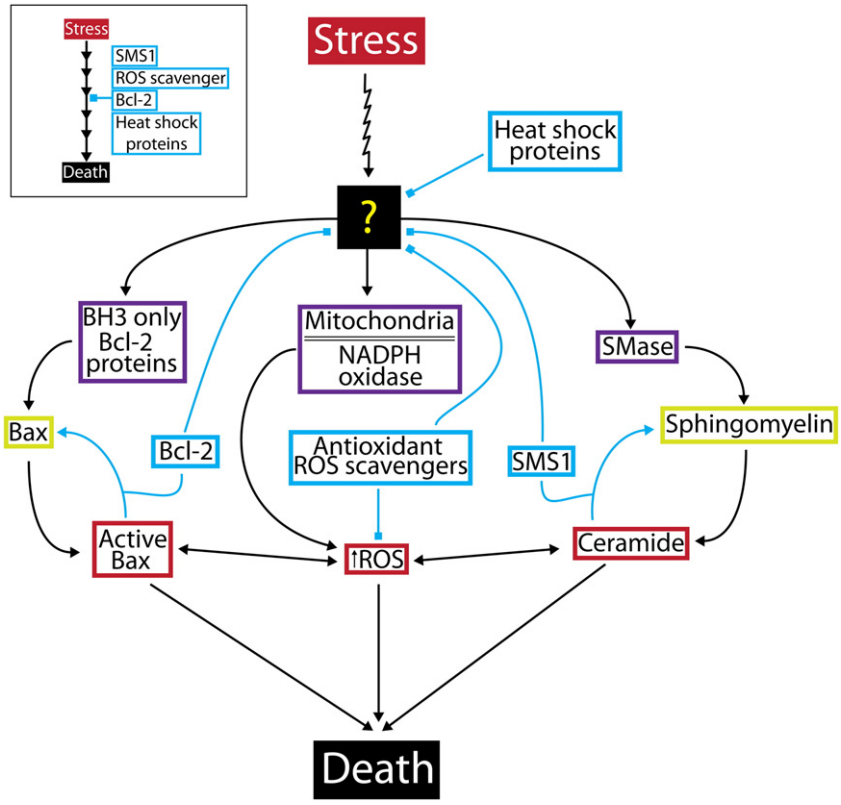

Fig. 2. Schematic representation of the processes involved in inducing stress mediated cell death and its inhibition by key anti-apoptotic proteins. The release of the apoptogenic mitochondrial factors is mediated by the action of at least three different pro-apoptotic messengers including active Bax, Reactive Oxygen Species (ROS) and the sphingolipid ceramide (shown as red boxes). The stress mediated activation of BH3 only Bcl-2 proteins, of mitochondria (or other ROS producing systems such as NADPH oxidase) and of Sphingomyelinase (SMase) (all three are shown in purple boxes) respectively leads to increased levels of active Bax, ROS and ceramide. Ceramide which serves as the substrate for SMS1, along with inactive Bax, are shown in green boxes. Anti-apoptotic genes have been identified that can prevent cell death in response to increases for all three factors (shown in blue boxes). Bcl-2 can prevent the effects of active Bax, ROS scavenging proteins can prevent the effects of ROS and the ceramide utilizing enzyme Sphingomyelin Synthase 1 (SMS1) can prevent the effects of ceramide. A common mechanism or target that serves to transduce stresses into the processes that activate the three different systems responsible for increasing active Bax, ROS or ceramide is depicted by a black box. A single common target that trifurcates is envisioned due to the observations that overexpression of any one of the three types of anti-apoptotic genes can prevent stress mediated cell death. Thus the stress mediated responses leading to death has characteristics of a linear as well as a series of branched pathways. The insert depicts a simplified model that illustrates the concept of a linear pathway where all anti-apoptotic genes can prevent stress mediated cell death. The cross-talk that occurs between the different branches in the pathway is extensive and can be shown to occur at many levels some of which are shown by connecting arrows. For example, ectopic expression of active Bax leads to activation of all three branches since increases in ceramide and ROS are also observed. Further insight is provided by the observation that overexpression of many other anti-apoptotic sequences such as the genes encoding a variety of chaperone or heat shock proteins can also prevent cell death in response to the activation of one or all three branches of the stress pathway. An alternative scenario that is not depicted, to explain the close interrelationships between the different processes would be a modified rheostat model. Cell death in response to stress occurs when a certain threshold concentration of pro-apoptotic second messengers is reached. Stresses increase the concentration of many of these messengers while any gene or process that decreases the levels of any of the second messengers reduces stress and decreases the likelihood that cell death inducing cascades are triggered.

and thus serve to mediate an increase in survival responses [76,87]. Thus Bcl-2 may simultaneously and independently inhibit both Bax and serve to activate cellular defense systems. The later function was supported by the observation that decreased Bcl-2 expression leads to increased oxidative stress while Bcl-2 overexpression leads to reduced oxidative stress [88,89]. An alternative scenario suggests that ROS may serve as a direct activator of the Bax activating BH3 Bcl-2 Bnip3 protein [90]. Further cross-talk is evident by the observations that increases in the levels of ceramide can serve to trigger increases in ROS while others have shown that increased ROS can increase ceramide levels [91–93]. The ability of ceramide to assist activated Bax in forming mitochondrial pores represents another manifestation of the cross-talk present in the system [94]. More recently, a direct role for the pro-apoptotic Bcl-2 protein Bak has been proposed for the production of ceramide in response to apoptotic stimuli [95]. In spite of this, very little is known regarding how stress is transduced into increases in ROS, ceramide or activated Bax (Fig. 2). In fact, there is no clear evidence to differentiate whether increases in ROS or ceramide or the activation of Bax represent the initial event serving to trigger stress-mediated apoptosis. Thus, the process by which stress initiates apoptosis remains undefined [13,75,94].

The difficulty in identifying and assigning function to pro-apoptotic factors is made easier by the identification of anti-apoptotic sequences that prevent the activation or promote a decrease in the levels of ROS, active Bax or ceramide. For example, overexpression of numerous genes encoding ROS scavengers such as glutaredoxins, peroxiredoxin, superoxide dismutase and glutathione peroxidase, the gene encoding the ceramide utilizing Sphingomyelin Synthase 1 (SMS1) or of the gene encoding the Bax inhibitory protein Bcl-2 can prevent stress mediated apoptosis in many cells [10,77,96–104]. In keeping with the intimate nature of cross talk between the three factors, any one of the three different anti-apoptotic genes can serve to prevent apoptosis in response to Bax, ceramide or ROS. Thus, somewhat paradoxically, increases in the levels of activated Bax, ROS or ceramide all can serve to activate apoptosis while individually blocking anyone of these is sufficient to prevent apoptosis. We have developed a schematic depiction of the interrelationships between the Bax, ceramide and ROS with stress and cell death (Fig. 2). In spite of the inadequacy of the model, it is quite clear that advances in our understanding of anti-apoptosis does lead to increases in our understanding of the paradigms involved in the processes of regulated cell death.

It is of interest to note that a number of lower eukaryotes, such as yeast, undergo stress mediated dependant programmed cell death (PCD) in spite of the fact they do not appear to have a Bax orthologue [58,105]. This is evidence in support of ROS or ceramide as the central mediator of apoptosis. Nevertheless, it should be noted that the existence of a possible functional homologue of Bax has been suggested by the observations that ectopically expressed mammalian Bax and Bcl-2 appear to retain their ability to regulate apoptosis in yeast [75]. In addition, as observed in mammalian cells, heterologously overexpressing active Bax in yeast leads to increases in stress mediated cell death that can be blocked by simultaneously overexpressing the Bax inhibitor Bcl-2 or genes encoding ROS scavengers or a ceramide utilizing protein [101,106–110].

In addition to ROS and ceramide a number of other intracellular second messengers such as calcium and the nucleotide 2′-Deoxyuridine 5′-Triphosphate (dUTP) have also been shown to trigger apoptotic responses [111–114]. Although a role for dUTP in selectively killing cells has been long ago identified in fruit fly development, more recent evidence suggests that it has a more widespread role in initiating pro-apoptotic responses [113,115,116]. This nucleotide is known to cause DNA damage and cell death when it is misincorporated into DNA [113,114,117]. In effect, elevated dUTP levels are responsible for the apoptotic inducing effects of many chemotherapeutic compounds that promote cell death at least in part by creating nucleotide pool imbalances (i.e. thymidylate synthase inhibitors) [113,118]. Further dUTP incorporation into the genome of viruses may be a common mechanism that is used by infected cells to kill viruses or to undergo suicide [114]. Not surprisingly, many viruses encode their own dUTPase [114]. Once again the importance of these second messengers is highlighted by the observations that calcium binding proteins such as fortilin as well as the dUTP metabolizing enzyme dUTPase are capable of preventing cell death in response to some stresses when overexpressed in cells [111,113] (Khoury and Greenwood, unpublished).

2.2. Negative regulation of apoptosis

Cells monitor their environment and continuously make decisions as to whether they should continue living. When faced with a potential apoptotic signal the cell wants to avoid triggering premature or unneeded apoptosis all the while it wants to make sure to initiate apoptosis if the signal is of significant intensity. This is achieved by balancing pro- and anti-apoptotic machineries [38,42,43]. In the lab we can determine the maximum dosage of a stress (a combination of time of exposure to and concentration of the agent used) that will give rise to no death [119–121]. Hydrogen peroxide (H_2O_2) is a commonly used agent to induce apoptosis and is an excellent stressor that can serve to illustrate this point. In our hands, dose response/viability curves using H_2O_2 have shown that 24 h exposure to 0.6 μM H_2O_2 for C_2C1_2 mouse myoblast cells and 4 h exposure to 0.8 mM H_2O_2 for wild type yeast are the maximum dosages causing no or little cell death in these cells. At this dosage of stress, the cells are not undergoing apoptosis because they are actively resisting cell death. Evidence that this must be true, is based on the observation that such mild non-apoptotic inducing stimuli is able to induce apoptosis in cells having reduced expression levels of a number of different genes encoding different anti-apoptotic proteins such as the lectin galectin 3, the Bcl-2 family members Mcl-1 and Bcl-xL as well as enzymes like sphingosine kinase-1 due to knock outs or siRNA [99,122–128]. Thus, the absence of anti-apoptotic genes increases sensitivity to sublethal apoptosis inducing agents. It follows that an increase in the levels of anti-apoptotic genes leads to increased resistance to apoptotic stimuli. Thus, the minimum dosage of a stress required to kill a cell that is overexpressing anti-apoptotic genes is increased. This leads to the workable definition of an anti-apoptotic gene as a sequence that decreases or increases cell survival in response to a given dose of stress if its levels are respectively decreased or increased [12,38,96,99,122–141]. Genetic redundancy in different anti-apoptotic processes make it so that a number of genes can prevent apoptosis when overexpressed while their loss does not enhance apoptotic responses. An impressive number of functionally diverse genes that behave as anti-apoptotic sequences have been reported (see Section 4.2). The number of yet to be characterized candidate anti-apoptotic genes identified in screens or as genes that are up-regulated in apoptotic resistant cells clearly indicates that the list is not yet complete [142–148].

It is worth mentioning that there are three well characterized anti-apoptotic family of proteins including FLICE-inhibitory proteins (FLIPs), Bcl-2 and Inhibitors of Apoptosis Proteins (IAPs) that are described in most discussions of caspase dependent apoptotic pathways (Fig. 1) [1,42,44]. Of great importance in the regulation of apoptosis is the Bcl-2 Homology domain (BH) domain containing family of proteins. This family contains both negative and positive regulators of apoptosis with Bax being the most studied pro-apoptotic member while Bcl-2 the most studied anti-apoptotic member [10,74]. Bcl-2 antagonizes the effects of Bax and prevents the release of cytochrome c. Bcl-2 function is not limited to inhibiting Bax since Bcl-2 can inhibit apoptosis in response to microinjected cytochrome c and when overexpressed in yeast cells in spite of the fact that the yeast genome does not encode a direct Bax orthologue [106,107,149,150]. In contrast to the intrinsic pathway, the initiation of the apoptotic signaling cascade by the stimulation of Death receptors appears to more closely resemble a traditional cytokine type signaling cascade [151]. Nevertheless, this pathway is also negatively regulated in order to prevent inappropriate cell death. FLIPs (FLICE Inhibitory Protein) represent the most commonly examined inhibitor of the extrinsic pathway. FLIPs contain the same DED domain as caspase 8 and can thus compete with and prevent caspase 8 activation by interfering with its recruitment to the activated receptor [152]. The third well-studied class of cell survival proteins is the family of Inhibitors of Apoptosis (IAPs). These serve to bind and inhibit both initiator and effector caspases thus they can regulate both forms of apoptosis [153]. This functional class of protein was first described in the genome of baculovirus and underlines the resources placed by viruses in controlling apoptotic responses [154].

Directly antagonizing pro-apoptotic proteins and increasing the expression levels of anti-apoptotic genes, including genes involved in metabolizing pro-apoptotic second messengers, are likely the most commonly reported pro-survival strategies [4,42]. Other ways to increase survival in response to stresses include a diversity of other processes, some of which like the receptor mediated activation of kinase cascades (i.e. Extracellular Regulated Kinases (Erk1/2) and Akt kinases) are rapid since they can occur in the absence of new RNA or protein synthesis [69]. Our understanding of the diversity of the anti-apoptotic processes, the diversity of the anti-apoptotic genes involved as well as the mechanisms by which some of these processes and genes function to counteract apoptotic responses has been greatly enhanced from the study of cells showing enhanced resistance to cell death inducing stresses and processes.

3. Anti-apoptotic and pro-survival pathways and processes identified in apoptotic resistant cells

Cells that show increased resistance to stress are characterized by their requirement for higher levels of apoptotic stimuli for cell death to be induced. A wide variety of cell types can show increased resistance which can be induced by a wide variety of different conditions. The ability to evade apoptosis has been shown to be induced by a range of different alterations including physiological changes such as the activation/up-regulation of mitogenic signaling pathways (i.e. Erk1/2, Akt), the inactivation/downregulation of certain apoptotic molecules (i.e. Fas receptor, Bax) [69,130,155,156]

to the up-regulation of a number of anti-apoptotic genes such as Bcl-2 and cFLIP [157,158]. Thus in the next sections we will describe conditions that serve to render cells more resistant as well as the wide diversity of known mechanisms that confer anti-apoptotic phenotypes to these cells.

3.1. Pre-conditioning

Brief sub-lethal periods of stopping and re-starting blood flow (ischemia/reperfusion) are found to induce a phenotype that is protective to the effects of longer periods of ischemia/reperfusion [52,53,159,160]. Although this process likely occurs in all cell types, it has been extensively studied (at least for metazoans) in the heart and the brain, historically due to the importance that ischemic events have in the etiology of heart attacks and strokes [52,53,159,161]. Consequently, we largely focus our discussion on these systems since our understanding of the process of pre-condition mediated anti-apoptosis is likely best understood in these cells. Ischemic pre-conditioning gives rise to two temporally distinct types of protection. Classical pre-conditioning provides a temporal window of protection that occurs minutes after the pre-condition stimulus (which usually consists of 3–4 short periods of ischemia/reperfusion) [52,53,160]. The protection can last up to 120 min and involves a number of signaling proteins including the activation of multiple protein kinase cascades such as ERK and Akt, many of which are known to have anti-apoptotic properties [53]. In response to the same stimuli, a second form of pre-conditioning, called late onset pre-conditioning is also induced. This provides long-term protection that lasts 24 to 72 h after the pre-condition stimulus [52,53,160]. This form of pre-conditioning requires protein synthesis and involves the increased expression of a number of genes that encode proteins such as heat shock proteins (HSPs), anti-oxidants, ceramide utilizing enzymes, as well as a number of other anti-apoptotic genes, many of which encode proteins of unknown function [52,53,162]. That these genes are anti-apoptotic is demonstrated by the fact many of them decrease ischemia/reperfusion mediated death when overexpressed in the hearts of transgenic mice [96,97,135,136,163]. Similarly, protection from apoptotic stimuli is also observed when individual anti-apoptotic genes are overexpressed in cultured cells [47]. In addition to increasing the expression of anti-apoptotic genes, it should also be noted, although not dwelled upon here, that the protection provided by late onset pre-conditioning might also occur via other mechanisms such as the decrease in the expression of pro-apoptotic genes such as Bax.

The protective effects of ischemic/reperfusion pre-conditioning can also be mimicked in cultured cells [119–121,164]. Thus in spite of the availability of a number of animal models, cultured cells including primary cultured cardiomyocytes and neurons have been extensively used to study pre-conditioning [165–168]. Of interest here, it was found that pre-conditioned like apoptotic resistant phenotypes are not exclusively dependant of the use of mild ischemia/reperfusion as the stimulus. In effect, resistance to apoptotic inducing doses of practically any apoptotic-inducing agent is sufficient to confer a cytoprotective pre-condition like phenotype. In mammalian organisms, the cytoprotective effects of pre-conditioning appears to be mediated by the release of a number of agents including agonists for G-protein coupled receptors (GPCRs) like adenosine, adrenergic and opioids [49]. Although these agonists can confer cytoprotective effects in cultured cells, their release is not responsible for mediating the effects of all pre-conditioning agents. A wide range of different agents and environmental stresses have been shown to induce pre-condition like effects. Global gene expression methodologies including gene chips, proteomics and subtractive hybridization experiments as well as candidate gene approaches reveal that increased expression of anti-apoptotic genes is also a common mechanism that serves to invoke increased survival phenotypes in response to a wide variety of different pre-conditioning agents and conditions in whole animals and in cultured cells [159]. Some examples include human fibroblasts subjected to microgravity stress on the space shuttle, cardiac cells of mice pre-treated with hydrogen sulfide showed increased protection against the stress of ischemia/reperfusion, the retina of hyperoxic and hypoxic conditioned mice pups, the nucleus accumbens region of the brain of rats in the early acute phase of alcohol withdrawal and exogenously supplied ceramide to primary rat cortical neurons, the use of heat pre-treatment to protect from stresses such as the ROS donor hydrogen peroxide as well as the use of low sublethal levels of the ROS donor hydrogen peroxide to protect against serum depletion mediated apoptosis [119–121,147,167,169–172]. In addition pre-condition like phenotypes that are at least partly dependant on the increased expression of survival genes is a highly conserved process that is observed in a number of different species including bacteria, yeast and lower metazoans [162,173–175]. The similarity in the process between metazoans and protozoans is such that many mammalian anti-apoptotic genes can functionally serve to protect yeast cells from stress mediated apoptosis [105,176].

Pre-conditioning mediated cytoprotection induced by sub-lethal levels of different stresses appears to be mediated by the increased expression of a core group of powerful anti-apoptotic genes. These include gene encoding ROS scavengers as well as heat shock proteins (HSPs) and other chaperones. HSPs actually represent a large number of different proteins that belong to a number of different sub-families [177,178]. Although originally identified as proteins whose expression are increased in response to heat stress, different HSPs are now known to be also induced and to protect cells from a variety of apoptotic inducing stresses as well as having functions in homeostasis such assisting in protein folding [179]. HSPs likely protect cells by assisting in refolding proteins denatured due to stresses as well as assisting to target damaged proteins for degradation. The HSPA/HSP70 sub-family, which consists of at least 13 different members, is one of the largest and most widely studied HSPs. A number of studies have demonstrated that overexpression of members of the HSP70 sub-family can protect cells from different apoptotic inducing stresses [180,181]. Other anti-apoptotic functions of HSP70 and other HSPs have been reported including preventing the release of pro-apoptotic factors such apoptosis inducing factor (AIF) from the mitochondria [182]. Although all HSPs are considered chaperones, there are a number of proteins that function as chaperones without being HSPs. Some of these chaperones with anti-apoptotic functions include members of the Bcl-2-associated anthanogene (BAG) and clusterin families [183,184]. Some of these proteins, like BAGs likely serve to inhibit apoptosis by acting as co-chaperones for other proteins like HSPs although there is recent evidence that BAGs may be cytoprotective by inducing autophagy (see also Section 5) [185,186]. This belies one of the central themes of anti-apoptosis that proteins capable of preventing or repairing stress mediated cell damage are likely to be cytoprotective [4]. In addition to commonly up-regulated genes, there appears to be subset of genes that are up-regulated by specific stresses. For example, DNA damaging agents will lead to the up-regulation of DNA repair enzymes that will then serve to protect DNA damaged cells [81]. In the absence of DNA damage, these genes are unlikely to be cytoprotective and thus will not be induced by agents not damaging DNA. One somewhat surprising finding is the observation that stresses that could be expected to illicit similar damages on a cell, such as two different donors of reactive oxygen species (ROS) can have significantly dissimilar patterns of altered gene expression [80,81]. This suggests that there is a large and complex repertoire of stress activated cytoprotective genes that are available for the cell faced with different stresses.

Although a number of permutations on the process of pre-conditioning that have been described, two of these including post-conditioning [187] and remote pre-conditioning [188,189] are worth discussing here. As mentioned above, administration of a pre-

conditioning stimulus prior to a major ischemia/reperfusion event in a tissue such as the heart will lead to cardioprotection as judged by a decreased infarct size. Surprisingly, post-conditioning is the phenomena where a pre-conditioning type stimuli administered after the cardiac apoptotic insult will still result in the same degree of cardioprotection. This has clinical implications since, patients are usually seen after and not before and ischemic/reperfusion event. Mechanistically, this suggests that anti-apoptotic processes can override apoptotic-inducing signals even after they have been initiated. On the other hand, remote pre-conditioning is a process that leads to protection at sites that are distant from the site that is subjected to a pre-condition regimen. Thus, a series of short ischemic/reperfusion events to a limb can lead to induction of a cytoprotection program in a remote area like the heart. This suggests that cells undergoing pre-conditioning release a factor or factors (like receptor agonists, as discussed above) that can diffuse and induce anti-apoptotic effects in other cells. The clinical application of remote pre-conditioning has shown some promise as well as some limitations [166,189,190].

3.2. Cancer

Normal cellular homeostasis is maintained by a balance between the processes of growth and cell death. Imbalances in either can lead to uncontrolled cell growth and the development of cancer [11,158,191]. Thus constitutive activation or increase of many mitogenic proteins such as myc, src and ras or growth promoting pathways such as mitogenic activated protein (MAP) kinases, epidermal growth factor receptor (EGFR) and phosphatidylinositol 3-kinases (PI3K) often lead to uncontrolled growth that serves to promote oncogenesis [69,156]. Alternatively, altered regulation of the process of apoptosis has also been linked to all the different processes of oncogenesis including initiation, progression and metastasis [4,34,35,43,45]. Given that the development of an anti-apoptotic phenotype is one of the hallmark characteristic that is required for cells to become cancerous, our understanding of the processes that can lead to anti-apoptosis is probably best characterized in cancer cells [38,43,158,192,193]. In effect, the prototypical Bcl-2 family member, Bcl-2 was originally identified as an oncogene gene whose expression was increased in most follicular lymphomas due to a reciprocal chromosomal translocation (t14; 18) [194,195]. Over-expression studies revealed that Bcl-2 was an atypical oncogene since it did not serve to promote growth instead it was found to prevent cell death in response to different stresses. These studies served as a prelude to the development of our understanding of the central importance of the different pro- and anti-apoptotic members of the Bcl-2 family in the regulation of cell death [74].

A variety of other alterations that lead to increased resistance to apoptosis has been described in different cancer cells [4,34,35,43,45]. These include a decrease in the expression of pro-apoptotic genes such as Bax as well as decreased signaling from death receptors. Nevertheless, the up-regulation of anti-apoptotic genes is likely the most commonly reported mechanism used to evade apoptosis. The genes identified to be up-regulated include the commonly observed anti-apoptotic genes such as Bcl-2 and c-FLIP. Other common anti-apoptotic genes that have been shown to be ubiquitously up-regulated include a variety of heat shock proteins and chaperones as well as genes encoding scavengers of reactive oxygen species (ROS) [4,46,60,196]. Characterization of genes up-regulated in cancer cells has also served and will likely continue to serve to identify many novel anti-apoptotic genes [142,145,146,148,197]. For example, Abtraham et al. [142] identified a number of up-regulated genes in HeLa cells. Of these, metalloproteinase 15 (MMP-15) was chosen for further study and it was shown that it prevented apoptosis when overexpressed in both HeLa and human lung adenocarcinoma. This suggests that in addition to its potential to promote tumor invasion in its role as an extracellular matrix proteinase, MMP-15 may also be involved in oncogenesis as an anti-apoptotic gene. The realization of the importance of the increased expression of many different anti-apoptotic genes in mediating the process of tumorigenesis has lead to development of pharmacological strategies in order to target these proteins as adjuvants to enhance the effects of existing therapeutics [44,126,127,133,134].

Anti-apoptotic phenotypes of tumor cells are developed in response to the stressful microenvironments, that include limitations on nutrients and oxygen availability, in which they develop [46,158,198]. These stresses are similar to the effects that sublethal levels of stresses have on all cells and are reminiscent to what occurs in response to pre-conditioning. Similar types of phenotypic changes occur in cancer cells that develop resistance to chemotherapeutic agents. For example, gene chip screens identified cell survival or anti-apoptotic genes as a major class of genes up-regulated in numerous cells that develop resistance to a multitude of chemotherapeutic agents including resistance to histone deacytylase inhibitors in colon cancer cell lines [44,145,148,199].

3.3. Synaptic activity and other neuronal processes

Neuronal activity serves to promote cell survival, at least in part, through the activation of neurotransmitter *N*-methyl-D-aspartate (NMDA) glutamate receptors [200]. The neuronal calcium transients elicited by the stimulation of NMDA calcium-permeable ion channels serves to activate a survival program that has similarities to the processes observed in pre-conditioning. Physiological, pharmacological as well as gene chip experiments indicate that early NMDA mediated cytoprotection involves activation of survival proteins like kinases while longer lasting cytoprotection involves the up-regulation of anti-apoptotic genes and the down regulation of pro-apoptotic genes. Recent papers by Bading's group has used gene chips to identify hundreds of genes that are differential expressed in response to NMDA stimulation or synaptic activity in cultured hippocampal neurons obtained from newborn mice [143,144]. Further, functional analysis of a subset of these genes served to identify Bcl6 and Btg2 as novel neuronal survival genes. A number of other up-regulated genes, including many that are categorized as Activity-regulated Inhibitor of Death (AID) genes, await further analysis. The increased synaptic activity observed in these kinds of studies is related to the formation of new neuronal connections that occurs during synaptic plasticity. These results suggest that stimulation of endogenous anti-apoptotic pathways may also have therapeutic potential in limiting apoptosis in neurological degenerative diseases such as Alzheimer's, Parkinson's or stroke [41,55,201]. The concept of invoking anti-apoptotic processes has also been explored for a number of other neurological diseases such as glaucoma [202]. Glaucoma is a neuro-ophthalmological disease that is a common cause of blindness that occurs because of inappropriate apoptosis of retinal ganglion cells (RGC). Although intraocular pressure (IOP) is a common risk factor, the exact PCD trigger remains largely unknown [203]. Nevertheless, the loss of trophic support is a likely factor given that neurotrophic agonists such as Brain Derived Neurotrophic Factor (BDNF) can play a protective role [203]. As all other cells examined, RGC's are capable of mounting pre-conditioned like protective defense mechanisms in response to mild stress. In RGC's, the expression of a number of potential anti-apoptotic genes is increased in response to different forms of stress [204]. One such gene heat shock protein 27 (hsp27) is induced by a variety of stresses including ischemic pre-conditioning [205]. In addition, its overexpression has been shown to increase resistance to stress mediated cell death in cultured rat ganglion cells [206]. This brings up the concept, which we will discuss in more detail later on (see section 4.5), that the ability to exploit the endogenous anti-apoptotic machinery to prevent stress mediated cell death is likely to be useful strategy to treat a variety of neurological diseases with increased

apoptosis including glaucoma, Multiple Sclerosis (MS), stroke, epilepsy, amyotrophic lateral sclerosis (ALS) [48,202,207–209].

A variety of other receptor agonists as well as other diffusible agents such as the autocoid neuroprotectin 1 (NPD1) are also capable of preventing apoptosis in neuronal cells [210]. NDP1 is produced in by the action of the 15-lipoxygenase on the essential fatty acid docosahexaenoic acid (DHA). Although the exact molecular targets of NDP1 are not well known, it does exert profound neuroprotective effects in response to multiple stresses including diseases states. In addition, NDP1 production is increased in response to stresses like oxidative stresses. These effects of NDP1 are illustrated in recent study that demonstrated that NDP1 enhanced the survival of retinal ganglion cells of animals that underwent optic nerve transection [211]. The observations that endogenous levels of NDP1 as well as the levels of 15-lipoxygenase gene expression were increased following the optic nerve axotomy suggests that NDP1 levels are part of the neuronal cells anti-apoptotic response.

3.4. Hypometabolic conditions

Many organisms go through a resting type phase that allows them to survive prolonged periods of severe stresses. Well-studied examples include hibernation as well as the phenomena of diapauses [212–214]. The later process is used to describe numerous phenomena such as the "dauer" stage in *Caenorhabditis elegans*, spore stages seen in many protozoans such as yeast and slime mold, as well as the pause that is observed in mammalian pre-implantation embryos [214]. Hibernation on the other hand is seen in a range of organisms but is probably best described as a "sleep-like" stupor observed in numerous animal species including many mammals. These dormancy stages allow for survival in stressful environmental conditions such as extremes in temperature and long-term decreased availability of nutrients including energy sources and water. Survival is enhanced by physiological adaptations such as decreased metabolism that serve to conserve energy as well as genetic adaptations that allows for the activation of genes encoding freeze tolerant proteins. These environmental stresses combined with the intracellular stresses that ensue (i.e., increased accumulation of waste products) are sufficient to induce significant cell death in the absence of stress adaptation. Similarities between resistance to dormancy and to ischemia/reperfusion have been noted [159,215,216]. In effect, as observed in preconditioning mediated resistance to ischemia/reperfusion stress, there is increased expression of anti-apoptotic genes in both animals that are dormant and that are arousing from hibernation. Many of the genes identified are ubiquitous such as HSPs, anti-oxidants and mitogenic kinases. Mitogenic kinases including ERK1/2 are thought to be anti-apoptotic by virtue of their ability to promote cellular proliferation while other kinases such as Protein Kinases A and C are sometimes pro- and sometimes anti-apoptotic [69]. Nevertheless there are reports on the identification of a variety of other genes of unknown function that suggest that increasing our understanding of the stress protective mechanism of hibernation will lead to the elucidation of novel anti-apoptotic processes many of which may have clinical value [216–220].

3.5. Global stress responses

In response to stress, cells have evolved defense mechanisms in order to prevent, repair and generally mitigate damage [4,60,177]. One of the earliest described pro-survival processes, originally identified as a global response to UV mediated DNA damage, was the bacterial SOS response in *E. coli* [81,221]. The mechanisms by which DNA damage is transduced into physiological and genetic responses to counter the negative effects of the stress are elegant and complex processes. Some of these are worthwhile discussing here in a little detail since they may be the best-characterized stress responsive systems and as such, they serve as models to develop our understanding of similar global stress responsive systems in eukaryotic cells [81]. In a simplistic way, the SOS system is in large part dependent on the constitutively expressed LexA sequence specific DNA binding transcriptional repressor. During normal growth, LexA is bound to and represses the expression of a number of genes containing a so-called SOS motif. Upon DNA damage, replication is stopped at the area of damage and this allows the RecA protein to bind to single stranded DNA that becomes exposed at the site of the stalled replication forks. This serves to activate the protease activity of RecA and together with other proteins, activated RecA assists in the degradation of the LexA protein. The decrease in LexA levels leads to transcriptional derepression and activation of the transcription of the LexA repressed genes. Thus, there is an increase in the levels of the expression of several genes, the products of which serve as the coordinated survival response to the damaged DNA. In a analogous fashion to DNA damage response, cells mount a global response to the stress of heat shock, the Heat Shock Response (HSR), a process that is largely mediated by an increase in the activation and synthesis of a specific transcription activator (σ^{32} in bacteria and Heat Shock Factor, HSF in eukaryotes) that occurs in response to the accumulation of denatured and misfolded proteins [60,177,222]. In the case of HSR, the genes that are induced largely consist of Heat Shock Proteins (HSPs) and proteases that act respectively as chaperones to assist in the refolding and in the degradation of misfolded proteins. Depending on the protein and the cellular context, misfolded proteins can be targeted for degradation by the well-known 20S proteosome, the lysosome or the autophagosome [178,223]. In bacteria, the DegP protein, which is a member of the highly conserved HtrA (high temperature requirement protein A) proteases, is an interesting example. This protein is a crucial stress response protein that has both chaperone and protease function and is thus involved in the recognition and the degradation of misfolded proteins [224]. Activation of existing proteins and pathways combined with changes in gene expression is a common theme that serves to mediate immediate and long-term protective strategies in response to multiple different stresses.

Similar, although more complex stress responsive processes are present in eukaryotic cells. Global stress responsive pathways have been shown for DNA damage, heat and cold shock, osmotic stress, oxidative stress, mechanical stress, hypoxia, starvation (autophagy), metabolic stress, the stress of unfolded proteins in the ER (Unfolded Protein Response, UPR) as well as the stress of caused by pathogens such as invading viruses [3,60,81,177]. There are a number of unique processes that occur in response to specific stresses. For example, osmotic stress brings about physiological changes to the levels of osmolytes that serve to rectify the stress-mediated alterations. This process has been well characterized in yeast and requires the activation of a specific MAP kinase cascade (HOG pathway) [225]. These global stresses will lead to PCD, via the activation of the typical pathways, if they are of sufficient intensity. Thus the overexpression of most common anti-apoptotic genes such as ROS scavengers and heat shock proteins will typically serve to delay or prevent cell death in response to global stresses [4,177,226].

3.6. Aging

Aging is a multifaceted progressive process that involves a gradual decrease in an organism's function that serves to decrease viability and to increase the risk of death [227]. Over the years, many hypotheses have been devised to help explain the defects that accumulate during the process of aging [228–232]. A central role for alterations in energy metabolism as well as an increase in the accumulation of ROS and subsequent increases in the accumulation of cellular damage have served as a focus for much research. As in apoptosis, these defects point to the mitochondria as a central regulator of aging. Although it has

been difficult to pin down in higher eukaryotes, it is nevertheless clear that aging is caused by PCD at least in lower eukaryotes [57,233]. The identification of the yeast sir2 (silent information regulator 2) and its functional counterparts in other species including the mammalian orthologue SIRT1 (Sirtuin 1) as proteins that extend lifespan have served to confirm the evolutionary conservation of the aging process [230,234]. The fact that SIRT1 can prevent apoptosis while other mammalian anti-apoptotic genes may serve to extend lifespan also strengthens the concept that aging mediated cell death is likely a programmed cell death involving the apoptotic or necrotic machinery [56,234,235]. In addition to SIRT1, there are a total of seven SIRT genes that encode class III histone deacytylases [234]. These serve in a variety of different cellular processes including senescence, aging, apoptosis, proliferation and cell cycle regulation. The identification of polyphenols from different food sources such as resveratrol from red wine as well as a decrease caloric intake (Calorie Restriction or CR) as processes that can activate of sir2/SIRT1 has served as a central theme and has also generated an enormous interest in aging/pharmaceutical research [230,232]. In spite of these successes, the search for regulators of the aging process continues [230]. For example, a recent study identified lithocholic acid as an intracellular lipid as a negative modulator of aging in yeast that could among other things negatively regulate mitochondrial mediated cell death [236]. Other intracellular modulators of aging include spermidine [235]. Activation of the protective effects of autophagy appears to be the mechanism by which some of these compounds including spermidine as well as sirtulins delay aging [237,238].

An alternative approach to aging research is focused on the differences that exist in the lifespan of different species [228]. Many invertebrates such as mollusks as well as mammals such as certain whale species can live hundreds of years [229,239]. Combined genomics and physiological approaches with long-lived species may yield clues as to the aging process. Research with some long-lived bat and bird species has identified ROS as being of central importance [231]. For example, the mitochondria of a long lived species of brown bats appear to produce less ROS per unit oxygen consumed than other similar but short lived animal species [240]. On the other hand, resistance to ROS mediated damage is higher in some long-lived bird species [241]. Overall, an understanding of the mechanisms that a cell has evolved to prevent aging will certainly increase our understanding of the regulatory mechanisms that serve to delay apoptosis.

4. Identification of anti-apoptotic sequences

Analysis of global gene expression profiles in apoptotic resistant cells has successfully identified a number of genes that are up-regulated in different types of apoptotic resistant cells [53,197,242–245]. Many of the genes identified in these experiments have known anti-apoptotic properties such as Bcl-2, Hsp72 or Hsp90 indicating that they may be directly implicated in the ability to evade apoptosis [196]. Although a possible anti-apoptotic role cannot be deduced from the sequences of many of the other up-regulated genes, it has been speculated that many of these represent potentially novel anti-apoptotic sequences. In spite of the fact that many new anti-apoptotic genes have been identified by characterizing some of these up-regulated genes, it nevertheless remains that there usually too many genes shown to be upregulated by gene chip analysis to blindly analyze every sequence for potential anti-apoptotic characteristics [142–148,169]. For example, although MMP15 is an example of a novel anti-apoptotic gene that was originally identified as being up-regulated in a tumor cell line, the same study reported a number of other up-regulated genes whose potential as anti-apoptotic regulators has not been characterized [142].

Alternative approaches have been successful in identifying anti-apoptotic genes. For example, the anti-apoptotic Bag protein was identified as a Bcl-2 interacting protein using a two-hybrid interaction screen that was subsequently found to enhance the pro-survival effects of Bcl-2 [246]. In genetic systems such as yeast and *C. elegans*, screening for mutants that show increased sensitivity to different stresses have lead to the identification of novel pro-survival genes [213,247]. Although many of these genes are specific to the model organisms, a large number of these have functionally conserved orthologues in mammalian cells, and given the interchangeability of many genes in these systems, it is likely that many will have the same function in mammals [16,105,176]. Although identical genetic screens cannot be carried out in mammalian cells, a number of approaches such as using global siRNA screens have nevertheless been fruitful in identifying apoptotic regulators [248–250].

4.1. Yeast as model system to identify novel mammalian anti-apoptotic sequences

Yeast is a genetic system that has served to unravel as well as identify genes involved in a number of basic processes such as cell cycle control, aging (the red wine anti-aging compound resveratrol was first identified in yeast) as well as autophagy [21,237,251–254]. The insights provided by yeast in developing the framework for our understanding of these and other basic cellular processes is exemplified by the fact that 2 yeast researchers (L. Hartwell for work with *Saccharomyces cerevisiae* and P. Nurse for work with *S. pompei*) were awarded the 2001 Nobel prize in medicine [254,255]. More recently yeast as well as most eukaryotic unicellular organisms have been shown to undergo genetically encoded cell death that is mechanistically similar to the process of mitochondrial PCD seen in metazoans [16,256–261]. A large number of different studies over the last ten or so years have served to demonstrate that the yeast *S. cerevisiae* is a widely used and effective model to study apoptosis [57,233,261,262]. Although yeast apoptosis was initially controversial, its acceptance is now widespread [57,105,263–265]. Given that yeast is such a powerful genetic system, dissecting out the process of PCD in yeast is likely to lead to increases in our knowledge of PCD in much the same way that yeast has served to increase our understanding of other basic cellular processes. In effect, the similarity and the functional interchangeability between many different yeast and human genes is so common [176,255], it is not surprising that mammalian genes identified as negative regulators of PCD in yeast screens, are also anti-apoptotic when expressed in mammalian cells [266–269]. Although yeast is emerging as a widely used model largely because of its amenability to genetic approaches, there are a number of other systems that have been developed that provide novel advantages for the study of cell death [59]. For example, studies of crustacean models of cell death have revealed similarities as well as differences in both pro- and anti-apoptotic processes [270]. For example, some animals like shrimp appear to have enhanced ability to tolerate viral infection by a process termed viral accommodation [271]. Thus, further studies in other model systems will likely identify novel anti-apoptotic processes.

Thus, the genetically tractable yeast provides an alternative strategy to screen for and identify novel anti-apoptotic sequences. A commonly used screening system involves the use of yeast strains that conditionally express a cDNA for an active form of the mammalian pro-apoptotic Bax [105,272–274]. Although yeast does not contain Bcl-2-like proteins, the heterologous expression of pro-apoptotic Bax or Bak in yeast serves to induce death in a process that is mechanistically similar to what occurs in mammalian cells [75,274–277]. Numerous groups have exploited the conditionally lethal Bax-dependent phenotype as a system to screen heterologous cDNA libraries and identify novel anti-apoptotic sequences [101,109,110,266,268,272,278,279]. Many of the genes thus identified have also served to shed light on the process of anti-apoptosis. For example, the identification of ROS scavenging proteins as suppressors of the lethal effects of Bax expression clearly implicates the role of ROS

in PCD in yeast [108–110]. The anti-apoptotic nature of some genes, like sphingomyelin synthase 1 (SMS1) [101], identified in such a screen has been confirmed in mammalian cells [100,138,280].

4.2. The repertoire of mammalian anti-apoptotic genes

The anti-apoptotic Bcl-2 is likely the most studied and potent anti-apoptotic gene and it displays many of the characteristics of the ideal anti-apoptotic gene [44,195]. Bcl-2 is ubiquitously and constitutively expressed so that its inactivation results in enhanced cell death in response to stimuli. It is up-regulated to prevent apoptosis under many conditions that serve to enhance cell survival including the stress that fast growing tumor cells must withstand. A commonly occurring chromosomal translocation resulting in increased expression of Bcl-2 is present in many tumors [194]. Thus Bcl-2 is responsible for one of the hallmarks or tumor formation in many cancers, namely the ability to evade apoptosis [11,158]. Functionally, it is well known as a suppressor of the pro-apoptotic Bcl-2 member Bax. In spite of this, Bcl-2 is likely to have other anti-apoptotic functions that are Bax independent [281]. In addition, Bcl-2 may be one of the earliest anti-apoptotic genes described. In effect early reports clearly identified that the oncogenic effects of Bcl-2 was due to ability to prevent cell death and not due any growth promoting properties [194]. Here we will discuss the large of other anti-apoptotic genes have now been described.

A comprehensive list of anti-apoptotic and cell survival genes is difficult to compile. An analysis of the results of searches of the existing literature on Pubmed, using keywords including anti-apoptosis and cell survival genes, revealed a multitude of papers that describe over 150 different unique genes. In addition, there are 785 anti-apoptotic gene entries in the Gene Ontology database (http://www.geneontology.org/). The later list is an over estimation since it contains the same gene from multiple species as well as certain amount of other types of redundancies such as the inclusion of genes encoding matching receptor–ligand pairs. Both lists are incomplete since they lack some anti-apoptotic type genes. This later part reflects the lack of a commonly used gene ontology for pro-survival genes as well as a few other problems such as the fact that many anti-apoptotic genes are also reported to be both anti- and pro-apoptotic genes. This later fact may reflect differences in the function of alternatively spliced variants, in different members of the same gene family as well as cell type specific differences. For example, the mammalian gene encoding transforming growth factor-beta stimulated clone-22 (TSC-22) is a leucine zipper containing protein that serves as a transcription co-factor [282] and it has been reported to be both pro- and anti-apoptotic [283–286]. The confusion is likely due, at least in part that there are four different alternatively spliced TSC22 genes in both the mouse and human genomes [285,286]. Further examples of genes with dual roles include ligands for certain G-Protein Coupled Receptors (GPCRs) that bind more than one receptor subtype. For example, adrenaline mediated stimulation of the β1- and the β2-adrenergic receptors respectively lead to pro- and anti-apoptotic responses [287]. What is nevertheless noteworthy is the diversity in the function of the different anti-apoptotic and cell survival genes. Depending on the classification used, there at least 11 different functional categories that are represented. They include the classical anti-apoptotic sequences such as Bcl-2, IAPs and cFLIP [10,42,152,288], chaperones including those involved in the proper folding of proteins after ER stress as well as a number of heat shock proteins [196,289–291], the genes encoding anti-oxidant proteins or free radical scavengers such as superoxide dismutase (SOD) [292–294], a number of different types of receptors including GPCRs, steroids, cytokines and receptor tyrosine kinases [65,71,200,295–300], enzymes including a number of kinases such as ERK1/2 as well as a varieties others such as sphingomyelin synthase and dUTPase [100,101,113,156,280,301], integrins and gap junctions like connexins [302,303], mitochondrial proteins including proteins involved in electron transport [268], a large number of different transcription factors including FOXO and NFκB as well as other DNA and RNA binding proteins some of which are involved in repairing DNA [304–307], proteins involved in regulating protein translation such as the eIF4G family member DPA5 [308] and a variety of bacterial and viral proteins many of unknown function that can inhibit cell death in their host [42,154,309].

Finally, there are a large number of anti-apoptotic genes that are categorized as functionally unknown. Not only are the mechanisms by which they prevent apoptosis not known, their basic function in the cell is often unknown. This is the case for the family of Gadd45 family of three proteins. GADD45 (Growth Arrest and DNA Damage inducible) are conserved genes that are inducible in response to stress and that can serve both pro- and anti-apoptotic functions [310]. Many other proteins are like the family of proteins called BAG. These represent a complex family of proteins that are conserved from yeast to plants to man [183]. As described above, they were originally identified as Bcl-2 interacting protein that had anti-apoptotic effects when overexpressed. They are classified as chaperones but how they function as anti-apoptotic proteins remains largely unknown. A recent study suggests that at least one family member may be involved in the UPR responses that protects from ER stress [311]. Another interesting example of a functionally orphan anti-apoptotic sequence is the human TMEM85 gene. It was originally shown to function as an anti-apoptotic gene by preventing Bax and ROS mediated cell death in yeast [312]. Although its function is still unknown, a recent study of the yeast orthologue (*YGL231c* now *ECM4*) suggests that it is part of multiprotein endoplasmic reticulum complex that appears to be involved in regulating ER stress [313]. These results are consistent with the previous observation that yeast cells lacking *YGL231c* are more sensitive to the apoptotic inducing effects of the Parkinson's associated α-synuclein [314]. In addition, the list of anti-apoptotic genes is likely to continue to get larger. Some of these new genes will come from the genes, that have been shown and that will likely be shown in the future, to be up-regulated in apoptotic resistant cells [142–148]. Other sources of novel anti-apoptotic genes will come from genetic screens [248,249,315]. For example, a number of groups have reported isolating multiple mammalian cDNA sequences that can prevent Bax mediated cell death in yeast but have yet to characterize most of these [101,266,268,272]. Thus, the examination of known anti-apoptotic sequences serves to highlight the diversity of the anti-apoptotic processes as well as illuminating the fact that significant gaps in our knowledge still exists.

4.3. siRNAs increase the repertoire of anti-apoptotic sequences

The traditional well known mechanisms controlling the levels of protein produced from a gene involves a number of different regulatory steps. These include processes that regulate the level of transcription of the gene, post-transcriptional events such as regulating the processing and the half life of the unprocessed and mature mRNA, post-translational mechanisms that regulate the rate of translation of the mRNA into protein as well as the half life of the protein itself. One of the most recent additions to these regulatory processes is RNA interference (RNAi) [316,317]. RNAi is a post-transcriptional mechanism that involves the production of small RNA molecules that are capable of binding to mRNA molecules and inhibiting their translation and possibly, at least in some species, enhancing the degradation of the mRNA. Although a great deal of information has been uncovered regarding the production and the processes involved in siRNAs, an in depth discussion is beyond our scope here but more information can be obtained from the existing reviews on the subject [318–320]. There appears to be over 700 different genome encoded siRNAs that are involved in regulating hundreds of different genes [318]. Our understanding of their

importance is likely incomplete but we do know that they are involved in regulating a multitude of cellular and physiological processes including apoptosis and thus they behave as global regulators. A well characterized example is miR21 [320,321]. The levels of miR21 are increased in number of cancers and its anti-apoptotic effects appear to be due to its ability to decrease the expression oncogenes including pTEN and TPM1 [318]. In a more recent study, miR21 was also identified as one 40 differentially regulated miRs in the hearts of pre-conditioned rats. The ability to downregulate or overexpress miR21 in vivo and in cultured cardiomyocytes suggested that increases in miR21 levels is directly involved in mediating the anti-apoptotic phenotype associated with pre-conditioning [322]. Further studies suggested that the gene encoding Programmed Cell Death 4 (PDCD4) may be the miR21 target in cardiac cells. Although the exact function of PDCD4 is not known, it nevertheless induces apoptosis when overexpressed in cultured cardiomyocytes [322]. Thus, a miT|R21 mediated decrease in the expression of a pro-apoptotic gene like PDCD4 may lead to the observed increase in cell survival. These as well as other types of screens for miRs will have diverse impacts on our understanding of the processes of anti-apoptosis. For example, Sheng et al. [315] carried out a complex but elegant reverse suicide screen using a mouse malignant glioma cell line engineered to survive if the expression of the anti-apoptotic activating transcription factor 5 (ATF5) is down regulated. They were thus able to determine that two kinase pathways, RAS-MAP and PI3 kinases lead to increased ATF5 expression and a cytoprotective phenotype by mediating an increase in the transcription of the anti-apoptotic MCL-1 gene.

4.4. Alternative splicing of anti-apoptotic genes

Alternative splicing is a common phenomenon of mammalian genes that often leads to the production of more than one protein from a single gene [323]. A recent investigation has suggested that 92–94% of human genes are alternatively spliced and that 86% of these genes produce low abundance splice variants [324]. Our own studies reflect this since we have shown that all four of the human Bax suppressors that we have characterized from our screen of mammalian cDNA libraries in yeast are encoded by complex alternatively spliced genes [101,286,312,325]. One of the prominent members of these genes encodes sphingomyelin synthase 1 (SMS1). SMS1 is likely to be anti-apoptotic by virtue of its ability to use the pro-apoptotic sphingolipid ceramide as a substrate as well as the fact that it produces the growth promoting diacylglycerol (DAG) [326]. The mouse SMS1 gene is composed of 12 exons that are alternatively spliced to produce three different proteins [327]. The 363 residue form of SMS1 is thought to be the enzymatically active protein while the C-terminally truncated forms of the protein are lacking more than half of the protein and appear unlikely to be active. This has number of functional implications including the observation that many of the proteins produced by alternative splicing lack a functional domain but retain their ability to interact with and often serve to inactivate the full-length functional protein. This type of alternative or regulated splicing appears to be a commonly observed phenomenon for genes encoding proteins that are involved in regulating stress and apoptosis in mammalian as well as yeast cells [328–330]. For example, the truncated form of the BH3 Bcl-2 member Nix, sNix, is anti-apoptotic by virtue of its ability to bind to and inhibit the pro-apoptotic Nix protein[331]. This serves to indicate that the repertoire of pro- and anti-apoptotic proteins will also require a complex understanding of the entire transcriptome and proteome [332,333].

4.5. Clinical implications of apoptosis

Disregulated apoptosis is involved in pathophysiologies of numerous diseases and disease processes [1,17,191]. Cancer and auto-immune diseases are the classical examples but not the only diseases where anti-apoptosis is increased. In contrast, an increase in apoptosis or a decreased ability to carry out anti-apoptosis is a prominent part of many diseases such as Alzheimer`s and Parkinson`s as well a number of pathophysiological processes such as ischemic strokes and heart attacks [8,41,55,334]. Although disregulated apoptosis is not necessarily the trigger that initiates many of these diseases, the ability to control apoptosis would likely go a long way as functional therapies. Consequently, there are a large number of studies that are trying to decipher the apoptotic processes disregulated in specific diseases as well as developing drugs that can block specific or general pro- and anti-apoptotic proteins and processes [34,41,50,55,198,335,336]. For example, decreasing the levels of the mRNA for the anti-apoptotic galectin-3 gene using siRNA increased the sensitivity of tumor cells to the death inducing effects of two different routinely used chemotherapeutic drugs cisplatin and 5-fluorouracil [122].

Given that caspases are key mediators of the cellular damage that occurs during apoptosis, it is not surprising that they have attracted a great deal of attention as potential drug targets [337]. In spite of the fact that caspase inhibitors exist, they have nevertheless been reported to have a limited ability to prevent cell death in different pathophysiologies [40,41,337,338]. This observation is consistent with the idea that in addition to caspase dependant apoptosis, cells have a multitude of different genetically programmed ways of killing themselves (i.e. autophagic and necrotic programmed cell death (PCD)) especially when apoptosis is blocked [25,338–342]. Thus a cell that faces conditions requiring suicide can do so in caspase dependant or independent manner [262,338]. Caspase independent processes leading to apoptosis can be mediated, at least in some circumstances, by the release form the mitochondria of pro-apoptotic proteins such as Endonuclease G (Endo G) and Apoptosis Inducing Factor (AIF) [15]. When endonuclease G is released from the mitochondria, it migrates to the nucleus and catalyzes nuclear DNA cleavage in stressed cells. AIF is a mitochondrially localized NADH oxidase that is also released due to the mitochondrial membrane permeabilization in stressed cells. Cellular damage is then mediated by cytosolic and nuclear localized AIF. Similar to what is observed with caspase inhibitors, anti-oxidant agents, which are known to prevent ROS mediated cell death in cultured systems, are not as effective in preventing cell death in the whole animal [40]. In contrast, the overexpression of a number of anti-apoptotic genes, including genes coding for caspase inhibitors such as IAPs and anti-oxidants proteins, leads to decreased cell death following ischemic/reperfusion injury or other pro-apoptotic situations in the heart and brain [41,97,98,135–137,163,343–345]. This is in line with the observation that anti-apoptotic genes are more anti-death genes that are capable of blocking caspase dependant and independent pathways [40]. It is thought that strategies that serve to mimic naturally occurring “anti-apoptotic” states are likely to have a greater clinical efficiency than drugs that inhibit pro-apoptotic proteins [4,40,41,48,346,347]. Thus strategies and methodologies are currently being developed that would promote increased levels of these anti-apoptotic sequences either by injecting recombinant proteins that can cross a cell's lipid bilayer and remain functional [40,50,348–351] or by injection of a cDNA (naked or viral) that can be taken up and expressed in the cell to make the anti-apoptotic protein [40,352,353]. The expression of such proteins in tissues such as heart is likely to be transient but this would be sufficient since anti-apoptotic protection would only be required for limited times after an ischemic/reperfusion event.

A further proof of the usefulness of anti-apoptotic genes to prevent apoptosis is provided by the biotechnology and pharmaceutical industries. Mammalian cell lines are routinely used to produce a variety of biopharmaceutical products such as recombinant proteins

and monoclonal antibodies. The production of these products generates a multitude of environmental and intracellular stresses that serves to induce apoptosis. For many years, cell lines that overexpress a variety of different anti-apoptotic genes such as Bcl-2, XIAP and Hsp72, have been generated in order to limit apoptotic cell death and to increase the yield of products produced [47]. The ability to limit apoptosis is also of interest in other biotechnologically important cells such as yeast [354].

5. Autophagy and autophagic death

The processes and regulatory mechanisms by which cells actually commit themselves to cellular suicide are not as cut and dried as described above. The cell has also evolved a multitude of other pathways that can be used to promote cell killing under appropriate conditions. The complexity and the cooperative nature of the cell death processes are apparent in Bax/Bak double knock out MEF cells [340–342]. Although these cells are unable to activate the normal pro-apoptotic cell death pathway, they will nevertheless undergo cell death using alternative pathways in response to appropriate stimuli. Early studies indicated that the death of Bax/Bak double knock out cells following apoptosis inducing stimuli was likely due to the activation of an autophagic process. Thus, the death was associated with autophagosomes and could be inhibited by chemicals inhibitors of autophagy and it was shown to be dependant of the autophagic genes APG5 and Beclin [342]. More recently, it was shown that ER stress mediated cell death in Bax/Bak double knock out cells was delayed but it appeared to occur via a process that had similarities to necrosis [341]. Autophagy was shown to be activated in response to ER stress in both wild type and Bax/Bak double knock out cells. In wild type cells, autophagy was protective since its inhibition served to enhance ER stress mediated cell death. In contrast, inhibition of autophagy served to protect Bax/Bak double knock out cells indicating that autophagy is involved in mediating cell death.

Studies of regulated cell death have lead to the identification of three major types of genetically programmed cell death (PCD) [1,8,355]. Type I PCD or apoptosis is the best-characterized form while autophagic and necrotic cell deaths are classified respectively as type II and III [1,18,356]. Although a great deal of information has been uncovered regarding the different types of PCDs, many more questions remain to be answered. One of the aspect that remains largely unexplored in any systematic way is the fact that the diversity in the processes involved in promoting PCD suggests that there also exists a large number of different proteins that can prevent the different "specialized" forms of apoptosis [38–41,346].

5.1. Autophagy protects from apoptosis

Autophagy, the process by which cells recycle cellular constituents, is a critical adaptation to starvation and plays an important role in normal cell function and in PCD [21,23,24]. Our understanding of autophagy was greatly accelerated by the identification, by genetic screening in yeast, of 30 or so conserved autophagic genes (ATG) necessary for the process of autophagy [357]. Numerous studies have since shown that these *ATG* genes function in a series of complex interrelated signaling cascades that are involved in carrying out and regulating autophagy [21]. At the macromolecular level, autophagy involves the formation and subsequent engulfment of cellular constituents destined to be recycled into structures called autophagosomes. The mature autophagosomes fuse with lysosomes (vacuoles in yeast) to make autophagolysosomes and the cellular cargo is then degraded into building blocks for the synthesis of new cellular contents or to be used for the energy requirements of the cell [20,25]. Different forms of autophagy exist including many specialized forms such as microautophagy, mitophagy and chaperone mediated autophagy [20,21,25]. These are mechanisms by which cells can get rid of specific proteins or specific subcellular portions. It is thought that constitutively low level of autophagy serves a general housekeeping function to rid the cell of unwanted or damaged material. Here we are more interested in macroautophagy that is activated in times of starvation in order to recycle large amounts of cellular material. This process is clearly of importance since blocking autophagy, either genetically or pharmacologically, leads to rapid cell death in response to starvation [21,358–360]. Autophagy has now been shown to be up-regulated by and serve to protect cells from a wide variety of other stresses including the stress encountered in many diseases such as cardiac ischemia/reperfusion and cancer [20,21,223,361–364]. One way autophagy can serve as an anti-apoptotic process, is by removing mitochondria damaged by stress-mediated increases in ROS (Reactive Oxygen Species) or activated Bax before they get a chance to release their pro-apoptogenic factors such as cytochrome c. The removal of other damaged cellular components such as ER that contain an excess of unprocessed proteins (ER stress) as well as other damaged components may also serve to decrease general stress and prevent apoptosis [360]. The ability to prevent aging mediated necrosis suggests that autophagy may be capable of protecting from extreme stress [235,365,366].

More widespread anti-apoptotic roles for autophagy has been suggested by a few recent studies [186,367–369]. One of these important observations involves a potential link between autophagy and pre-conditioning [22,369,370]. Pre-conditioning refers to the cytoprotective effects that occur when cells are treated with sub threshold and sublethal levels of an apoptotic stimulus [52,162] (see Section 3.1). The up-regulation of different anti-apoptotic genes, in a tissue specific manner, has for quite a while been considered a satisfactory explanation for the effects of preconditioning. More recent studies suggest that pre-conditioning protects cells by an up-regulation of autophagy [22,369,370]. Of similar potential far reaching importance for our understanding of the process of anti-apoptosis is the observation that the cytoprotective effects of overexpressing anti-apoptotic genes may be due to their ability to up-regulate autophagy [186,367,368]. A couple of recent studies have suggested that some anti-apoptotic sequences such as BAG1 and Hsp20 may function to prevent cell death by activating autophagy. This makes a certain amount of inherent logic given that the anti-apoptotic phenotype associated with pre-conditioning is due, at least in part, to the up-regulation of anti-apoptotic genes. It follows that many of the up-regulated anti-apoptotic genes can prevent apoptosis when overexpressed. Since the evidence that the anti-apoptotic phenotype of pre-conditioning can also due to increased autophagy, it seems that the over-expression of anti-apoptotic genes may be a common phenomena responsible for this phenotype. The classical definition of an anti-apoptotic sequence, that in addition to suppressing cell death when overexpressed, cells must show an increased sensitivity to apoptotic stimuli in cells lacking the gene. This is certainly the case for many genes such as ROS scavengers and different heat shock proteins [99,122–128]. These types of anti-apoptotic proteins are likely to play a direct role in the cells anti-apoptotic repertoire. An up-regulation of autophagy is also unlikely to be responsible for the antagonist effects of other anti-apoptotic processes such as the ability of Bcl2 to directly interfere with the pro-apoptotic function of activated Bax [10]. On the other hand the up-regulation of autophagy may account for other anti-apoptotic scenarios that cannot be easily explained, such as the ability of Bcl-2 to protect cells in a Bax independent manner [149,150]. These represent exciting developments because an up-regulation of autophagy may be a general mechanism by which the myriad of anti-apoptotic genes, many of which with unknown function, serve to prevent cell death. Such a scenario would explain how the deletion of some anti-apoptotic genes does not lead to increased sensitivity to apoptotic inducing stimuli, although it should be noted that other

scenarios such as the redundancy in different anti-apoptotic pathway may be a simpler explanation. Nevertheless, the concept that autophagy is central to the process of anti-apoptosis is in line with the complex cross talk that is already known to occur between the different PCDs [281,339,355,356,371].

5.2. Autophagic mediated cell death

Type II PCD was coined autophagic cell death since the typical markers of apoptosis were absent and numerous autophagosomes were observed in the dying cells. Although there is a great deal of evidence that autophagy can lead to cell death, there is now a growing movement that is re-evaluating how strong is the evidence for the widespread occurrence of autophagic cell death [25]. One of the strongest examples in support of this challenge comes from inhibitory studies. The cytoprotective role of autophagy is easily demonstrated in response to many stresses since the inhibition of autophagy leads to enhanced cell death [21]. Therefore, it is argued that blocking autophagy should enhance cell survival in cells undergoing type II autophagic cell death [25,365]. The inability to prevent cell death by blocking autophagy may be due to several factors including the number of limited studies that have addressed the issue as well as the fact that pharmacological inhibitors used to block autophagy are rather non-specific. In addition, most genetic approaches used in mammalian cells involve siRNAs and that such knockdowns of anti-autophagic genes may not be sufficient to prevent autophagy [25,372–374]. The ease by which strains having knockouts of autophagic genes can be used facilitates our ability to address these and other questions in yeast [57,235,375].

Differing opinions regarding a potential role for autophagy in autophagic type PCD remains given that there are a number of other examples that argue for the importance of autophagic cell death

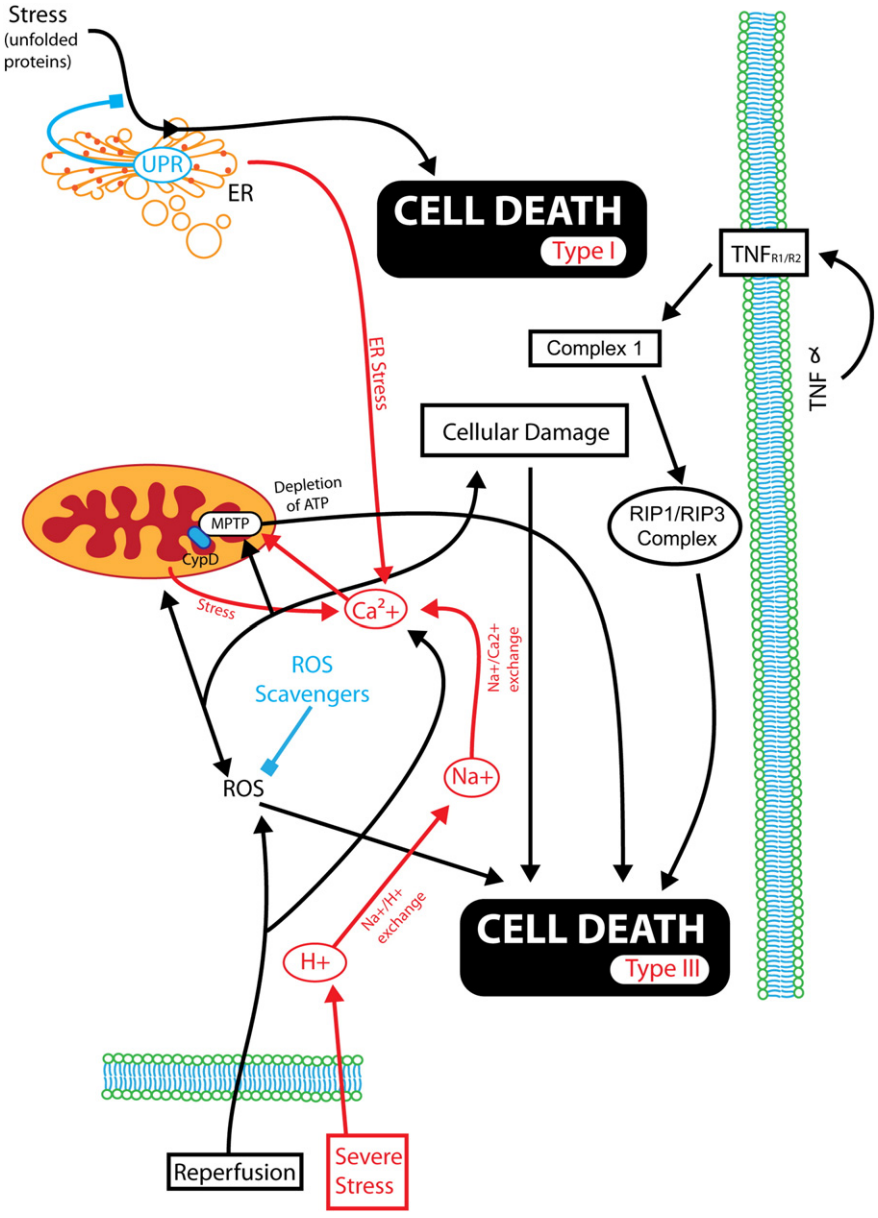

Fig. 3. Autophagy or type II PCD. Nutrient depletion mediated activation of TOR (Target of Rapamycin) is the best characterized mechanism that serves to activate autophagy. In its simplest form, autophagy is best known as a complex cellular process that is activated in response to the stress of nutrient deprivation that serves to recycle cellular constituents in order to promote survival. A great deal of evidence is accumulating that this form of autophagy is activated by many mild forms of stresses, including pre-conditioning, in order to serve as the central cellular control site to prevent premature or inadvertent cell death from all three PCD processes. Type II PCD or autophagic cell death can occur in response prolonged autophagy as well as in other circumstances such as when type I PCD is blocked (not shown, see text for details).

[223,363,373,376]. For example, autophagic like PCD occurs in response to apoptotic stimuli in cells that are unable to carry out apoptosis due to pharmacological inhibition or due to specific gene knockouts (double Bak and Bax KOs) [25,342,377]. Thus it is argued that autophagic cell death is an important backup mechanism to ensure cell death is carried out. The consensus seems to suggest that autophagy is protective at first but death is observed in cells subjected to prolonged stress that results in prolonged activation of autophagy [378–380] (Fig. 3). It remains to be determined if autophagic death following prolonged stress is due to cellular exhaustion and/or depletion of cellular components or if it is due to the activation of a specific PCD mechanism that serves to actively kill cells. Our preliminary results, favours the later since we have identified a human sequence that was found as a Bax suppressor in yeast that can prevent cell death in response to prolonged periods of starvation in yeast or when autophagy is activated with the TOR inhibitor rapamycin [381]. The observation that cell death could be delayed with a specific gene suggests that autophagic cell death is a genetic process that is regulated and not simply a death brought upon by exhaustion. The fact that we could not prevent autophagic cell death with all of our Bax suppressors suggests that autophagic cell death does not function by activating common apoptotic pathways. The similarities, differences and cross-talk between autophagic and apoptotic cell death is a current topic of high interest [17,191,339,355,356,382].

5.3. Clinical implications

The growing realization of the importance of autophagy in the physiological responses to stresses as well as its importance in pathophysiological processes such as cancer, neurological and cardiovascular diseases is quite obvious from the shear number of reviews published in the first half of 2010 [20,26,237,238,355,383–405]. In cancer it is noteworthy that many autophagic genes are tumor suppressors while a large number of others function as oncogenes. Basal autophagy is thought to function to inhibit the development of tumours while increased autophagy is seen in tumours cells that are stressed because of treatments with chemotherapeutics [362,380,406]. Thus autophagic inhibitors are currently being used and many more are being developed to serve as adjuvants to chemotherapeutics [362,380,406]. In contrast, activation of autophagy in response to stresses such as ischemia may promote cardiac cell survival and thus the development of compounds capable of enhancing autophagy is of interest. The most striking illustration of the potential and far reaching importance of autophagy is the fact that a decrease in aging mediated cell death is observed upon autophagy induction in all species examined so far including yeast, worms, flies, mice and primates [227,235,366]. Thus the identification of novel targets involved in regulating autophagy and autophagic cell death will increase our knowledge of PCDs and may lead to increase therapeutic targets [223,336].

6. Necrotic death

Necrosis or type III PCD is the cell death that is observed in response to severe stresses such that occurs after physical injury or prolonged ischemia [1,2,18]. In fact excessive amount of most apoptotic inducing stimuli will lead to necrosis. Thus, it is common for dose dependant response to apoptotic stimuli to serve to identify sublethal, apoptotic inducing as well supralethal or necrosis inducing levels of stimuli. The mechanisms responsible for triggering necrosis have traditionally received little attention because it was thought to be just a physical process that was not regulated. Evidence is accumulating that strongly suggests that necrosis can be regulated and can occur as an alternative apoptotic independent genetically encoded cell death pathway [18,30,249]. The term necroptosis has been coined to differentiate the regulated form of necrosis from the accidental type of cell necrotic death [338,407]. The identification of chemicals capable of inhibiting necroptosis as well as siRNAs involved in regulating the process strongly suggests that in many cases the cell death process is regulated [18,249,408]. Although necroptosis can occur as part of normal physiological processes such as certain aspects of development, it is common only in cells in which the normal apoptotic pathway is blocked. Thus necroptosis, like autophagic cell death, may serve the function of being a backup system for cellular suicide if the main apoptotic pathway is defective [18,56]. Cross-activation of autophagic (via activated calpain) and mitochondrial (via increased Ca^{++}) death pathways may also contribute to necrotic cell death [33] (Fig. 4). Mechanistically, necroptosis is associated with a depletion in ATP levels and increases in Ca^{++} levels from both

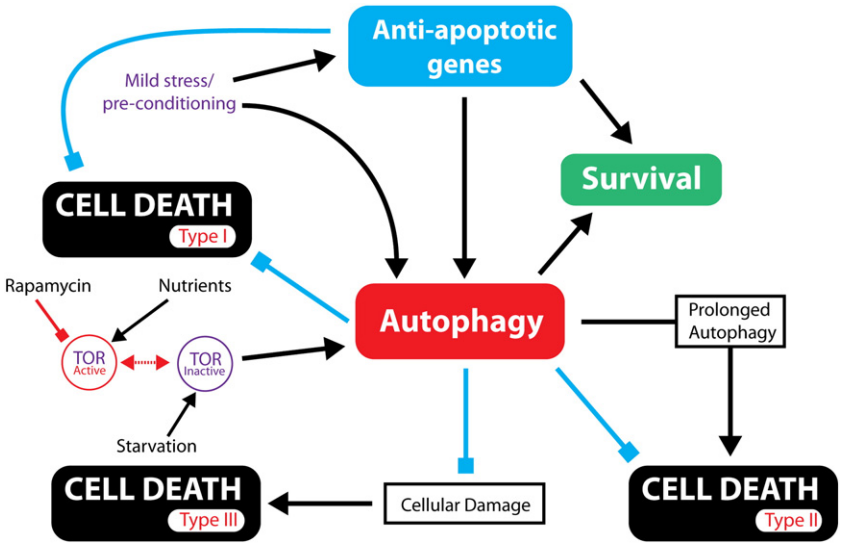

Fig. 4. Necrosis or type III PCD. A genetically encoded form of necrosis is recognized as a form of type III PCD and is often called necroptosis. This process is most commonly observed in conditions of acute stress such as the severe ischemia that occurs following a stroke. This leads to a depletion in the levels of ATP which is one of the better characterized hallmarks of type III PCD. Some intracellular processes such as the accumulation of unfolded proteins that lead to stress in the endoplasmic reticulum (ER, shown as red folds) also serve to activate type I PCD by mediating an increase in the release of calcium (Ca^{+2}) that can cause mitochondrial damage and the release of pro-apoptogenic factors (not shown). The increase in calcium can also serve as the mediator of cross-talk since it can also activate type III or necrotic PCD. Stimulation of TNF receptors, well known to induce extrinsic apoptosis, may also lead to cell death by necroptosis via the RIP3 complex./RIP3 complex.

external and ER sources. Increases in Ca^{++} can activate calpains that can lead to lysosomal rupture and the release and activation of proteases such as cathepsins and cellular destruction. Necrotic cell death has recently been shown to play an important role in cell death associated with aging in yeast and mammalian cells [235,409]. Further, it was found that the addition of spermidine can protect aged cells from necrotic death via a process involving the induction of autophagy [235].

Clinically, necroptosis occurs in all tissue subjected to ischemia but the process has received more attention with respect to ischemic brain injury [33]. Areas of severe ischemia die by necrosis while less severely affected cells undergo apoptotic cell death. It is thought that the development of inhibitors of necrosis would have beneficial effects on stroke patients. In spite of the recent knowledge of necroptosis, many questions remain including what are the mechanisms responsible for the rupture of the lysosome? Even though calpain activation is associated with this event, there is no evidence that blocking calpain will prevent rupture or necrosis. Identification of targets of calpain would be useful in further delineating the processes involved in triggering necrosis. Some clues as to the mechanism(s) mediating increases in the lability of the lysosomal membranes comes from the observation that it is more prevalent following the degradation of iron rich materials due to increase in redox active iron within the lysosomes. The fact that intralysosomal chelation agent desferrioxamine protects against cell death is consistent with this concept [410]. Thus specific conditions may serve to prime the cell for necrosis.

7. Alternative forms of programmed cell death

There are a number of other forms of PCD that have been documented [36,191]. Many of these processes like anoikis (greek, homelessness), mitotic catastrophe and pyroptosis (greek, fire or fever) were first identified as being triggered by unique stimuli, respectively as detachment of cells from their substratum (or from the neighboring cells), premature entry into mitosis and infection by a variety of organisms such as *Salmonella* [37,45,411]. Although there are a number of unique features associated with these processes, such as the activation of caspase 1 for pyroptosis, it remains to be determined if any of these alternative processes are unique forms of PCD or if they, like necroptosis (see above) represent subforms of the existing types of PCD [36,191]. Nevertheless, studies of the mechanisms used to escape cell death from these other forms of PCD have identified some novel mechanisms used to prevent cell death as well as serving to develop therapeutic strategies for a number of pathologies. For example, avoiding anoikis mediated cell death is a common and likely necessary feature of tumor cells that are undergoing metastasis [34,45]. Studies of metastasizing cells have lead to the identification of genes such as the focal adhesion protein Talin1 and the neurotrophic receptor TrkB as anti-anoikis genes [412,413]. On the other hand, bacteria and viruses have developed a variety of strategies to prevent host mediated self-destruction including activating the endogenous anti-apoptotic processes and genes or by expressing their own anti-apoptotic genes [42,51]. Studies with these kinds of inhibitors will be useful in delineating the unique and common features of these types of PCDs.

8. Perspectives

The cellular mechanisms responsible for preventing cell death in response to increasing stresses and to the activation of apoptotic pathways represent complex and diverse mechanisms. Although our understanding of anti-apoptosis has increased dramatically over the last few years much remains to be elucidated. Nevertheless, a number of recent developments clearly indicate that our ability to manipulate the endogenous anti-apoptotic processes, as opposed to inhibiting apoptosis per se, will lead to functional therapies for a number of diseases and pathophysiologies. Finally, one promising area of research that has not been covered in this review is the emerging importance of human embryonic stem cells. These cells can be used to differentiate into a variety of specialized cell types and thus provide a source of purified specialized cells that can be used to shed light on cell type specific anti-apoptotic processes [414].

Acknowledgments

Work in MTG's laboratory is supported by NSERC, the ARP program at the Royal Military College and the Heart and Stroke Foundation of Canada.

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