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Multi-author Reviews

Apoptosis – the story so far...

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Abstract. The process of programmed cell death, or apoptosis, has become one of the most intensively studied topics in biological sciences in the last two decades. Apoptosis as a common and universal mechanism of cell death, distinguishable from necrosis, is now a widely accepted concept after the landmark paper by Kerr, Wyllie and Currie in the early seventies [1]. Different components of the death machinery in eukaryotes are discussed in this issue.
Key words. Apoptosis; necrosis; macromolecular degradation; oncogenes.

Introduction

Cell division, growth, differentiation and finally death are highly regulated events during the normal development of cells. Studies on dying cells reveal two distinct types of death, 'necrosis' and 'programmed cell death'. The two processes are fundamentally different in their nature and their biological significance. Necrosis, or 'accidental' cell death, is the nonphysiological or passive type of cell death [2], and it is usually caused by extreme trauma or injury to the cell [1]. During necrosis chromatin adapts a highly flocculated form, and the DNA from these cells is digested randomly to give a smear when analysed by agarose gel electrophoresis. The main feature of necrosis is an increase in cell volume. This occurs because of the loss of control of ion flux resulting in changes in osmotic pressure as Na^+, K^+, Ca^{2+} and Mg^{2+} move down their respective concentration gradients. This in turn leads to uptake of water, giving rise to high amplitude swelling of the cell and its organelles. Irreversibility of the changes that occur in the cell is usually heralded by disruption of the mitochondrial structure. The rapid increase in cell volume results in membrane rupture and cell lysis [3]. Release of the dying cells' contents into the extracellular space can cause further injury or even death of neighbouring cells, and may result in inflammation or infiltration, leading to further tissue damage [4].

The concept of a programmed physiological cell death, on the other hand, was suggested since the early days of developmental biology and embryology, and refers to the type of cell death that occurs at a specific time during the development of the organism. Glucksmann clearly emphasized the existence of this phenomenon for the first time in 1951 [5]. In the 1960s the concept of programmed cell death was revived. So-called physiological cell death was reported by many groups to occur during development under a wide range of circumstances and conditions [6–11]. Subsequently, hormones and/or growth factors were identified as the chemical signals required for this type of cell death without having a toxic effect on nonresponsive cells [12].

The first direct evidence for the existence of two distinct types of cell death came from histochemical studies of lysosomal changes in hepatic ischemia by Kerr and co-workers in the 1960s and 1970s [1, 13, 14]. Kerr observed development of rounded masses in dead hepatic tissue and noted morphological differences between this form of cell death and necrosis. These differences initially caused some confusion, and the process was mistaken for a variation of necrosis and was called 'shrinkage necrosis' [13]. The following year Kerr, Wyllie and Currie proposed the name 'apoptosis' [1].

Intracellular alterations during apoptosis

Apoptosis is the most popular and fashionable death mechanism from the research point of view [for reviews, see refs 15–20]. It has been described as a form of cellular suicide, since death appears to result from induction of active processes within the target cells [21]. The term 'apoptosis' was derived from a Greek word that describes the process of leaves falling from a tree or petals from a flower [1]. The process of apoptosis is morphologically and biochemically distinct from necrosis. Classical apoptosis involves margination and condensation of nuclear chromatin at early stages (py-

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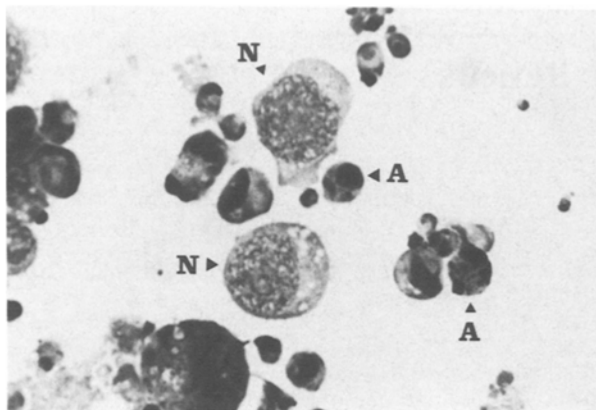

Figure 1. Morphological features of HL-60 cells undergoing apoptosis. Cells were treated for 4 h with 5 μg/ml of camptothecin. N = normal cells, A = apoptotic.

knosis), cytoplasmic shrinkage, membrane blebbing, nuclear fragmentation and finally formation of apoptotic bodies. Considerable biochemical changes occur within the apoptotic cell to facilitate neat packaging and removal of apoptotic bodies by the neighbouring cells (fig. 1).

One of the cellular modifications occurring in apoptotic cells is in the cytoskeleton. The plasma membrane becomes untethered and undergoes rapid blebbing or zeiosis [22]. There is some evidence suggesting the involvement of microfilaments and microtubules, two components of the cytoskeleton, in the progression of apoptosis. Inhibition of protein kinase C (PKC), which is involved in the assemblage of microfilaments, by staurosporine and cytochalasin B prevents formation of apoptotic bodies [23]. Microfilaments are composed of actin filaments; in the absence of actin polymerization, cells undergoing apoptosis, lose cell volume but do not fragment into apoptotic bodies [23]. On the other hand, disruption of microtubules is also reported to induce apoptosis [24].

Tissue transglutaminase, Ca^{2+}-dependent protein-glutamine γ-glutamyltransferase, has also been shown to be induced and activated in liver hyperplasia and glucocorticoid-treated thymocytes [25]. This enzyme cross-links cytokeratin, a component of cytoskeleton, through ε-(γ-glutamyl)lysine bonds. During apoptosis there is a significant increase in transglutaminase mRNA, protein, enzyme activity and protein-bound (γ-glutamyl) lysine [25]. It is thought that transglutaminase activity may stabilize apoptotic cells and inhibit membrane leakage by forming a shell around the cell.

A critical part of apoptosis is the efficient recognition and removal of these cells by phagocytes [26–30]. This involves rearrangement and biochemical alteration of the plasma membrane in the dying cell. There are a number of different biochemical changes which occur in the membrane of apoptotic cells; one such change results in alteration of carbohydrates on the plasma membrane, helping preferential binding of macrophages to apoptotic cells [26]. Recognition of apoptotic cells by macrophages can also be mediated via the vitronectin receptor (CD36) [30]. Another significant change in the membrane of apoptotic cells is the loss of membrane phospholipid asymmetry, detected by externalization of phosphatidylserine at the surface of cells that enables their recognition by macrophages [27]. Development of fluorescently labelled Annexin V, which binds specifically to phosphatidylserine residues, enables detection of this externalization in cells undergoing apoptosis [31]. However, it should be noted that in in vitro culture conditions where phagocytic cells are absent, apoptotic cells and their fragments lyse in a process very similar to necrosis. This is termed secondary necrosis.

Cell volume shrinkage during apoptosis is due to budding of the endoplasmic reticulum. Vesicles thus generated migrate and fuse to the plasma membrane and release their contents into the extracellular region. This process requires energy [adenosine triphosphate (ATP)], since water is moved against the osmotic gradient and up to 30–50% of the cell volume is reduced [22]. Mitochondria, which remain structurally and functionally intact during this process, provide the necessary energy.

Some of the active processes in the dying cell include specific patterns of DNA, rRNA and protein degradation. Three patterns of DNA degradation are already recognized to occur during apoptosis. One or more of these may occur during the progression of apoptosis in a single cell. These are single strand nicks [32, 33], large DNA fragmentation of 50–200 kbp [34, 35] and finally nucleosome size fragments of 180–200 bp size [36–38]. Internucleosomal DNA fragmentation was first demonstrated in glucocorticoid-induced apoptosis in thymocytes [37]. It is now suggested that at early stages of apoptosis single strands of DNA are nicked; this is followed by fragmentation into 50–200 kbp (large fragments) and eventually into nucleosomal fragments (i.e. size of DNA wrapped around a histone octamer). The ladder pattern produced at the late stage during most apoptotic cell deaths is a result of cleavage of internucleosomal linker DNA, and is suggested as the biochemical hallmark of apoptosis [37]. One or more nuclear endonucleases are suggested to be responsible for this pattern of DNA fragmentation, since isolated nuclei can be induced to produce the same pattern [39–41]. A number of endonucleases have been identified in different cell systems with different ion requirements for activity. For example, in thymocytes the endonuclease is Ca^{2+}/Mg^{2+}-dependent, whereas the endonuclease in HL-60 cells appears to function independently of these ions [41]. Figure 2 demonstrates a typical internucleosomal DNA ladder on agarose gel.

A selective and specific cleavage of 28S rRNA, with no effect on 18S rRNA, has been reported in a number of

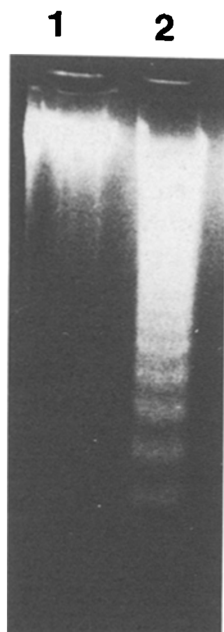

Figure 2. Photograph of a 1.5% agarose gel electrophoresis of DNA extracted from HL-60 cells. Lane 1, untreated; lane 2, cells treated with 5 μg/ml of camptothecin for 4 h. The ladder pattern is a result of ~200 bp internuclosomal DNA fragmentation.

cell systems [42, 43]. While working on gene expression during cAMP-induced apoptosis in IPC-81 cells, Houge and co-workers first observed this peculiar pattern of rRNA fragmentation [42]. This selective rRNA fragmentation has been shown to correlate positively to internucleosomal cleavage of DNA in a number of cell lines studied [42, 43].

A role for proteases in the apoptosis machinery has also been suggested [44]. The initial evidence for such involvement came from studies on apoptosis induced by cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. These cells induce apoptosis by attaching themselves to target cells and releasing the contents of their granules, which contain a number of serine proteases. One such enzyme, granzyme B/fragmentin-2, has been shown to cleave at Asp residues [45]. More recently, several mammalian proteases have been discovered that have homology to *ced-3* [46], which is one of the death genes of the much investigated nematode *Caenorhabditis elegans*. These proteases include interleukin-1β converting enzyme (ICE), CPP-32/apopain, ICH1/Nedd-2, TX/ICH-2, MCH-2, -3 and -4 and MIH-1, all of which induce apoptosis when transfected into cells. Some of the substrates of these proteases, which have been shown to be cleaved during apoptosis include poly-(ADP-ribose) polymerase (PARP), lama B1, α-fodrin, topoisomerase 1 and the 70-kDa protein component of the small nuclear ribonucleoprotein U1 [44, 47, 48]. Of these, PARP, which is a substrate of CPP-32, has received considerable attention in recent years. The PARP enzyme is involved in DNA repair; it is activated by DNA nicks and is recruited to sites of damage where it activates DNA repair enzymes [49]. PARP is cleaved rapidly during apoptosis induced by a variety of agents, suggesting that this may be an integral event in the apoptosis process. Cleavage of PARP prevents its DNA binding ability and thus compromises the response to DNA damage [50, 51]. Furthermore, PARP has a negative regulatory effect on the Ca^{2+}/Mg^{2+}-dependent endonuclease [52] which cleaves DNA during apoptosis.

Cellular signalling during apoptosis

An elaborate network of signalling systems leads to the regulation of physiological processes such as cell-cell communication, proliferation and differentiation. Signal transduction is also thought to play a key role in the onset of apoptosis, and this may be mediated by an increase in intracellular Ca^{2+} levels, PKC or cAMP/PKA. One example is that of activation-induced cell death (AICD) in T-cell lymphocytes. AICD is so called because many hematopoietic, or myeloid, cells can be induced to undergo apoptosis by cross-linking specific receptors or Ags with specific antibodies. AICD in many cell types is accompanied by the morphological features of apoptosis [53–56]. The response of T cells to CD3-ligand binding is proliferation in post-thymic cells, whereas in intrathymic cells the response is apoptosis [57, 58]. Early observations by Kaiser and Edelman in 1977 showed that glucocorticoid-induced cell death involved Ca^{2+} influx in lymphocytes [59]. Later they demonstrated that this type of cell death can be mimicked using calcium ionophores [60]. Based on these observations, it appears that intracellular Ca^{2+} levels may initiate the signal for cell death in this system.

The role of protein kinases and phosphatases in apoptosis is unclear. Protein kinases transfer the terminal phosphate group of ATP to serine/threonine or tyrosine residues in substrate proteins, while phosphatases remove phosphate from these proteins. One of the classical signalling pathways is that of PKC [61], a multifunctional serine/threonine, proteolytically activated, phospholipid-dependent protein kinase that responds to increased intracellular levels of Ca^{2+} and utilizes diacylglycerol as second messenger [62].

Kizaki and colleagues reported that treatment of mouse thymocytes with phorbol esters, which activate PKC, induces apoptosis and that the PKC inhibitor H7 inhibited apoptosis induced by A23187 [63]. However, most of the evidence to date indicates that PKC activation inhibits apoptosis. An example of this is inhibition of thymocytes by PKC to undergo apoptosis induced by glucocorticoids, A23187 and anti-CD3 antibody [57, 64]. On the other hand, Martin and Cotter reported that PKC may not be involved in apoptosis of certain cell lines like HL-60 [24].

Similarly, the role of protein phosphatases (PPs) during apoptosis is not clear-cut. Boe and co-workers [65] reported that a number of cell lines react to okadaic acid (OA) by undergoing morphological changes typical of apoptosis. These findings were in line with work carried out by Samali and Cotter on a number of leukemic cell lines (unpubl. observ.), while others [66] reported that inhibition of PP activity blocks apoptosis in some other cell lines.

These reports appear to suggest that the role of PKC and PPs in apoptosis is cell-type dependent and that protein activation/modification rather than de novo protein synthesis may play an important role in the mechanism of apoptosis.

Apoptosis may also be induced by activation of Fas signal [56, 67, 68]. Apo-1/Fas (CD95) is a transmembrane molecule belonging to tumour necrosis factor (TNF) and the nerve-growth-factor receptor family characterized by cysteine-rich extracellular domains [69]. Cross-linking of Fas molecule with anti-Fas antibody or its natural ligand (Fas ligand) can result in a rapid and massive induction of apoptosis. Cross-linking of Fas is suggested to result in activation of specific signals which are thought to involve production of ceramides. Ceramides are the product of sphingomyelin hydrolysis in response to extracellular stimuli and are thought to be a possible mediator of cell death [70].

Oxygen radicals and antioxidants in apoptosis

Oxygen is a necessary molecule for a number of metabolic processes, but its by-products are highly toxic. Reactive oxygen species (ROS), like peroxides, superoxide and hydroxyl radicals, are suggested as mediators of apoptosis [71–73]. ROS are known to induce cell death under a variety of conditions [22]. Interestingly, many of the agents commonly used to induce apoptosis also induce oxidative stress in the cell, and a number of antioxidants, radical scavengers and metal-ion chelators have been shown to inhibit characteristic features of this type of cell death [74–76].

Genetic control of apoptosis

Since the early years of the 'apoptotic age', the programmed nature of apoptosis suggested the existence of one or more death genes. In the 1980s, work by Cohen and others [38, 39, 77] demonstrated that DNA fragmentation associated with apoptosis could be inhibited by pretreating cells with inhibitors of macromolecular synthesis. This suggested a requirement for novel protein synthesis in apoptosis, at least in the immune system. Subsequent work by Martin and co-workers demonstrated that both actinomycin-D and cycloheximide by themselves could induce apoptosis in a number of cell lines [78]. Taken together, these observations suggested that apoptosis can occur via both macromolecular-dependent and -independent pathways.

Identification of deathless mutants of *C. elegans* initiated the search for mammalian equivalents of a cell death gene (*ced*). Central to the process of programmed cell death in *C. elegans* are the *ced-3* and *ced-4* genes. The mutant deathless worms had abnormal *ced-3* and *ced-4* genes, suggesting that the product of normal genes must activate cell death (see ref. 79 for review). The *ced-3* gene was found to show significant homology to human ICE, ectopic expression of which induced apoptosis in fibroblasts [80]. This suggests that ICE and *ced-3* are both functionally and structurally related.

In recent years enough evidence has been gathered to suggest a role for the protein products of a number of proto-oncogenes and tumour suppressor genes in the regulation of apoptosis. These can be grouped into genes whose products are positive or negative regulators of apoptosis. For example, wild-type p53 and *c-myc* are both inducers of apoptosis [81–84]. These two genes were originally identified because of their role in the regulation of cell proliferation. Although deregulated c-myc expression has a potent proliferating effect on the cell, it may also induce apoptosis. The decision to proliferate or die via apoptosis in c-myc overexpressing cells depends on the presence or absence of extracellular survival factors.

Like c-myc, p53 has also been recognized as a key regulatory element in apoptosis. p53 is a transcription factor which plays an important role in the mechanism of DNA repair in normal cells. When a cell encounters agents that cause DNA damage, p53 halts cell cycle progression in G0/G1 by transcribing mitotic inhibitors like p21/Waf1 and Gadd45. During this time, the cell attempts to repair its damaged DNA. If the damage to the DNA is irreparable, p53 triggers apoptosis. But if this regulatory function of p53 fails, cells with mutations in their DNA can progress through the cell cycle. In cancer cells with no functional p53, restoration of normal p53 function either induces spontaneous apoptosis or renders the cells susceptible to apoptosis induced by DNA-damaging agents. Normal p53 also regulates the expression of a number of key regulatory proteins (e.g. bcl-2 and bax) involved in apoptosis [85, 86].

The *bcl-2* gene was identified at the chromosonal breakpoint of t(14;18) bearing follicular B-cell lymphomas. *bcl-2* is a unique oncogene in that it blocks apoptosis rather than promoting proliferation. Bcl-2 has been localized to mitochondria, endoplasmic reticulum and nuclear membrane. Bcl-2 appears to have antioxidant properties and is thought to inhibit apoptosis by preventing oxidative damage to cellular constituents [87]. Work by Korysmeyer's group revealed that bcl-2 heterodimerizes with a homologous partner protein called bax (bcl-2-associated X protein) [88]. It is now sug-

gested that cell death or survival depends on the ratio of bcl-2 to bax (i.e. overexpression of either bcl-2 or bax induces homodimerization, thereby offsetting the balance between survival and death). Additional apoptosis-regulating members of this family are bcl-x_L, which represses cell death, and bcl-x_S which favours cell death.

The oncogenic members of the abl family of tyrosine kinases are also implicated in the regulation of apoptosis [89–93]. Experimental observations by McGahon and co-workers, using antisene oligonucleotides to the bcr-abl fusion protein has clearly demonstrated that bcr-abl is a potent inhibitor of apoptosis [90–92]. In another experiment they transfected HL-60 and A1.1 cells with a temperature-sensitive v-*abl* mutant. The protein product of this gene at permissive temperature adopts the wild-type conformation and confers resistance to apoptosis. Furthermore, this resistance is shown to be independent of bcl-2 and bax levels [92].

The E1A and E1B oncogenes of the DNA tumour virus adenovirus encode proteins which are potent regulators of apoptosis. E1A initiates both cell proliferation and apoptosis. E1A also causes p53 accumulation, which results in the regulation of bax and bcl-2 [94]. E1B, on the other hand, functions in a manner similar to bcl-2 to inhibit apoptosis [95].

Members of the ras family of proteins play essential roles in the control of normal cell growth and may induce transformation. Certain evidence has led a number of groups to advocate that, as well as inducing transformation, ras can also prevent cell death, like the bcl-2, bcl-x_L and E1B oncogenes. Overexpression of ras is also shown to inhibit apoptosis in a number of cases [96–98], giving us an alternative for how the ras gene can become oncogenic.

The retinoblastoma gene product, Rb, was first identified as a suppressor of tumour formation and has since been implicated as a regulator of several key cellular processes, including cell cycle arrest, differentiation and apoptosis. The viral oncoprotein, E7, of papilloma virus inactivates Rb function, and when E7 was expressed in the retinas of transgenic mice, rather than developing retinoblastomas, the retina cells underwent apoptosis at a time when they normally would be undergoing terminal differentiation [99, 100].

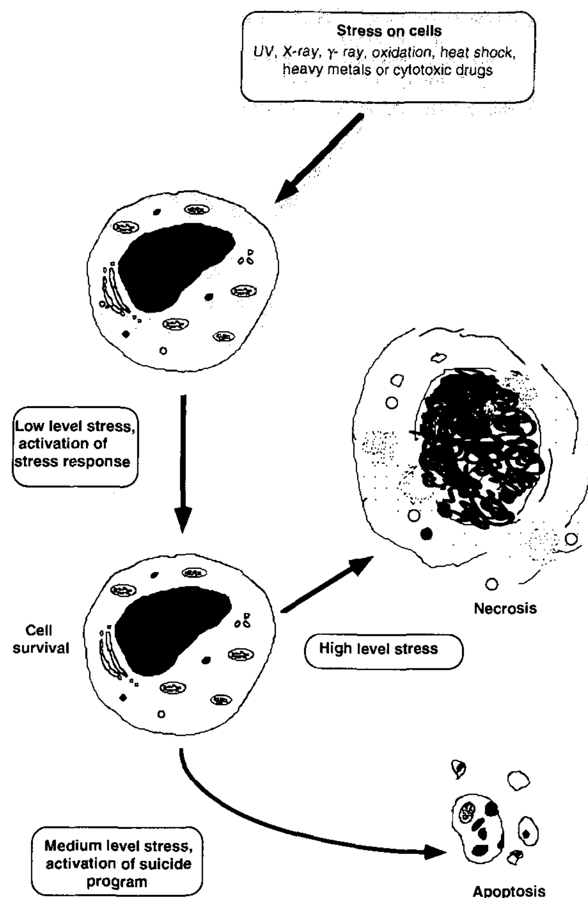

Figure 3. Schematic representation of dose-dependent induction of cell death. Type and severity of stress determine the cell's response, that is, cell survival or death. In general at low levels of stress molecular and biochemical changes occur within the cell allowing cell survival. However, these changes fail to protect the cell as levels of stress increase, and a programmed cell death is the result. Under extreme conditions the cell is unable to regulate its own demise and necrosis is the predominant type of cell death.

Adaptive response to apoptosis

In in vitro conditions cell survival or death, via apoptosis or necrosis, appears to be dependent on the type and intensity of the death stimulus (fig. 3). At low levels of stress, cells are capable of protecting themselves by altering their biochemistry. However, as the intensity of the stress increases, cells activate the machinery for their own demise. As the stress level is further increased, the cell is no longer capable of regulating its own death, and uncontrollable necrosis takes over. The work carried out in our own laboratory has shown that apoptosis may be induced by low concentrations or levels of almost all those stimuli that cause necrosis [101].

The ability of cells to develop resistance to changes in the normal growth environment is well documented. A number of different phenomena enable cells to resist the harsh effects of a single toxic agent or exposure to cytotoxic levels of many lethal agents. Most of the toxic agents that cells may encounter are capable of inducing apoptosis. Therefore, this resistance to cytotoxic agents can be viewed as an adaptive response to apoptosis. A good knowledge of the adaptive response to cell death is of great importance in management of human malignancies, and several groups have reported such a response [102–104]. This adaptive response appears to be under genetic control and demonstrates similarity to the mechanism of drug resistance and/or thermotolerance. A number of different genes and their protein products appear to be involved in this response, depending on the

type of stressor involved. These include heat shock/stress proteins (hsp) [105], whose main function in time of stress is to afford protection to cells. There is strong evidence suggesting that induction of hsps coincides with acquisition of tolerance to higher doses of the stress which otherwise may be lethal to the cell, a phenomenon known as thermotolerance [105]. Heat-shocked or thermotolerant cells show a greater degree of resistance to oxidative stress [106, 107] and to apoptosis induced by hyperthermia [103], growth factor withdrawal [102] or cytotoxic drugs [104], suggesting a possible role for heat shock-induced proteins in the resistance mechanism.

Another group of proteins that play an important role in cells' resistance to metal toxicity [108] and to oxygen radicals [109] is the metallothioneins (MT). These proteins belong to a family of genes that encode low molecular weight cystine-rich metal-binding proteins. These proteins can also be induced in some mammalian cells by glucocorticoids, interferons and stress conditions.

An increase in the glutathione (GSH)-metabolizing system provides the cell with another potential mechanism for resistance to cytotoxic drugs. GSH is the prominent thiol present in many cells. It appears to be involved in resistance to cellular oxidation, since depletion of GSH has been shown to increase the sensitivity of cells to oxidative stress. GSH also appears to be the substrate for many phase II-detoxifying enzymes. These include glutathione S-transferase, glutathione reductase and glutathione peroxidase. GSH concentration could also be modulated by heat shock, and its intracellular levels can modify hyperthermic toxicity [110, 111].

Many cells that express multidrug resistance (MDR) also overexpress the *mdr* gene, which encodes P-glycoprotein (P-gp). P-gp is a membrane-associated glycoprotein of approximately 170 kDa that actively pumps drugs out of cells [112, 113], enabling cells to withstand lethal concentrations of drugs.

In a cell population the development of resistance to cell death is a result of increased expression or activity of one or more of these proteins [114, 115]. Some of these proteins have very specific functions, whereas others may have more general 'housekeeping' functions. Taken together it becomes obvious that the adaptive response to apoptosis is a result of a complex interaction between newly synthesized or activated proteins.

Apoptosis in disease

Several diseases are associated with deregulated apoptosis, resulting in either inappropriate induction or suppression of cell death. An increase in apoptosis is seen in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis [116]. In acquired immune deficiency syndrome (AIDS) apoptosis is responsible for the depletion of T cells [117–120].

Suppression of apoptosis can also lead to disease situations. In many cancers, altered gene expression results in increased longevity of cells. In follicular lymphoma, for example, constitutive expression of bcl-2 inhibits apoptosis [121]. Similarly, an activated form of *c-abl*, namely *bcr-abl*, renders myeloid cells resistant to apoptosis in chronic myeloid leukemia [89, 90]. Many human cancers are associated with mutations in the p53 gene [122], which can lead to failure of such cells to undergo apoptosis.

Autoimmune diseases may result from inhibition of apoptosis, allowing the persistence of self-reactive B and T cells. A role for dysfunction of apoptosis via the Fas pathway has been suggested for systemic lupus erythematosus (SLE). These patients have a mutated form of Fas which is no longer anchored in the plasma membrane [123]. Therefore, there is an elevation in the levels of soluble Fas in the serum which can block the Fas apoptosis pathway in these individuals. It has been postulated that in SLE dysfunction of apoptosis could result in the inappropriate longevity of autoreactive B cells.

Therefore, control of cell death, either its induction or inhibition, serves as a potential strategy for therapeutic intervention [104, 116–118, 120, 124].

Conclusion and outlook

After two decades of research and development in cell death areas, it is now universally accepted that programmed cell death is an essential strategy for maintaining the dynamic balance and equilibrium of living systems and is observed to occur as a normal mechanism in development and homeostasis. Classification of cell death is now based on morphological and biochemical criteria or their circumstantial occurrence, or a combination of both. Although morphological characterization of apoptosis and its features distinguishable from necrosis have been well documented, our progress in understanding the mechanisms underlying the process has been quite slow.

The significance of apoptosis is based on the fact that apoptotic cells tend to be 'environmentally friendly' and package their contents into membrane-bound vesicles, ready for ingestion by phagocytic cells, without releasing their contents into the intracellular matrix, and hence there is no inflammatory response. Apoptosis is also an altruistic cell death, in that damaged or injured cells commit suicide to allow the neighbouring cells to continue to proliferate without being affected by the death of the neighbour. In addition, sacrifice of individual abnormal cells benefits the whole organism.

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