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Cellular communication during apoptosis.

Comunicación celular durante la apoptosis.

Angana Sengupta[1], Kalpataru Halder[2*]

[1] Post Graduate Department of Botany, [2] Department of Molecular Biology

Brahmananda Keshab Chandra College, 111/2 B. T Road, Kolkata-108, India

*Corresponding author email: kalpataruhalder@outlook.com.com

ABSTRACT

Apoptosis is a biological process to destroy cells. It is very much necessary for the normal growth and function of multicellular organisms. If there is any abnormality in controlling the death of cell, it can lead to a range of diseases like cancer, autoimmune disorders, or degenerative disorders. Apoptosis is triggered by a number of different signalling pathways each of which is activated by the actions inside or outside the cell. But all apoptosis signalling pathways congregate on the same system of cell dismantling process that is triggered by caspases (a family of cysteine-aspartate proteases) which slice proteins where aspartate residues are found in a particular sequence. Destruction and elimination of predestined cells is proficiently done by degrading of essential proteins of cell, degradation of DNA, and phagocytosis by other adjacent cells.

Keyword: apoptosis, cell biology, DNA, proteins

RESUMEN

La apoptosis es un proceso biológico para destruir células. Es muy necesario para el crecimiento y funcionamiento normal de los organismos multicelulares. Si hay alguna anomalía en el control de la muerte celular, puede provocar una variedad de enfermedades como cáncer, trastornos autoinmunes o trastornos degenerativos. La apoptosis se desencadena por varias vías de señalización diferentes, cada una de las cuales se activa por acciones dentro o fuera de la célula. Pero todas las vías de señalización de la apoptosis se congregan en el mismo sistema de proceso de desmantelamiento celular que es desencadenado por las caspasas (una familia de cisteína-aspartato proteasas) que cortan las proteínas donde se encuentran los residuos de aspartato en una secuencia particular. La

destrucción y eliminación de células predestinadas se realiza de manera competente mediante la degradación de proteínas esenciales de la célula, la degradación del ADN y la fagocitosis por otras células adyacentes.

Palabras clave: apoptosis, biología celular, ADN, proteínas.

INTRODUCTION

Different types of cellular interactions are the basic mechanism for constructing organs and maintaining homeostasis in multicellular organisms. The degrees of cell colonisation, cell proliferation, and cell demise determine the number of cells in an organ (Raff MC, 1996). It is obvious that impetuous damage of cell is responsible for cell death but the death of most cells in animals occur through a predetermined pathway, because there are some particular signalling events. Apoptosis, autophagic cell death, and necrosis are the three kinds of cellular destruction pathway (Galluzzi et al., 2007). In the apoptosis destructions of cells are characterized by a reduction in the cellular volume, condensation of the chromatin, and nuclear fragmentation (Galluzzi et al., 2007). This type of cell death is one of the most fundamental biological functions, which removes unnecessary or potentially detrimental cells by activating a genetically-encoded suicide program. However, this process was widely accepted, only when it was discovered that in the multicellular organisms the destruction of cell is subject to predetermined program (Ellis et al., 1986; Vaux et al., 1988) and after the demonstration that the diseases like cancer (Strasser et al., 1990; Mc Donnell and Korsmeyer, 1991) autoimmune ailments (Strasser et al., 1991; Watanabe-Fukunaga et al., 1992), and perhaps degenerative maladies (Barr and Tomei, 1994; Thompson, 1995) may happen due to the abnormalities in cell death regulation.

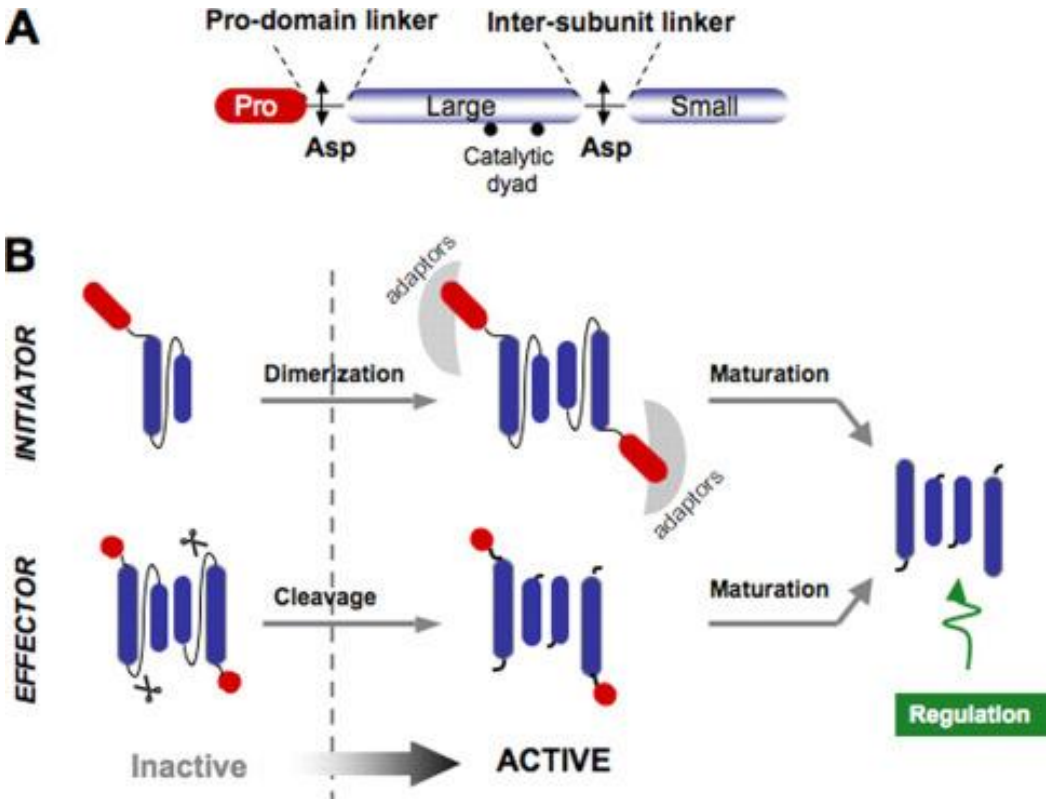
Programmed cell death is activated by the two major types of cellular signalling process: the intrinsic pathway (initiate in the mitochondria) and the extrinsic (initiate through the death receptor) pathway. The extrinsic pathway includes the interaction between the specific ligand and receptor on the cell surface. For example, when cytotoxic lymphocytes produce signalling molecules for death receptors (DRs), which are the subgroup of the TNFR family (tumor necrosis factor receptor), it can kill the biologically transformed or infected cells, provided that they also produce ligand specific DRs. Normally DR-driven cell destruction is crucial for proper functioning of immune system and to maintain the balance among all the organs of body for their survival and correct function, whereas the apoptotic pathway in mitochondria is generally triggered in a cell-autonomous method. In most extreme stress conditions, such as defects in DNA repair or DNA damaged by genotoxic agents, or the accumulation

of too much unfolded proteins in the ER, cell induce the programme for destruction (Xu and Shi, 2007; Green and Lambi, 2015).

In contrast, the devoid of any signal which are responsible for normal cellular growth may result to the death of cell. This process is very much important for the expansion of vertebral nervous system. It has been measured that almost 50% neurons produced expire throughout this procedure (Buss et al., 2006). Part of the reason for this sort of cell loss is that some neuronal progenitors fail to adequately migrate or innervate towards their targets, resulting in a lack of neurotrophic stimulation factor. Finally, oncogenes (such as Myc) can induce apoptosis as a preventative step against the development of cancer. This is assisted by a pathway of cell destruction which is dependent on p53 protein. This p53 is activated in presence of abnormal mitogenic signals caused by mutation or overexpression of oncogene (Sever and Brugge 2014).

Current developments have led to the identification that in apoptotic pathway four types of molecules are functionally most important. These are the caspases, the adaptor proteins, TNF-R (tumor necrosis factor receptor) proteins, and proteins of the Bcl-2 family.

Caspases: In most cells, triggering of programmed cell death usually leads to the activation of caspases, a group of cysteine proteases, which in turn facilitate the autodestruction of the cell. Caspases usually present in the cell as inactive zymogens known as procaspases, which are proteolysed for producing the active forms. In the mammalian system till date minimum 14 caspases have been discovered (Alnemri et al., 1996; Kumar and Lavin, 1996; Nicholson and Thornberry, 1997). These enzymes identify a tetrapeptide motifs X-X-X-Asp (X can be any amino acid) of their target proteins and cleave on the C-terminus of that aspartic amino acid. Caspases are produced in the cell as inactive precursor, which have very low affinity towards its substrate. The stimulated caspases have the ability to cleave various types of cellular proteins as well as cytoplasmic membrane proteins (Nicholson, 1999), resulting in the breakdown of that cell (Xu and Shi, 2007). The completely active caspase enzymes are composed of four subunits of which two subunits are of ~20 kDa and two subunits of ~10 kDa (Strasser et al., 2000). The formation of these subunits is mediated by the proteolysis of caspase. The accumulation of at least some inactive precursor of caspase is necessary to induce self-processing (Srinivasula et al., 1998). Certain caspases, predominantly effector caspases, cleave and deactivate essential proteins of cellular system, such as repair enzymes for DNA, p53-inhibitor (e.g., MDM2), lamin, protein kinase Cδ and gelsolin (Nicholson and Thornberry, 1997). Caspase-mediated protein cleavage can also stimulate enzymes either directly or indirectly (Strasser et al., 2000).



(A) Caspase organization: The catalytic domain is preceded by a prodomain, which is made up of two subunits connected covalently. The (auto) proteolysis sites at Asp residues are highlighted. (B) Mechanisms of activation: Monomers that are activated via dimerization of prodomain are known as initiators. Executioners are dimers that are activated by intersubunit linker cleavage. Additional proteolytic activities mature the caspases after activation, making them more stable and susceptible to control. (Pop C & Salvesen GS, 2009)

Adaptor proteins: The connection between the effector and regulator molecules which are responsible for the apoptosis is actually established by some proteins also known as adaptor proteins. The adaptor proteins build bridges between regulator proteins of apoptosis and cysteine-aspartate proteases i.e., caspases and therefore it helps in the establishment of physical association among members of the three types of molecules. Adaptor proteins associated with caspases or TNF-R family members are naturally enabled by homotypic connections between domains known as DD (death domain), DED (death effector domain), and CARD [caspase recruitment domain (Ashkenazi and Dixit 1998; Hoffman et al., 1997)]. When a receptor molecule of TNF-R family containing a DD, associate with

the DD of the adaptor protein molecule by homotypic interactions, it allow the caspase aggregation and activation (Boldin et al., 1995; Chinnaiyan et al., 1995). The DED, additional domain found in adaptor molecules, is involved in caspase recruitment and accumulation.

TNF-R cross-linking does not stimulate all originator caspases, and not all originator caspases have a death effector domain. CARDs are found in pro-caspase-2, pro-caspase-9 of mammalian system, as well as in Ced-3 of *C. elegans*, and their particular adaptors Apaf-1 and Ced-4 (Adams and Cory 1998).

Tumor Necrosis Factor Receptor Family: Tumor necrosis factor-receptor family members have various actions. These receptors can activate multiplication, survival, diversity, or death (Ashkenazi and Dixit, 1998; Nagata, 1997) subject to the types of cells and the signals that the cell receives. TNF are the ligand which are structurally related and belongs to a family that can activate these receptors. The majority of these ligands are generated as trimers which are normally exist as bound to the membrane, and it seems that signalling requires common receptor cross-linking (Tanaka et al., 1998; Schneider et al., 1998; Stresser et al., 1998). CD95 (also known as APO-1or Fas) and TNF-RI, in addition certain other fellows of this family have a cytoplasmic region known as DD, that is crucial for triggering programmed cell death (Itoh and Nagata, 1993). Death receptors are the common name for members of this subfamily.

Much has also been learned about other ligands responsible for stimulation of death and their receptors. TRAIL/APO-2L (TNF-related apoptosis-inducing ligand; TRAIL) triggers type I cell death favourably in cells which are transformed, and it is produced in various types of tissues (Wiley et al., 1995). DR4, DR5, DcR1 and DcR2 these are the four receptors so far have been recognized for TRAIL/APO-2L, although only DR4 and DR5 can prompt type I cell death. DcR1 and DcR2 cannot induce cell death because they devoid of intracellular and transmembrane regions or the death domain, respectively, (Pan et al., 1997; Walczak et al., 1997; Degli-Esposti et al., 1997a).

The Bcl-2 Family: A number of proteins that have fundamental resemblance to Bcl-2, the classical inhibitor of programed cell death, had found in recent years (Adams and Cory, 1998). The Bcl-2 family is generally classified into three groups based on their primary function and presence BH-regions (Bcl-2 homology regions) (1) proteins that oppose programed cell, (2) pro-apoptotic that forms pore in the mitochondrial outer and (3) BH3-only proteins which are pro-apoptotic. A BH3 domain is included in all BCL-2 family proteins and is one of four BH domains involved in protein-protein interactions (Kale et al., 2017). Anti-apoptotic and pore-forming proteins (multi-BH domain proteins) have all four BH domains and a tertiary structure which is exceedingly well-preserved. This particular structure forms a groove that can bind the hydrophobic BH3 domain. Therefore it serves like BH3

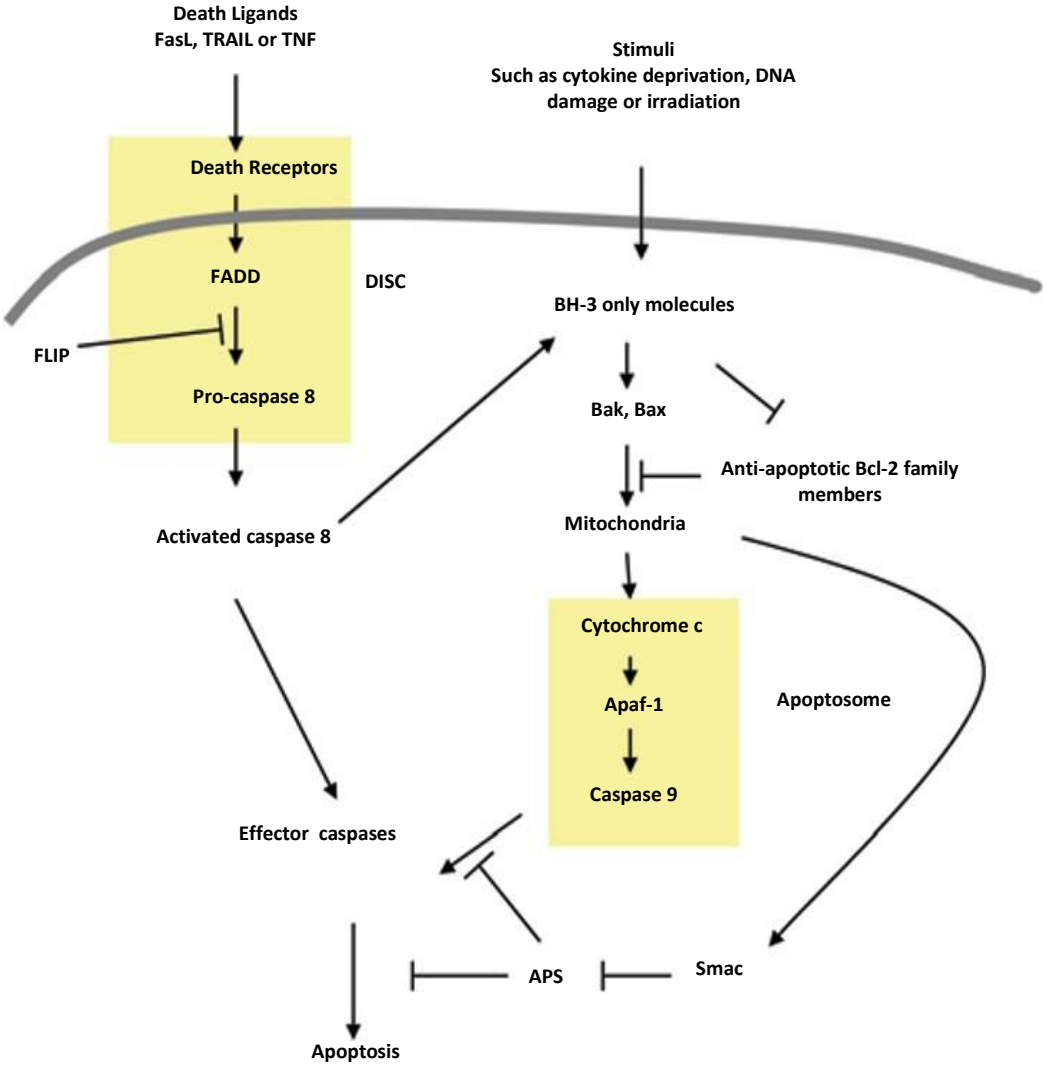
domain receptors from other family members (Kale et al., 2017). Mammalian Bcl-x_L, Bcl-w, A1/Bfl-1, Mcl-1, and Boo/Diva, *C. elegans* Ced-9, as well as variety of other homologous to virus also increase cell survival and share three or four regions with with Bcl-2 (Boise et al., 1993; Gibson et al., 1996; Choi et al., 1995; Lin et al., 1996; Kozopas et al., 1993; Hengartner et al., 1992) . Bax, Bcl-xS, Bak, and Bok/Mtd are distantly related mammalian proteins which include two or three BH regions that enhance cell death in stressful situations (Oltvai et al., 1993; Chittenden et al., 1995; Farrow et al., 1995; Hsu et al., 1997).

The most effective proteins for activating cell death are those with only a BH3 region and no other structural similarity to the Bcl-2 family or any other currently known protein. Bad, Bik/Nbk, Bid, Hrk/DP5, Bim/Bod, and Blk proteins of mammalian system and Egl-1 protein of *C. elegans* are all pro-apoptotic molecules (Yang et al., 1995; Han et al., 1996; Wang et al., 1996; Inohara et al., 1997; Hsu et al., 1998; Hegde et al., 1998; Conradt and Horvitz, 1998). Pro-apoptotic and proteins of the Bcl-2 family which are anti-apoptotic can associate with each other physically (Oltvai and Korsmeyer, 1994).

Different post-translational changes regulate the action of diverse pro-apoptotic proteins of Bcl-2 family. Akt or protein kinase A driven phosphorylation regulates Bad activity (Dutta et al., 1997; Harada et al., 1999), caspase-mediated proteolysis activates Bid (Luo et al., 1998; Li et al., 1998), and association with the Dynein motor complex regulates Bim activity (Puthalakath et al., 1999). It's likely that these molecules function to prevent the destruction of cell at different locations, and that different apoptotic signaling molecules cause cell death by triggering different Bcl-2 family members. Bcl-2 family members that promote apoptosis are not the only ones who undergo post-translational alteration. Phosphorylation has been demonstrated to control Bcl-2 and Bcl-xL(Ito et al., 1997; Chang et al., 1997), and Bcl-xL and Ced-9 can be the target of caspase as their substrates (Xue et al., 1997; Cham et al., 1998).

SIGNALING PATHWAY

Early studies utilizing the nematode *C elegans* delivered the foundation for understanding the molecular mechanisms that drive apoptosis; after that these studies were then applied to apprehend mammalian systems (Hengartner and Horvitz 1994; Chennaiyan et al., 1997; Duan and Dixit, 1997). In the mammalian system, there are two basic mechanisms to apoptosis: an extrinsic pathway triggered by death receptors and an intrinsic pathway controlled by mitochondria. For the extrinsic pathway to function, external stimuli must attach to the receptors on the cell surface. Alternatively the intrinsic pathway, responds to cues from within the cell, such as radioactivity and certain chemotherapeutic drugs, to trigger apoptosis signaling through the release of mitochondrial factors.



Pathways of apoptosis. The extrinsic apoptotic signalling pathway is shown on the left, while the intrinsic apoptotic signalling pathway is shown on the right. The activation of caspases brings these pathways together. Apoptosome and DISC are indicated in yellow (Xu and Shi, 2007).

EXTRINSIC PATHWAY

When death receptors come into contact with certain equivalent "death ligands," a structural change occurs in these receptor molecules and that is communicated inside the cell via the plasma membrane. Within seconds of ligand contact, these receptors activate caspases, resulting in apoptotic cell death within hours. Three significant cell death receptor/ligand pairings have been identified: (1) Fas and Fas ligand (FasL); (2) DR4, DR5 and TNF-related apoptosis inducing ligand (3) TNFα and TNF receptor (Itoh et al., 1991; Suda et al., 1993; Wiley et al., 1995; Pitti et al., 1996). All these death receptors are the representatives of TNFRSF which contains common extracellular domain that have the variable number of pseudo repeats of

region rich with cysteine (Smith et al.,1994), only one domain that is integrated into the membrane and one cytoplasmic domain (DD) which is about 80 amino acids long and preserved throughout the evolutionary process and associates with adaptor proteins (Tartagalia et al., 1993).

Fas-FasL Pathway: Fas is the most widely investigated among all the receptors connected to the death of cell. The aggregation of Fas trimers is triggered by Fas's particular interaction with the signalling molecule, FasL which is anchored to the membrane. This allows the DD in Fas' cytoplasmic tail to quickly recruit the DISC (Medema et al., 1997). Fas, an auxiliary protein termed Fas-associated death domain (FADD) (Chinnaiyan et al., 1995), and pro-caspase 8 make up the DISC. FADD is a ubiquitous adapter protein that facilitates signalling by TNFRSF members that include the DD domain (Kabra et al., 2001). FADD is composed with a death effector domain (DED) in its N-terminus and a death domain (DD) in the C-terminus. FADD is recruited by Fas when these receptors accumulate by its appropriate stimuli, a relationship that is mediated by the highly conserved DD motif shared in both proteins. FADD's N-terminal DED is unmasked by its connection with Fas via their C-terminal DDs, which permits in turn to associate Fas signalling complex to the pro-caspase 8 (Muzio et al., 1996; Boldin et al., 1996). Because the expression of a dominant-negative version of FADD entirely abolishes Fas-stimulated cell death, the activated FADD protein is absolutely necessary for Fas-mediated programmed cell death (Wajant et al., 1998). When DISC is formed it signals the pro-caspase 8 to proteolysis by itself and produce activated caspase 8. In the next step pro-caspases 3, 6, and 7 are then cleaved by activated caspase 8 (also known as FADD-like IL-1 converting enzyme (FLICE)). Enzymes that repair DNA, structural proteins of cell as well as nucleus, and inhibitors which inhibit endonuclease are among the cellular substrates cleaved by activated caspase 3. Furthermore caspase 3 may also stimulate additional caspase like caspase 6 and 7, which are ordinarily available in its inactive state. Therefore it intensifies the programmed cell death and also ensures to complete the process efficiently (Xu and Shi, 2007).

The TRAIL-DR Pathway: TRAIL is a type II protein bound to the membrane and can be released from the membrane by cysteine proteases to produce a soluble version, similar to other TNF family ligands. DR4, DR5, DcR1, DcR2, and OPG (osteoprotegerin) these are the five receptors for TRAIL, exist in both humans and mice (Pan et al., 1997; Irmler et al., 1997; Simonet et al., 1997; Pan et al., 1998). Only DR4 and DR5 have functioning DDs that facilitate apoptosis activation, but the decoy receptors don't. Because the death domain and the domain for integral part of the membrane is missing from DcR1. Membrane-bound as well as the genetically modified soluble versions of TRAIL, triggered apoptosis in a wide range of altered cell lines from various sources (Wiley et al., 1995; Degli-Esposti et al., 1997b). Because normal cells do not possess decoy receptors and tumor cells do, it is thought that TRAIL may particularly destroy tumour cells, however this is debatable. In asthmatic patients, TRAIL

expression was considerably higher in the epithelium, smooth muscle of vesicle and airway, and interstitial tissue than in non-asthmatic participants (Robertson et al., 2002).

The TNFα-TNFR1 pathway: TNFα is a cytokine that affects variety types of cell in a pleiotropic manner. It has been determined to be a significant modulator of inflammatory reactions. Three identical polypeptide chains of 157-amino-acid assembled and formed as a homotrimer in TNFα. There are two receptors for TNFα: TNFR1 (or p55), which has a death domain (Himmler et al., 1990), and TNFR2 (or p75), which does not have a death domain (Gray et al., 1990; Schall et al 1990). In this pathway initially, the TNF trimer associates with the extracellular binding site of its receptor TNF-R1. This in turn induces a conformational change in the intracellular domain of the receptor and leads to the dissociation from inhibitory protein which blocks the death domain inside the cytoplasm. The TNF receptor-associated death domain (TRADD) is an adaptor protein that recognizes the combined TNF-R1 intracellular domain and deploys RIP, TNF-R-associated factor 2 (TRAF2), and FADD. TNF-R1 is recruited by these proteins, which recruit critical enzymes that initiate signaling events. FADD recruits caspase 8 to the association of TNF-R1, and there it is stimulated by auto-proteolysis and triggers a flow of proteolytic reactions that begins the journey towards apoptosis. Two signalling complexes are involved in TNFR1-activated programmed cell death. TNF binding to TNFR1 attracts TRADD, RIP1, and TRAF2 to form a complex association (complex I) which is bound to the plasma membrane and activates NF-κB quickly. When the complex I completely formed the structure of TRADD and RIP1 are modulated and detach from TNFR1, then TRADD (and or RIP1) attaches to FADD, causing caspase 8/10 to be recruited, producing another cytoplasmic complex (complex II) and causing apoptosis. If the latter complex arises, the FLIP levels define it. When complex I successfully activate NF-κB, adequate amount cellular FLIP are raised to prevent complex II creation and death. Complex II signals for the destruction of cells only when the first signal from complex I unable to induce NF-κB (Michaeu et al., 2003).

INTRINSIC SIGNALING PATHWAY

In mammalian cells, the apoptosis also occurs in mitochondria where the crucial permeabilization of outer membrane of mitochondria occurs and when it occur the induction of apoptosis is certain. Different caspases are activated by MOMP (mitochondrial outer membrane permeabilization) resulting in apoptosis by releasing specific proteins from the mitochondrial inter-membrane space.

Usually MOMP is prevented by the members of that Bcl-2 family which are anti-apoptotic in nature. In B cell lymphomas the distinct oncogene Bcl-2 was identified first where it inhibited the

death of the cell (Bakshi et al., 1985 Tsujimoto et al., 1985). Bax and Bak, can directly result in MOMP (Danial and Korsmeyer, 2004). In the cell where Bax and Bak are deficient apoptosis usually do not occur (Lindsten et al., 2000; Cheng et al., 2001). BH3-only proteins can activate inactive Bak and Bax in most of the cells. As soon as, Bax and Bak increases the mitochondrial permeability (outer membrane) cytochrome *c* become available which act as proapoptotic.

The anti-apoptotic Bcl-2 family proteins hinder this activation of Bax and Bak. This may occur when Bak and Bax are sequestered and thereby their activation is prevented or when BH3- only protein which activate apoptosis are inhibited .Sensors for apoptotic stimuli are BH-3 only proteins (Huang and Strasser, 2000). BH3-only proteins are activated in response to stimuli, such as cytokine deficiency when MOMP occurs, there is leakage of proteins. Then there is interaction between WD40 domain of cytosolic APAF-1 and the cytochrome c, (Liu et al., 1996) consequently there occurs a conformational shift of APAF-1, allowing it to oligomerize and encourage apoptosome formation (Zou et al., 1997; 1999). Pro-caspase 9 and APAF-1 both have caspase recruitment domains and though those domains attachment between proform of caspase 9 and apoptosome occurs and ultimately there is formatiion of activated caspase 9. The caspase 9 after being activated, in turn activate caspase 7 and caspase 3 by specific cleavage action. Another mithochondrial component AIF also regulates apoptosis (Susin et al., 1999).The anti-apoptotic redox-active enzymatic component of AIF gives it a double function- it may function in the survival of cell or in the death of the cell. AIF induced apoptosis has the ability to condense and also to fragment the nucleus.

OTHER DIFFERENT APOPTOTIC PATHWAYS

Different from caspases, granzymes are a class of serine proteases that also cause cell death. NK cells and T cells use a special process by which they remove virus -infected cells. The cytotoxic granules via unknown sources deliver granzymes and perforin to the specific cells where they are targeted. Each granzyme species triggers a different set of apoptotic signaling pathways (Sarin et al., 1997), both the pathways which depend on caspase and which do not induce / may induce apoptosis by granzyme B (Tartagalia et al., 1993), where different substrates of caspases at downstream is cleaved. CAD endonuclease maybe activated by granzyme B while caspase 3 and 8 may be cleaved, ICAD and Bid are also cleaved. Granzyme A has the capability to nicking the one strand of DNA and can cause cell death in the absence of caspases (Fan et al., 2003). Granzymes have recently been proven to cause apoptosis in cells that carry those (Yamada et al., 2003). Apoptosis may be mediated by calpains (Gil-Parrado et al., 2002). Mammalian calpains is made up of two proteins which are universal,

two proteins which are specific to stomach and a protein which is specific to muscle that total five proteins. Caspases and calpains have certain substrates in common. Bax is cleaved by the enzyme Calpain (Wood et al., 1998), calpains are necessary for Bax activation and apoptosis in neutrophils. (Yousefi et al., 2006). There has recently been evidence of cross- talk between caspases and calpains (Neumar et al., 2003). More research into protease-induced cell death should reveal caspase-independent mechanisms.

APOPTOSIS IN REGULAR BIOLOGICAL CONDITION

Scientific literatures report that under some particular situations certain different types of cells may undergo apoptosis by a many chemicals, which serve as a proof that sometimes a particular may be significant, clinically and physiologically. Animal development is dependent on cell death. Some cells die during the process of development where the doomed cell does not require pro-apoptotic signals from the adjacent cells to die (Coucouvanis et al., 1995). Indeed, it is quite rightly thought that surrounding cells offer survival signals in many of these events, and growth hormone deficiency or/and defect in cell attachment may trigger the death of the cell (Raff, 1992). Anti-apoptotic members of the Bcl-2 protein family can often inhibit these paths to cell death which are referred to as death by neglect (Strasser, 1995a). Mice showed particular organogenesis if they do not possess Bcl-xL or Bcl-2, which in turn confirms this theory (Motoyama et al., 1995). Cues may originate from the cells which are nearby may be necessitated to induce apoptosis where the developing cells die in a planned manner (Nakagawa et al., 2000). This activity could be performed by death receptors and their ligands. Defect in the heart and early mortality of the embryo suggests that the TNF-R family plays a function in the development - this occur due to deficiency of caspase-8 or FADD (Yeh et al., 1998). Functional overlap between related molecules is believed to explain the lack of evident developmental abnormalities in those mice that are deficient in TNF-R families or TNF (Ashkenazi and Dixit, 1998). There are different ways by which the physiological active death of cells occurs- by two mechanisms. In neural tissues Caspase-3, caspase-9 along with Apaf-1 is required, and the Bcl-2 protein family regulates death by neglect (Kuida et al., 1998; Yoshida et al., 1998). In the thymocyte which are cultured and if those are devoid of caspase-9 or APAF-1, the impulsive destruction do not look abnormal, but it is also true at the same time that Apaf-1 and /or caspase-9 is not essential for death by neglect in all cases (Yoshida et al., 1998). This could indicate that Apaf-1 can activate another initiator caspase in caspase-9–null cells, or that mammals may have other adaptors which are supposed to be like Ced-4.

At various stages of cell development, apoptosis causes cell death in several organs. To find

out the mechanism of physiological death of cells preventable by Bcl-2, Bcl-2 transgenic mice were utilized. In the animals where the receptor for interleukin is deficient, the Bcl-2 expression regenerates the normal T lymphocyte formation and function. Bcl-2 expression fail to prevent demise of some thymocytes having receptor for antigens which are auto-reactive or lacking a receptor for pre T-cell, which suggests different mechanisms where one is blocked by Bcl-2, but not by other mechanisms (Strasser et al., 1994; Akashi et al., 1997). The fundamental activities of Bcl-2 proteins were understood by gene knockout technology. Mice lacking Bcl-2 have more cell death during morphogenesis and mature lymphocytes die prematurely (Nakayama et al., 1993, 1994), as in the mature lymphocytes and growing kidney expression of Bcl-2 is generally more (Veis et al., 1993; Marino et al., 1994). Suprisingly, no increase in apoptosis was detected in other organs like intestine, neurological system etc where there is widespread expression of Bcl-2 (Merry et al 1994). In few of the tissues along with Bcl-2 expression, great production of Bcl-xL occurs, these findings reflect that there are members in the Bcl-2 family who oppose apoptosis and are redundant in function (Gonzalez-Garcia et al., 1994). This is the fact that most of the physiological induction of cell death usually occurs in Bax/animals which in turn supports the idea that Bcl/Bax heterodimers are not required for apoptosis or cell survival.

APOPTOSIS AND DISEASE

It is undeniable that aberrations in apoptosis results in the progression of disease. The gene for Bcl-2 protein is found on chromosome 18 and transfer of this gene to a different chromosome is seen in many B- cell leukemias and lymphomas. The chromosome 18 possesses the gene for Bcl-2 protein and in many lymphomas and B-cell leukemias occur when this gene is transferred to other chromosome. In the mice where it has been done Bcl-2 is overexpressed in lymphocytes resulting more likely to develop cancer/tumor than the normal offspring (Strasser et al., 1990; Ma Donell et al., 1991), though the gene was first discovered in the form of proto-oncogene (Bakshi et al., 1985). When this gene works on its own along it cannot function as tumor producing gene, but when it combines with other oncogenes that favours growth it works well in tumorogenesis (Strasser et al., 1990; Jager et al., 1997). When Bcl-2 is amplified, cell survival is prolonged thus promoting the chance of acquisition of more oncogenic mutations consequently more chance of developing tumor. Though recently it has been found that there are apoptosis favouring representatives of Bcl-2 who can suppress the development of tumor. In the Bax gene mutation have been discovered in some cancers in large intestine (Rampino et al., 1997).

In Bax/mice epithelial cell of choroid plexus are changed rapidly when there is a particular form

of the simian virus 40 large -T antigen, which have been produced transgenically and it is even a more striking fact (Yin et al., 1997).

Many medicines which work on cancer cell works by induction of apoptosis. Cancer producing cells and genes which accelerate transforming cell death, play an important role on the efficiency of those medicines which works against cancer. If Bcl-2 is expressed more, Bax become inactive tumor cells are protected from apoptosis in short term but also increases in long term survival by retaining clonogenicity in tumor cell where treatment done with medicines which works against cancer or with irradiation with gamma-ray (Strasser et al., 1994). In governing to responsiveness of cancer cells to therapy, proclivity for death by mitosis and tendency towards triggering of apoptosis come into play. Many anti-tumor drugs work by triggering apoptosis in cancer cells. Role of caspase in favour or against these medicines are being extensively studied. In many of the cells where apoptosis is experienced majority of caspases are found in the active form, the same we see in the cells the tumor which is treated with medicines which works against cancer Nicholson et al., 1997, Ferrari et al., 1998; Fulda et al., 1998).

Abnormal cell survival has effects other than cancer. When there is invasion by pathogen, the cells multiply rapidly, and when the disease is eradicated this responding cells die in an extremely fast way by apoptosis (Golstein et al., 1991; Raff, 1992; Strasser, 1995b). In some case production effector molecules which may work as a harmful one may be extended due to the longevity of stimulated lymphocytes. Longer response to immunity system (humoral) and are abnormal assemblage of plasmocytes ensure when Bcl-2 shows more expression in the transgenic mice's lymphocytes (only B) or deficiency of Bim, which can ultimately develop to lethal systemic lupus erythematosus like autoimmune illness (Strasser et al., 1991; 1992). If there is any change in the gene in CD95 or there is any change in ligand of CD95, that can produce swollen lymphnodes and body's immune response can attack its own cells in mice as well as in man, added to the growing body of evidence indicating effector cells act to prevent the attack where self-attack self (Watanabe-Fukunga et al., 1992; Takahashi et al., 1994; Adachi et al., 1995).

The death of cell caused by viruses and other microscopic invaders can be prevented by apoptosis. As a result, many of these diseases have developed ways to prevent host cells from dying, allowing them to replicate and/or persist (Vaux et al., 1994; Tschopp et al., 1998). When cells detect metabolic disturbances induced by viral infection, they can stimulate the apoptotic machinery. The adenovirus protein E1A, for instance, stimulates viral replication while also inducing death in host cells by activating the tumor suppressor protein p53 (Lowe and Ruley, 1993). Two proteins of adenovirus, E1B 55Kd protein, which directly affects with p53 activity, and E1B 19kD protein, a homologous of Bcl-

2, which prevents apoptosis signaling farther downstream, can prevent this pathway to apoptosis (Chiou et al., 1994). Several additional viruses include Bcl-2 homologs, which are thought to protect host cells from apoptosis caused by stress or a lack of growth factors (Vaux et al., 1994; Tschopp et al., 1998).

CONCLUSION

There is actually communication between these intrinsic and extrinsic pathways. Different apoptotic pathways have different functions depending on the types of cell and signaling component and other environmental factors. For example,when active caspase 8 (responsible for slicing and making the effector caspase active) is deficient in quantity, then caspase 8 may proteolyse Bid which take over as a main route for apoptosis. This proteolysis of Bid gives rise tothe pro-apoptotic tBID fragment that in turn stimulates the release of cytochrome*c* from mitochondria which in turn activates caspase 9 (Hengartner et al., 1992; Oltvai et al., 1993). Then caspase 8 be cleaved by Caspase 9 which in turn initiates a positive feedback loop that enhances the caspase 8 signal.

FUTURE PERSPECTIVE

The intensity of cell death investigation is frenzied, which has unfortunately resulted in a great deal of uncertainty due to a plethora of contradictory articles. It is very unfortunate that data have been collected from the system where the changed cell has been expressed more and that is used to draw many inferences on many process as for example interaction in between proteins . One should exercise due caution of the cultured transformed lines of cells where there is unexplained structural changes in the regulator (DR), because when the control of cell death is disregulated it may result in tumor (Strasser et al., 1990, 1997). So study should be carried out preferably in the cells which are normal. We also feel that a better comprehension of cell death regulation is required before creating therapeutics that target the apoptotic signaling machinery.

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