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## Apoptosis and Other Alternate Mechanisms of Cell Death

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### ABSTRACT

The normal cell has its own homeostatic mechanism. A slight deviation in this mechanism leads firstly to an adaptive response in the form of hypertrophy, atrophy etc. But sometimes when adaptive response exceeds a limit also culminates to cell injury which ultimately leads to cell death. Irreversible form of cell injury leads to cell death in the form of necrosis, apoptosis and autophagy and by other alternative ways of necroptosis, anoikis, entosis and cornification. Necrosis and apoptosis are main mechanisms of cell death in mammalian cells. Necrosis is accidental, uncontrolled and un-programmed cell death which leads to cellular swelling, pyknosis, karyolysis, karyorrhexis, disruption of cell membrane and inflammation. Apoptosis is a programmed and energy dependent pathophysiological phenomenon leading to cellular shrinkage but no cell membrane rupture and no inflammatory response. Apoptosis can be mediated by extrinsic, intrinsic and perforin/granzyme pathways, leading to activation of execution caspases and finally protein cleavage, cross linking and DNA-fragmentation. Extrinsic pathway involve ligand (FasL, TNF $\alpha$ ) and receptors (FasR, TNFR) interaction which bind to adapter proteins Fas Associated Death Domain (FADD) and TNF $\alpha$  Receptor Associated Death Domain (TRADD) with activation of initiator caspases-8. Intrinsic pathway involves cytochrome c release along with pro-apoptotic proteins and inhibits anti-apoptotic proteins, leads to cytochrome c interaction with Apaf-1, thus activation of pro-caspase-9. Overall, cell death have clarified many aspects of this fundamental process and brought to the attention of scientists its role in a large number of different diseases. The present review describes apoptosis and other alternate mechanisms of cell death with biomedical and veterinary perspectives.

**Key words:** Apoptosis, caspase, perforin, granzyme, pyroptosis, autophagy, necrosis, entosis, mitotic catastrophe, cell death, biomedicine

### INTRODUCTION

The term apoptosis (a-po-toe-sis) was first used by Kerr, Wyllie and Currie in 1972 to describe cell death (Kerr *et al.*, 1972). But first evidence about Programmed Cell Death (PCD) was given by Kerr and he called it as shrinkage necrosis (Kerr, 1970, 1971). Apoptosis is a Greek word which means "Falling off" like leaves from a tree in autumn (Chowdhury *et al.*, 2006; Kerr *et al.*, 1972).

Apoptosis is referred as type 1 and necrosis as type 3 cell death (Chowdhury *et al.*, 2006). It is one of the forms of Programmed Cell Death (PCD) which keeps balance between normal and dying cells (Hanahan and Weinberg, 2011). The other forms of Programmed Cell Death (PCD) include autophagy and programmed necrosis and these all forms can be differentiated on the basis of their morphology (Bialik *et al.*, 2010).

Apoptosis is an irreversible, genetically determined vital component of various processes which includes normal cell turnover, development and functioning of immune system, embryonic development, hormonal dependent atrophy and chemical cell death etc., designed to eliminate unwanted host cells through a coordinated and energy-dependent biochemical process. This leads to activation of cysteine rich proteases called as “Caspases” and involve a complex set of events which connect initial stimuli to the final demise of the cell (Shalini *et al.*, 2015; Elmore, 2007). Apoptosis can be involved in physiological as well as pathological processes. Any dysregulation in apoptotic mechanism can lead to tumor formation, congenital anomalies and autoimmune diseases (Mason *et al.*, 2013; Wahl *et al.*, 2013). It can acts as defense mechanism for any damage caused by noxious agents (Norbury and Hickson, 2001). Caspases present in an inactive form, exists as pro-caspases and during apoptosis cleaved into large and small subunits which are hetero tetramer in nature. This process is under strict control (Wang and Youle, 2009). During apoptosis cell shrinkage and pyknosis are seen firstly. Pyknosis is most characteristic feature of apoptosis (Elmore, 2007).

There are many modes of cell death as autophagy, necroptosis (Roychowdhury *et al.*, 2013) but necrosis and apoptosis are of major importance (Shuh *et al.*, 2013). The most important alternative mode of cell death is necrosis which is toxic, energy independent, uncontrolled and a degradative process which occur after cell death. Necrosis is a process which leads to cell death via karyolysis, pyknosis, karyorrhexis and cellular swelling while apoptosis leads to cell death via cell shrinkage, pyknosis and karyorrhexis. On histopathological examination it is seen that apoptotic cells occurs as single cells or in small clusters of cells while necrotic cells are often in group. After karyorrhexis extensive plasma membrane blebbing occurs forming apoptotic bodies which contains organelle and nuclear fragments in their cytoplasm (Elmore, 2007). Cells of myeloid series i.e., macrophages are main cells involved in apoptotic cells phagocytosis and thus can result in passive necrosis (heterophagic necrosis) of phagocytized apoptotic cells (Silva, 2010; Henson and Hume, 2006; He *et al.*, 2009; Odaka and Mizuochi, 1999; McIlroy *et al.*, 2000).

Apoptotic cells does not involve any inflammatory reaction as involved by necrotic cells because their plasma membrane remains intact and apoptotic cells are immediately engulfed by macrophages called as “Tingible body macrophages” so that not getting enough time to release their anti-inflammatory cytokines into the interstitial tissues (Elmore, 2007). One important biochemical characteristic which is responsible for early phagocytosis of apoptotic bodies is outward flapping of phosphatidylserine which is normally facing inward and located outer lipid bilayer of cell plasma membrane. It is noticed that Fas, caspase-8 and caspase-3 are mainly responsible for phosphatidylserine externalization on stressed RBCs. This phosphatidylserine produce “Eat me” signals and it is one of the most ubiquitous molecule in multicellular organisms (Elmore, 2007). This process of phagocytosis of apoptotic bodies are too fast making it very difficult to visualize these with light microscope (Earnshaw, 1995; Au *et al.*, 1997).

Other molecules with such action on cell membrane can be Annexin-1, Annexin-5, thrombospondin-1, calreticulin while in necrotic process due to loss of plasma membrane integrity there is release of intracellular contents into the interstitial tissues thus leading to inflammatory response. In general point of view both apoptosis and necrosis are different but sometimes can occur together forming “Apoptosis-necrosis continuum” (Elmore, 2007). Sanguinarine is an

antineoplastic drug which leads to tumour cell death via apoptosis as well as necrosis (Weerasinghe and Buja, 2012). It has been demonstrated that apoptotic process can be converted into necrosis depending upon availability of caspases and ATPs inside the cells (Elmore, 2007). The other alternate mechanisms of cell death like necroptosis include necrotic morphology without caspase activation (Galluzzi and Kroemer, 2008; Vandenabeele *et al.*, 2010; Han *et al.*, 2011). The cell death caused by many pathogens includes many features of apoptosis (Gao and Kwai, 2000; Hay and Kannourakis, 2002). The apoptosis is found to produce effects in neurological disorders also (Hengartner, 2000; Ranger *et al.*, 2001) HIV induces apoptosis both in infected as well non-infected CD4+T cells (Holm and Gabuzda, 2005; Cummins and Badley, 2010).

**APOPTOSIS-MECHANISMS AND DIFFERENT PATHWAYS**

There are three main apoptotic pathways including; death receptor pathway (extrinsic) mitochondrial pathway (intrinsic) and perforin-granzyme pathways. It has been cleared that all the three pathways are converged to a common execution point. Caspases are the major highly conserved cysteine dependent aspartate specific acid proteases which are present as inactive form in body cells and acts as biochemical regulator and executioner of apoptotic cells and need activation by protease cascade and leads to cell death (Alnemri *et al.*, 1996; Lavrik *et al.*, 2005; Shimizu *et al.*, 1996). Once caspases are activated no reversal happens. The role of caspases (Alnemri *et al.*,1996) and their 14 types were identified (Lavrik *et al.*, 2005). Figure 1 depicts the different pathways of apoptosis. There are 14 caspases known, categorized as shown in Table 1 (Elmore, 2007).

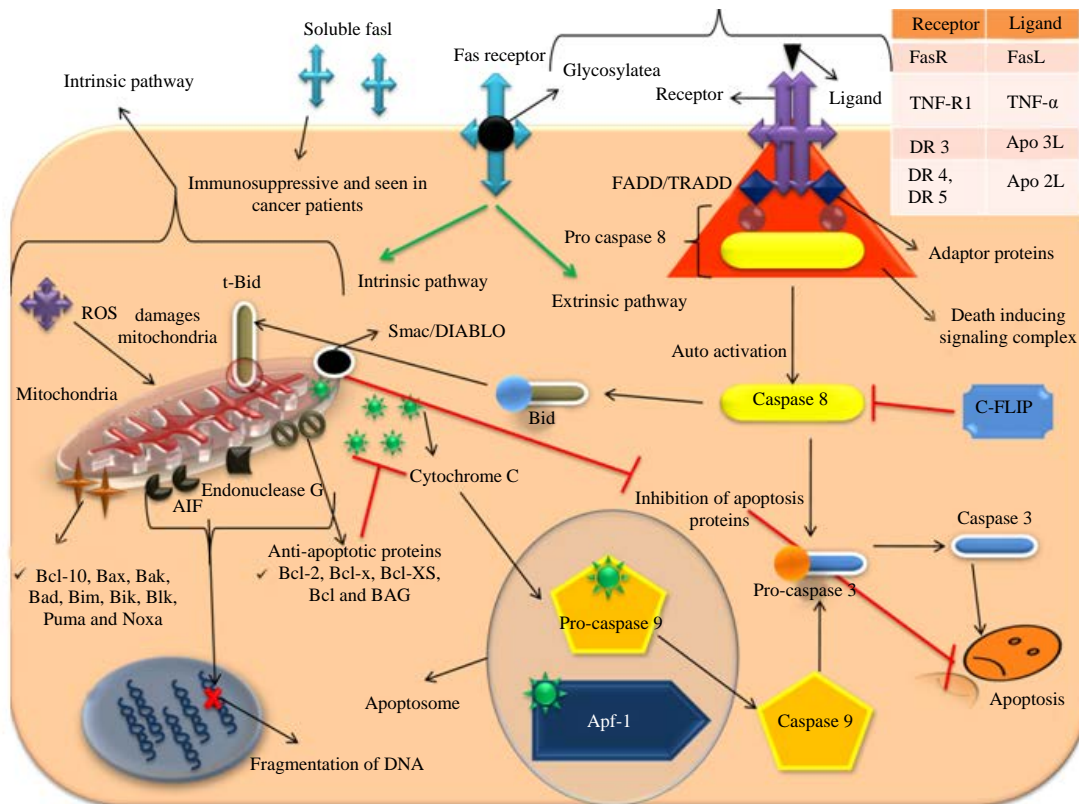


Fig. 1: Different pathways of apoptosis

Table 1: Different types of caspases

Types	No.
Initiator caspase	2, 8, 9, 10
Effector or executioner caspase	3, 6, 7
Inflammatory caspase	1, 4, 5
Others	11, 12, 13, 14

The inflammatory caspases present in the form of a complex called as inflammasome containing a protein NALP-1 and this complex produce immune response by activating IL-1beta and IL-18 (Martinon and Tschopp, 2004). Caspase-14 is one which is concerned with keratinocyte differentiation and also have role in prevention from UV rays and water loss (Denecker *et al.*, 2007, 2008).

**Extrinsic pathway:** It is a receptor mediated pathway which involve binding of death receptors on the cells. These death receptors are transmembrane proteins which contains cysteine rich extracellular domains (CDRs) (Chowdhury *et al.*, 2006; Elmore, 2007). These death receptors include members of TNF receptor superfamily and bind with corresponding ligands. Major receptor ligand pairs are as FasR-FasL, TNF-R1-TNF- $\alpha$ , DR 3-Apo 3L, DR4-apo 2L, DR5-apo2L. The FasR-Fas, IFN and TRAIL (TNF-related apoptosis- inducing ligand or Apo2-L) and TNF-R1-TNF-alpha are best models to study this pathway (Elmore, 2007; Ashkenazi and Dixit, 1998; Schulze Osthoff *et al.*, 1998). Out of all these, Fas is a glycosylated type-1 transmembrane receptor that can activate intrinsic as well as extrinsic pathways (Elmore, 2007; Peter and Krammer, 1998; Nagata, 2000). Binding of FasR-FasL/TNF-R1-TNF- $\alpha$  leads to the recruitment of adaptor proteins i.e., FADD/TRADD which binds with receptor depending upon ligand receptor interaction involved. These adaptor proteins then dimerise with procaspase-8 thus form Death Inducing Signaling Complex (DISC) and undergo auto activation of procaspase-8. This activated caspase further activates execution caspase. A C-FLIP an inhibitor of extrinsic pathway exists in three forms: c-FLIPL, c-FLIPs and c-FLIPr. The c-FLIP block recruitment of procaspase 8 and 10 thus inhibit signaling pathway (Elmore, 2007; Golks *et al.*, 2005; Hussein *et al.*, 2003; Earnshaw *et al.*, 1999). The death ligand binds with death receptor and create binding site for adaptor protein and form DISC complex (O'Brien and Kirby, 2008). The DISC complex initiates and activates procaspase 8 (Karp, 2008).

Before that the mitochondrial transmembrane potential is lost, DISC leads to activation of extrinsic pathway. Caspase-8 is responsible for cleavage of c-terminal of BH3 member of Bcl-2 family from Bid to tBid (truncated Bid) which comes to outer mitochondrial membrane leads to loss of mitochondrial transmembrane potential thus cytochrome c is released. It means Bid is responsible for cross-talk between mitochondrial and death receptor dependent pathways (Elmore, 2007; Li *et al.*, 1998; Luo *et al.*, 1998; McIlwain *et al.*, 2013). Bid is having role in relaying signals from surface of cells to mitochondrial membrane (Luo *et al.*, 1998). The soluble form of Fas-L is immunosuppressive in nature and seen in cancer patients (Ueno *et al.*, 1999; Kavathia *et al.*, 2009). The Reactive Oxygen Species (ROS) are important factor to induce apoptosis which leads to mitochondrial damage thereby leads to aging of the cells (Bernhardt *et al.*, 2014; Hur *et al.*, 2014; Wallace, 2010). The recruitment and oligomerization of caspase-8 in the DISC result in its autocatalytic activation and is critical for the initiation of cell death (Juo *et al.*, 1998; Varfolomeev *et al.*, 1998).

**Intrinsic pathway:** It is not a receptor mediated pathway but is an intracellular pathway which can involve positive as well as negative signals. These stimuli leads to change in membrane

permeability Thus, Membrane Permeability Transition (MPT) pores are opened and pro-apoptotic proteins come out into cytosol. These proteins includes cytochrome c, Smac/DIABLO and HtrA2/Omi. Most important among these proteins is cytochrome c which bind with Apaf-1 and pro-caspase 9, this entire combination of all these 3 is called as “Apoptosome” (Elmore, 2007). Cytochrome c is the main component required for caspase-9 activation. Anti-apoptotic Bcl-2 family members strongly regulate this pathway via inhibiting cytochrome c (Tsujiimoto *et al.*, 1985; Reed, 1998; Shimizu *et al.*, 1999). Ratio of pro-apoptotic and anti-apoptotic Bcl-2 members is an important feature for mitochondrial membrane permeability (Chowdhury *et al.*, 2006). The cleavage and full activation of caspases depends upon close proximity of enzymes thus leads to conformational change in activation complex (Luthi and Martin, 2007; Tadokoro *et al.*, 2010).

The BH3 proteins are responsible for pro-apoptotic proteins (Bax and Bak) assembly into mitochondrial membrane pores and change of membrane permeability leads to release of cytochrome c via Mitochondrial Permeability Transition Pore((PTP) or MPT or Voltage Dependent Anion Channels (VDAC) (Nguyen *et al.*, 1993; Hussein *et al.*, 2003; Green and Reed, 1998; Tsujimoto and Shimizu, 2002). Thus caspase-9 gets activated but during this activation Smac/DIABLO and HtrA2/Omi has very important role to inhibit Inhibitor of Apoptosis Proteins (IAP), thus Promote Apoptosis. The ser-pin Crm from cowpox virus as well as p35 protein of baculovirus acts as pan-caspase inhibitor (Miller, 1999; Xu *et al.*, 2001; Renatus *et al.*, 2000).

Including above pro-apoptotic proteins certain other proteins like AIF, endonucleases G and Caspase Activated DNAase (CAD) are also released from mitochondria during apoptosis in later stages. Out of these Apoptosis Inducing Factor (AIF) and endonuclease G acts independently to caspases while CAD needs cleaving by caspase 3. The AIF leads to fragmentation of DNA into ~50-300 kb pieces while endonuclease G leads to cleaving of nuclear chromatin into oligonucleosomal DNA fragments. Condensation of nuclear chromatin in this stage produced by AIF and endonuclease G is called as “Stage 1 condensation”. While later on CAD which enters into nucleus is cleaved by caspase 3 and produce pronounced stage of condensation called as “Stage 2” condensation (Elmore, 2007).

An important family of proteins i.e., Bcl-2 (plays an important role to govern mitochondrial permeability) which include pro-apoptotic as well as anti-apoptotic proteins. Pro-apoptotic proteins include Bcl-10, Bax, Bak, Bad, Bim, Bik, Blk, Puma and Noxa which help in apoptosis while anti-apoptotic proteins include Bcl-2, Bcl-x, Bcl-XS, Bcl-w and BAG. Puma and Noxa both leads to P53 mediated apoptosis, as Puma leads to increase Bax level thus increase the rate of release of cytochrome c while Noxa bind with anti-apoptotic molecules and thus activate caspase-9. Mutations of proapoptotic BH3-only protein genes have also been found to contribute to cancer development. Besides the Bcl-2 protein family, the tumor repressor p53 is frequently mutated in cancer cells (Fulda and Debatin, 2006). The TP53 is a tumor suppressor gene which is very important regulator of Bcl-2 family. The P53 is a tetrameric stress response protein acts as a break to cell cycle. It binds to DNA and further:

- Arrest cell cycle at G1 phase and thus provide time for DNA repair and plays role in angiogenesis, cell differentiation and apoptosis (Chowdhury *et al.*, 2006; Amaral *et al.*, 2009; Vousden, 2009; Vousden and Ryan, 2009)
- If repair is not possible it mediates apoptosis via Bax up regulation or down regulating Bcl-2. Thus helps in mitochondrial dependent pathway (Owen-Schaub *et al.*, 1995; Park *et al.*, 1997)

**Perforin/granzyme pathway:** It is a CTL-induced apoptotic pathway able to kill virus infected and tumor cells via releasing perforin granules through the pores to target cells. Granzyme A and B are important components of granules released. Granzyme B can activate pro-caspase 10 by cleaving at aspartate residues, also leads to cleavage of caspase inhibitors like inhibitors of caspase activated DNAase (ICAD). It also uses intrinsic pathway to amplify the death signals by Bid cleavage and inducing cytochrome c release. It can directly activate caspase 3 thus capable of direct induction of execution phase of apoptosis. While granzyme A is a caspase independent pathway and is involved in cytotoxic T cell induced apoptosis (Elmore, 2007).

**Execution pathway:** It is the final pathway of apoptosis where all the previous pathways are merged. This pathway is mediated by execution caspases-caspase-3, caspase-6 and caspase-7. Caspase-3 is most important one among all. The intrinsic and extrinsic pathways converge at caspase-3 (Wong, 2011). It activates endonucleases as bind with ICAD and CAD is released which undergo chromatin condensation. Caspase-3 also leads to reorganization and disintegration of the cell into apoptotic bodies. A huge range of pathogens have been found to cause cell death by means of apoptosis (Gao and Kwai, 2000; Hay and Kannourakis, 2002; Weinrauch and Zychlinsky, 1999). Some bacteria cause apoptosis by toxins or protein synthesis inhibition, many viruses and parasites also acts as mediators of apoptosis (Hay and Kannourakis, 2002; Moss *et al.*, 1999; James and Green, 2004; Gavrilescu and Denkers, 2003).

**Bacteria-induced cell apoptosis:** Bacteria are capable to induce apoptosis by many mechanisms including pore forming proteins, inducing death machinery of dead cells and by secretion of many protein inhibitors (Lancellotti *et al.*, 2006). The bacteria always have affinity towards host tissues thus oftenly involved with apoptotic mechanisms (Lancellotti *et al.*, 2009). Several bacterial species affects central nervous system like *Streptococcus pneumonia* (pneumococcus), *Hemophilus influenzae* B and *Neisseria meningitidis* (meningococcus), *Listeria monocytogenes* (Schuchat *et al.*, 1997). *Mycobacterium tuberculosis*, *Treponema pallidum*, *Borrelia burgdorferi*, *Rickettsiae*. These agents cause meningitis and agents like *Staphylococcus aureus* and *Streptococcus* species causes brain abscess (Bartzatt, 2011; Beckham and Tyler, 2012). *Borellia* infection causes damage to oligodendrocytes and *Brucella abortus* causes gliosis of astrocytes and apoptosis (Ramesh *et al.*, 2008; Samartino *et al.*, 2010; Parthasarathy and Philipp, 2012). Table 2 presents the bacterial mediated apoptotic mechanism.

**Viral proteins affecting apoptosis:** There are several viruses which are known to induce apoptosis (Clarke and Tyler, 2009) which helps to evade the virus from the host defense mechanism (Nakanishi *et al.*, 2008; Ehrhardt and Ludwig, 2009). Virus codes for several proteins that have central role in apoptosis like E1A 12S and 13S proteins, E3, E4 of adenovirus, E2 and E7 of papilloma viruses, NS1 of parvovirus, apoptin (VP3) of Chicken Infectious Anemia Virus (CIAV), SV40 large T antigen and HN protein of Newcastle disease virus and tat of HIV-1, Nonstructural protein ORF3 of porcine circovirus type 2 (Lin *et al.*, 2011), HSV-1 (Perkins *et al.*, 2003), coxsackievirus B3 (Kim *et al.*, 2004), reovirus (Clarke *et al.*, 2004), *Swine influenza virus* (Choi *et al.*, 2006) and poliovirus (Autret *et al.*, 2007), *Infectious bursal disease virus* (IBD) (Wei *et al.*, 2011). The NS1 protein of different viruses exploits various mechanisms in causing cell death like arrest in cell cycle, production of Reactive Oxygen Species (ROS) thereby leading to mitochondrial damage and cell death, destruction of the cytoskeleton leading to necrosis, release

Table 2: Mechanism of bacterial induced apoptosis

Bacteria	Mechanism involved	References
<i>Shigella</i>	Induces apoptosis in macrophages by caspase-1 activation	Kim <i>et al.</i> (1998), Islam <i>et al.</i> (1997), Zychlinsky <i>et al.</i> (1996) and Hilbi <i>et al.</i> (1998)
<i>Salmonella</i>	Induces apoptosis in macrophages by caspase-1 activation	Hersh <i>et al.</i> (1999) and Weinrauch and Zychlinsky (1999)
<i>Escherichia coli</i>	Activation of caspase-8 thus induce cytochrome c release	Li <i>et al.</i> (1998) and Luo <i>et al.</i> (1998)
<i>Yersinia</i>	Leads to apoptosis of macrophages by translocation of YopJ or YopP molecules into macrophages	Mills <i>et al.</i> (1997) and Monack <i>et al.</i> (1997)
<i>Pseudomonas</i>	Leads to upregulation of CD95/CD95 ligand	Grassme <i>et al.</i> (2000)
<i>Helicobacter pylori</i>	Produce VacA toxin thus increase mitochondrial membrane permeability	Lancellotti <i>et al.</i> (2006)
<i>Neisseria</i>	Produce porin protein PorB1B which on interaction with HeLa cell mitochondria and leads to calcium efflux and leads to apoptosis of cells in brain	Drabick <i>et al.</i> (1999) and Massari <i>et al.</i> (2000)
<i>Legionella</i>	Leads to apoptosis of macrophages and alveolar epithelial cells and this process is regulated by Dot/Icm type 4 like secretion system	Byrne and Swanson (1998) and Gao <i>et al.</i> (1997, 1999)
<i>Listeria</i>	Release Lly-O toxin and act on mitochondrial membrane	Lancellotti <i>et al.</i> (2006)
<i>Mycobacterium</i>	Produce apoptosis of macrophages via TNF- $\alpha$ and caspase-1 dependent pathway	Fratazzi <i>et al.</i> (1997), Keane <i>et al.</i> (1997) and Rojas <i>et al.</i> (1997, 1999)
<i>Chlamydia</i>	Undergo caspase independent apoptosis via overexpression of apoptosis. The main gene which is over expressed includes, Bax	Xiang <i>et al.</i> (1996)
<i>Coxiella</i>	TNF- $\alpha$ mediated apoptosis	Dellacasagrande <i>et al.</i> (1999)
<i>Rickettsia</i>	Basically blocks apoptosis thus having pro-apoptotic activity but apoptosis occurs if rickettsia induced NF-kappa B is inhibited	Clifton <i>et al.</i> (1998)
<i>Streptococcus pneumoniae</i>	Caspase dependent as well as caspase independent both pathways are activated. The Apoptosis Inducing Factor (AIF) is concerned with apoptosis induced by this bacterium	Parthasarathy and Philipp (2012) and Lancellotti <i>et al.</i> (2009)
<i>Staphylococcus aureus</i>	Activation of caspase-8 and 3	Kinsner <i>et al.</i> (2006)
<i>Brucella abortus</i>	TNF/TNFR-1 mediated extrinsic pathway	Samartino <i>et al.</i> (2010)
<i>Bacillus anthracis</i>	Zn metalloprotease inhibit MAPK pathway leads to cell death	Favaloro <i>et al.</i> (2012)
<i>Clostridium difficile</i>	Enterotoxin A, B leads to cytochrome c release	Ulett and Adderson (2006)

of cathepsin B causing cell death, induction of Jun NH<sub>2</sub>-terminal kinase (JNK) pathway (Wei *et al.*, 2011) and even sometime direct destruction of the DNA (Marcellus *et al.*, 1996; Webster *et al.*, 2001; Nuesch and Rommelaere, 2006; Di Piazza *et al.*, 2007; Dhama *et al.*, 2008; Hristov *et al.*, 2010; Noteborn, 2004; Kumar *et al.*, 2011).

The VP3 protein of chicken anemia virus is a 13.6 kDa small protein which has the property of inducing apoptosis and hence this protein is called as apoptin. Apoptin induces apoptosis only in transformed cells and not in normal cells hence it seems to be better candidate for cancer therapy (Tavassoli *et al.*, 2005; Natesan *et al.*, 2006; Dhama *et al.*, 2013; Gupta *et al.*, 2015). In tumour cells, apoptin is phosphorylated and mainly nuclear whereas in normal cells it is unphosphorylated, cytoplasmic and becomes readily neutralized (Ko *et al.*, 2005). Table 3 depicts the role played by viral proteins in apoptosis. The c-Jun NH<sub>2</sub>-terminal kinases (JNK) is a central components of signal transduction pathways which is involved in the regulation of cell proliferation and differentiation, cytokine production, apoptosis and cell survival. It is being utilized by several viruses for optimal virus replication. The JNK pathway modulates the mitochondrial pathways of apoptosis. The JNK is required for the release of proapoptotic molecules such as Bax from the cytosol to the mitochondria and cytochrome c from the mitochondria to the cytosol (Lei *et al.*, 2002; Tournier *et al.*, 2000) and thus regulating cell apoptosis. The IBD virus alters this signaling pathway. Reports are conclusive over its role that its inhibition reduces the accumulation of



Table 3: Role of viral proteins in apoptosis

Virus	Cancer type	Protein	Mechanism
Epstein virus	Burkitt's lymphoma, hodgkin lymphoma, nasopharyngeal carcinoma, gastric carcinoma	EBNA3C	Binds with Rb and promote cycle progression
		EBNA1	Inhibit p53 induced apoptosis
		LANA1 kaposina	Inhibit p53 induced apoptosis
		E6	Inhibit p53, Bak, procaspase 8
Human herpes virus 8	Kaposi's carcinoma, cervical cancer, oropharyngeal cancer and anal cancer	E7	Pleotropic effect
		E2	Activates caspase-8 and Inhibit c-FLIP
		Tax	Regulate cell cycle and apoptosis
Human T-cell leukemia virus	T-cell lymphoma	Tax	Regulate cell cycle and apoptosis
Influenza virus (H3N2)	Influenza virus infection	FasL and Fas R initiator	Over expression of FasL and FasR
Hepatitis B	Hepatocellular carcinoma	HBx	Activate caspase-3 and 8
Hepatitis C	Hepatocellular carcinoma	Core, NSSA and NS3	Induce p53 mediated apoptosis

Fuentes-Gonzalez *et al.* (2013) and Wada *et al.* (1995)

Table 4: Role of parasites in apoptosis

Parasite	Mechanism	References
<i>Plasmodium falciparum</i>	leads to caspase-8 and 9 activation, ROS mediated	Esslinger <i>et al.</i> (1994)
<i>Toxoplasma gondii</i>	Mainly Fas mediated apoptosis.	Bienvenu <i>et al.</i> (2010)
<i>Trypanosomiasis</i>	Fas mediated	De Oliveira <i>et al.</i> (2007) and Rodrigues <i>et al.</i> (2008)
<i>Entamoeba histolytica</i>	Fas and TNF receptor mediated	Bienvenu <i>et al.</i> (2010)
<i>Cryptosporidium parvum</i>	Fas/FasL mediated	Bienvenu <i>et al.</i> (2010)
<i>Trichinella spiralis</i>	Pro-inflammatory cytokines mediated	Cliffe <i>et al.</i> (2007)
<i>Clonorchis sinensis</i>	Increase Fas and caspase-3 in liver	Bienvenu <i>et al.</i> (2010)
<i>Leishmania donovani</i>	Inhibit apoptosis through (granulocyte monocyte-colony stimulating factor) GM-CSF production	Barcinski and DosReis (1999)

viral mRNA and viral protein synthesis followed by causing a lowered production of infectious virus particles. Several viruses such as reovirus, rotavirus, poliovirus and influenza A virus have shown mitochondria-mediated apoptosis by the JNK pathway (Clarke *et al.*, 2004; Autret *et al.*, 2007; Martin-Latil *et al.*, 2007).

**Main mechanisms of parasites induced cell apoptosis:** The apoptosis is evident in multicellular organisms (Kerr *et al.*, 1972) but it has some controversial existence in unicellular protozoan parasites (Welburn *et al.*, 2006; Vercammen *et al.*, 2007). Table 4 shows the role played by parasites in apoptosis.

**Role of apoptosis in cancers:** The many of the viral proteins have ability to interact with apoptotic pathways and induce cancers in the cells. However, some of the viral proteins can promote the apoptotic process but only in early stages of the infection not in transformation process (Fuentes-Gonzalez *et al.*, 2013). In general apoptosis is concerned with many of the diseases conditions but sometime increased apoptosis expression mechanisms can be used in treatments of many of the neoplastic conditions (Wong, 2011). Alteration in proteins in the apoptotic pathway leads to different types of cancer (Table 5). Similarly under certain disease conditions there is increase in the expression of apoptotic proteins (Table 6) (Favaloro *et al.*, 2012; Hay and Kannourakis, 2002; Moss *et al.*, 1999; James and Green, 2004; Gavrilescu and Denkers, 2003; Butler *et al.*, 1998; Hahne *et al.*, 1996; Su *et al.*, 2015; Lee *et al.*, 2010).

**Over-expression of apoptosis:** Favaloro *et al.* (2012), Simunovic *et al.* (2009), Barcia *et al.* (2007, 2011) and Tian *et al.* (2009) studied about the over expression of apoptotic proteins.

Table 5: Alteration of apoptotic proteins and their outcomes

Alteration	Outcome
<b>Bcl-2 family proteins alterations</b>	
Bcl-2 alteration	Hodgkin disease, breast cancer
Bax alteration	Brain tumor
BH3 protein decrease (Bid)	Chronic myelomonocytic leukemia
P53 gene mutation	Li fraumenic syndrome
Apaf 1 inactivation	Melanomas, glioblastomas
Altered caspase activity	c-FLIP compete FADD, IAP activation
CD95 (Fas) inactivation-	Hepato-carcinoma, esophageal cancer
Bax inactivation	Colo-rectal cancer metastases
Caspase-8 inhibition	Neuroblastoma

Table 6: Conditions leading to over expression of apoptotic proteins

Diseases	Mechanism
<b>Immunosuppressive</b>	
AIDS	HIV Tat protein leads to Fas mediated apoptosis
<b>Neurodegenerative diseases</b>	
Alzheimers's diseases	Beta-plaques, increases Fas and TNFR (tissue necrotic factor receptor)
Parkinson diseases	Lewy body accumulation in neuron, Fas, TNFR mediated apoptosis
Hutington disease	Htt protein activate caspase-6 and 8
Amylotrophic lateral sclerosis	Cu, Zn, SOD (superoxide dismutase) mutation trigger cytochrome c release
<b>Heart and brain diseases</b>	
Myocardial ischemia	Increase ORS and Bax and fall in Bcl-2
Stroke (Brain ischemia)	Fas/FasL mediated apoptosis

## Use of anti-apoptotic therapy

### Anti-apoptotic agent:

- IAP stimulation (XIAP, Survivin) stroke, spinal cord injury
- Caspase inhibition by Z-VAD-fmk myocardial infarction
- ICE inhibitor rheumatoid arthritis
- PARP inhibitor reperfusion injury
- BAX inhibitors protect cells from injury

**Assays used:** In apoptotic pathways DNA cleavage occurs in two sages:

- Topoisomerase 2 cleaves DNA into 200-300 kb sized fragments
- DNase1/DNase2 breaks DNA into oligonucleosome sized fragments. Table 7 depicts the list of different tests employed for identification of apoptosis

Other techniques includes Flow cytometry, immunohistochemistry and use of DNA staining fluorescent dye like Hoechst 33342 help to demonstrate chromatin condensation (Chowdhury *et al.*, 2006). One important characteristic of apoptosis is that it shows characteristic DNA ladder by agar gel electrophoresis stained with ethidium bromide and visualized with UV light (Elmore, 2007). Flow cytometry is one of the relevant method to assess the number of live or fixed cells in a cell population per second (Toduka *et al.*, 2012) and also the injury induced by nano-particles (Prina Mello *et al.*, 2010).

## SOME ALTERNATIVE FORMS OF CELL DEATH

**Necrosis (Type 3 cell death):** There are some other forms of cell death like necrosis which is a non-apoptotic, passive, unregulated, accidental form of death (Farber, 1994; Kanduc *et al.*,

Table 7: Tests used for identification of apoptosis

Alterations	Assay used
<b>Cytoplasmic alterations</b>	
Apoptotic cells	H and E stain, toluidine stain
Smaller apoptotic bodies	TEM (gold standard)
Phagocytosis of apoptotic bodies	TEM
<b>DNA fragmentation</b>	
Endonuclease degradation products	DNA Laddering technique (DNA agarose gel electrophoresis) TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) assay
Caspase detection	Western blot, Mab, Poly. Ab
Detection of apoptotic and necrotic cells	Hoechst and PI staining
Apoptotic and pro-apoptotic genes	PCR micro assay
Membrane alteration	PS by FITC labeled Annexin V (for early stage of apoptosis)
DNA fragmentation	Histone ELISA
Early detection of apoptotic cells	Comet assay
<b>Mitochondrial assay</b>	
Cytochrome c release, Bax, Bcl-2	EM, fluorescence

TEM: Transmissible electron microscopy, PCR: Polymerase chain reaction, ELISA: Enzyme linked immune sorbent assay, EM: Electron microscopy, Source: (Elmore, 2007; Shi, 2002; Gong *et al.*, 1994; Bortner *et al.*, 1995; Lecoeur *et al.*, 2001; Godard *et al.*, 1999; Cai *et al.*, 2013; Hankins *et al.*, 2015; Leventis and Grinstein, 2010; Ciftci *et al.*, 2013; Dhama *et al.*, 2010; Su *et al.*, 2015)

2002). But sometimes necrosis is controlled also like apoptosis (Vandenabeele *et al.*, 2010; Van Herreweghe *et al.*, 2010). Word necrosis is a Greek word which means “Death or dead body” (McCall, 2010). Necrosis leads to clumping of chromatin, swelling of organelles followed by cellular swelling, depletion of ATP, mitochondrial damage, loss of calcium homeostasis, accumulation of oxygen-derived free radicals and defects in membrane permeability. Thus leads to inflammatory response in contrast to apoptosis (Golstein and Kroemer, 2007a; Wyllie *et al.*, 1980; Searle *et al.*, 1982; Kepp *et al.*, 2009). It produces cell organelles disintegration more rapidly and rupture of plasma membrane and leakage of pro-inflammatory molecules due to non- physiological processes like shock, hypoxia, trauma etc (Thompson, 1995; Schwartzman and Cidlowski, 1993; Cohen, 1993). Necrosis is a major form of cell death including neurodegenerative diseases, heart diseases, toxicity, muscular dystrophy, ischemia and infections (Yamashima, 2004; Millay *et al.*, 2008; Kennedy *et al.*, 2009; Challa and Chan, 2010; Fujimoto *et al.*, 2010; Whelan *et al.*, 2010). All apoptotic cells which fail to be engulfed by phagocytes undergoes autolytic program i.e., secondary necrosis (Wyllie *et al.*, 1980; Schulze *et al.*, 2008).

Apoptosis and necrosis are main models involved in cell death (Majno and Joris, 1995, 2004) but autophagy represents another model which is involved in cellular remodeling, nutritional deprivation and in certain disease processes (Golstein and Kroemer, 2007a). Apoptosis is the fastest mode of cell death while the necrosis and autophagy is seen after apoptosis is vanished (Cherlonneix, 2008). In many processes apoptosis is not major mode of cell death in that case termed as “Oncosis” is used as cell death is accompanied by cellular swelling (Majno and Joris, 1995). This name was given a long years back by Von Recklinghausen and Rudolph Virchow (Weerasinghe and Buja, 2012).

In recent years it has been seen that initial apoptosis undergoing cells undergo oncosis later on, which is known by many names like programmed death, programmed necrosis, type 3 necrosis and necroptosis (Kerr, 1970; Jaeschke and Lemasters, 2003; Webster, 2007; Golstein and Kroemer, 2007b; Kung *et al.*, 2011; Konstantinidis *et al.*, 2012; Whelan *et al.*, 2012). But it has been seen that a highly regulated programmed process called as necroptosis, which is induced by TNF- $\alpha$  (Degterev *et al.*, 2005). Necroptosis is morphologically similar to necrosis (Galluzzi *et al.*, 2011). Rip1 was found be involved in signaling pathway of necroptosis. Rip1 kinase leads to the formation of complex in the presence of TNF- $\alpha$  (Micheau and Tschopp, 2003). Rip1 polyubiquitinated in complex and ultimately leads to IKK pathway activation and translocation of NF-kappa B which

acts as transcription factor (Micheau and Tschopp, 2003). Enzymes like CYLD, Rip3 binds with Rip1 via Rip Homotypic Interaction Motif (RHIM) and thus leads to phosphorylation and form cytosolic complex 2 formation which is very critical for necroptosis (Wang *et al.*, 2008). After treatment with TNF- $\alpha$  and z-VAD-FMK it has been found that RHIM and kinase domains of Rip1 and Rip3 both are important for necroapoptosis (Zhang *et al.*, 2009; Cho *et al.*, 2009). Rip1 is found to be very important for Rip3 phosphorylation and both these proteins form a complex called as necrosome (Cho *et al.*, 2009; He *et al.*, 2009). Rip1 and Rip3 are not important for apoptosis but Rip3 is must for necroptosis (Zhang *et al.*, 2009). This kinase pathway is basic pathway which separates apoptosis from necroptosis (Buchheit *et al.*, 2012).

**Autophagy:** It is another type of cell death, also called as type 2 cell death and occurs in eukaryotic cells where leads to degradation of dying cell components inside phagocytic vacuoles. Autophagy is supposed to be a Programmed Cell Death (PCD) occurring during normal embryonic life (Elmore, 2007; Levine and Klionsky, 2004). Autophagy like other forms of cell death is capable to induce diseases in plants as well in animals (Coll *et al.*, 2011; Van Doorn *et al.*, 2011; Liu and Bassham, 2012). This mechanism is mainly concerned with degradation of proteins and cytoplasmic organelles (Levine and Klionsky, 2004). Process of autophagy is a PCD which resembles with apoptosis and entirely dependent on protein synthesis as well as continuous ATP production as it is an energy dependent process (Schwartzman and Cidlowski, 1993; Ohsumi, 2001; Huang and Klionsky, 2002; Gozuacik and Kimchi, 2004; Debnath *et al.*, 2005). It can be associated with physiological as well as pathological processes (Mehrpour *et al.*, 2010). Autophagy undergo caspase independent pathway but also shows significant features of apoptosis but it doesn't show DNA laddering (Cohen, 1991). The FADD death domain induces both apoptosis and autophagy in epithelial cells (Thorburn, 2008). The autophagy includes micro-autophagy, macro-autophagy and chaperone mediated autophagy (Mizushima and Komatsu, 2011).

**Pyroptosis:** It is phylogenetically old process and involves vacuolization, degradation of cytoplasmic components and chromatin condensation to some extent (Clarke, 1990; Bursch *et al.*, 2000; Bursch, 2001). This pathway is caspase-1 dependent (Hersh *et al.*, 1999; Brennan and Cookson, 2000). This form of cell death is mediated by mitogen activated protein kinases, TNF receptor family members or insulin like growth factor1 (Broker *et al.*, 2005). This caspase dependent cell death is seen in macrophages which is infested with some of the microorganisms like *Listeria monocytogenes* (Cervantes *et al.*, 2008), *Yersinia pseudo-tuberculosis* (Bergsbaken and Cookson, 2007) and *Legionella pneumophila* (Molofsky *et al.*, 2006; Zamboni *et al.*, 2006).

**Entosis:** It is one of the highly regulated and non-canonical cell deaths which occurs as a result of ECM-detachment nutrient deficiency. It is seen in many cancers and categorized as a "Cell-in cell cytological phenotype" (Chowdhury *et al.*, 2006; Overholtzer *et al.*, 2007; Overholtzer and Brugge, 2008). It is a caspase independent (Overholtzer *et al.*, 2007) as well as an active process (Yang and Li, 2012).

**Mitotic catastrophe (mitotic failure):** It is a form of cell death occurring because of defective mitosis which occurs due to excessive DNA damage leading to tetraploidy or endopolyploidy where different check points of cell cycle are deregulated (Castedo *et al.*, 2004). It is accomplished by mitotic arrest but still its mechanism is unclear (Vitale *et al.*, 2011; Galluzzi *et al.*, 2012).

## CONCLUSION

Many pathways are responsible to cause cell death as discussed in this review but apoptosis is one associated with physiology as well as pathology of cells. This mode of cell death is energy dependent and is associated with caspases. The apoptotic pathways vary among cells. The different cells respond differently to different microbial agents, toxins, parasites and inflammatory agents produced in turn. The different agents trigger different apoptotic pathways and caspases. Although many apoptotic and anti-apoptotic proteins are involved in different apoptotic pathways but still research is required in this field in a deeper prospective as well as in therapeutic side.

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