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Physiologic to Pathologic Cellular and Molecular Levels of Elusive Cell Death Programs and Their Manipulative Action

Bina Kashyap[1] and P Sridhar Reddy[2]*

[1]Department of Oral Pathology, Buraydah Private Dental College, Saudi Arabia

[2]Department of Oral and Maxillofacial Surgery, Buraydah Private Dental College, Saudi Arabia

Abstract

The balance of cell death and cell formation in multicellular organisms is crucial to maintain proper development, tissue hemostasis and immune regulation. Any dysregulation, at cellular and molecular level, results numerous pathologies. Cell death often evolve as host defense system, in response to pathogens, eliciting inflammation with certain molecular, cellular, biochemical, morphological and physiological changes through various cell death programs. This article reviews major types of cell death (apoptosis, autophagic cell death, necrosis and pyroptosis) as a host defense factor or mediated by inflammation.

Keywords: Apoptosis; Autophagic; Hemostasis; Inflammation; Necrosis; Pathologies; Pyroptosis

Introduction

Development and homeostasis of multicellular organisms is maintained by the equilibrium between cell existence and cell death. Cell death is a fundamental process occurring early from development, maintaining homeostasis and protective immune regulation in a multicellular organism. The dysregulation in the controlled cell death mechanism will be associated with numerous pathologies [1].

Early in 1960, apoptosis was considered the only standard programmed cell death form Programmed Cell Death (PCD) is necessary for many biological and functional processes, such as the developing of organs, epithelial cell renewal and selection of lymphocyte for immunity. Though, cell death is not developmentally programmed, it is a sign of stress, injury or infection and is associated to the tissue damage and disease progression and various pathologies. Inflammation is a protective immune response system persuaded in response to infection/injury that in turn is vital for well-organized host defense and repair of tissue. Uncontrolled excessive and/or prolonged inflammatory responses mainly chronic inflammation causes tissue damage and contributes to the pathogenesis of various acute and chronic inflammatory diseases [2-4].

Cell death is generally divided as either programmed or passive. The programmed cell death, apoptosis, requires cellular metabolic energy and is mediated by cell defined pathways and effector molecules, while the passive form of cell death, necrosis, occurs hysterically due to extracellular stresses. During defensive action, programmed cell death act in a protective manner, by the death of infected cells so as to reduce microbial infections, to isolate infected cells from uninfected neighboring cells, and alert the host immune system through danger signals and inflammatory mediators [1,5].

Literature review mentions different types of cell death, often defined by either morphological criteria or at cellular, molecular and biochemical levels. Some of the cell death are classified as apoptosis, necrosis, and autophagic cell death or associated with mitotic catastrophe. Galluzzi et al. [6] mentioned that cell death is defined based on enzymological criteria, including the involvement of different classes of proteases (caspases, calpains, cathepsins and transglutaminases) and nucleases, on functional aspects (programmed or accidental, physiological or pathological) or on immunological characteristics (immunogenic or non-immunogenic).

Apoptosis is the major cell death pathway and is caspase-dependent. Caspase-independent

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Correspondence:
Bina Kashyap, Department of Oral Pathology, Buraydah Private Dental College, Buraydah, Saudi Arabia, Tel: +966-504663028; E-mail: binakashyap@yahoo.co.in

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mechanisms can cooperate with (or substitute for) caspases in the execution of lethal signaling pathways. The necrotic cell death pathway is mediated through the serine/threonine kinases Receptor Interacting Protein 1 (RIP1) and 3 (RIP3). The signaling involving caspase-1-mediated cell death is termed pyroptosis which is different from traditional caspase dependent apoptosis. "Autophagic cell death" is a type of cell death occurring together with (but not necessarily by) autophagic vacuolization [7-9].

Apoptosis

In 1972, the term "Apoptosis" was used for the first time to describe a form of cell death that literally means "falling off or dropping off". Apoptosis is broadly studied and the underlying cellular and molecular signaling events are well characterized. Morphological change is noticed in apoptosis, affecting single cell or small group of cells, is a step wise process, which includes cell shrinkage, chromatin condensation, membrane blebbing, nuclear collapse with continuous blebbing, apoptotic body formation and finally lysis of the apoptotic bodies. The biochemical events of apoptosis require gene expression, protein synthesis, energy consumption to make it an active process. There will not be any inflammatory reaction but shows few macrophages, for the removal of the apoptotic bodies [10].

Apoptosis follows two main pathways: Intrinsic pathway and the extrinsic pathway. It involves two main proteins; one control mitochondrial integrity namely the Bcl-2 (B Cell Lymphoma 2) family of proteins, and the other mediates the execution of apoptosis namely cysteinyl aspartate-specific proteases or caspases. Caspases plays a crucial role in apoptosis and is further subdivided as motivator/initiator (caspase-2, -8, -9, -10) and executioner/killer (caspase-3, -6, -7) caspases [9,11] (Figure 1).

Intrinsic pathway is activated by various insults, such as genetic damage and cytotoxic insults, and acts through the mitochondria, which is controlled by the Bcl-2 family of proteins. In homeostatic conditions, Bcl-2 family has anti-apoptotic and pro-apoptotic members. The anti-apoptotic Bcl-2 family members maintain mitochondrial integrity by preventing the pro-apoptotic Bcl-2 family members (Bax and Bak) from causing mitochondrial damage. During cellular stress, the inhibition of pro-apoptotic Bax and/or Bak is relieved, which undergoes oligomerization and formation of a channel in the mitochondria, through which cytochrome c (cyt c) is released into the cytosol. Cyt c binds with Apaf-1 (Apoptotic peptidase activating factor 1) and ATP (Adenosine Triphosphate), to form a stage for recruitment and initiation of caspase family of protein mainly procaspase-9, known as the apoptosome. Caspase-9 activates the downstream executioner/killer caspases-3, -6 and -7, which initiates the execution of apoptotic cell death [7,9].

The extrinsic pathway initiates stimulation of death receptors belonging to the Tumor Necrosis Factor Receptor (TNFR) family, which includes TNFR, Fas (First apoptosis signal) and TRAIL-R (TNF Related Apoptosis Inducing Ligand-Receptor). These receptors can induce a variety of cellular responses, including proliferation, differentiation and cell death after stimulation from various insults. Apoptosis begins with the formation of a Death-Inducing Signaling Complex (DISC) which includes Fas-Associated Death Domain (FADD). FADD recruits the initiator caspases-8 and/or -10. Apart from, Fas and TRAIL-R, TNFR1 aggregation also takes place which leads to the progressive formation of two complexes. Complex I is formed at plasma membrane and consists of TNFR1, TNFR-Associated Death Domain (TRADD), TRAF2 (TNF Receptor

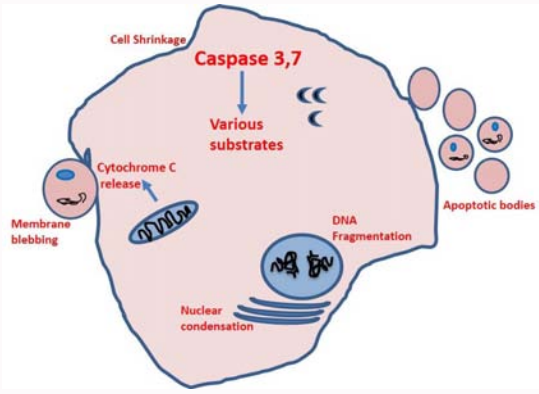

Figure 1: Caspase (3,7) dependent pathway for apoptosis.

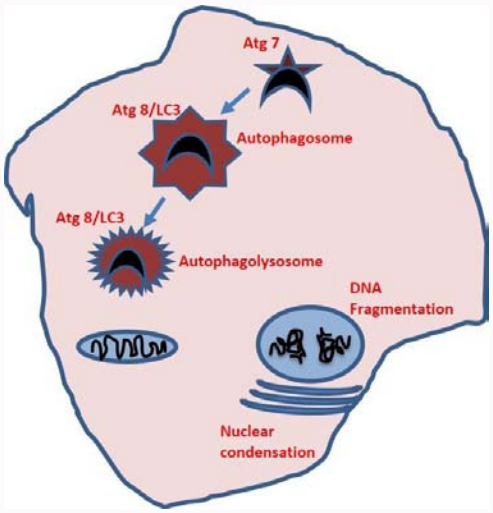

Figure 2: ATG mediated autophagic cell death.

Associated Factor 2), RIP1 (Receptor Interacting Protein 1), cIAP1 (Inhibitor of Apoptosis Protein 1) and cIAP2 (Inhibitor of Apoptosis Protein 1). Complex II is formed by endocytosis of TNFR1, which is equivalent to the DISC induced by FasL and TRAIL and includes TRADD, FADD, and caspase-8 and/or -10. Activation of caspase-8 and -10 leads to activation of executioner caspases and progress to cell death [9,12,13].

Under physiologic condition, apoptosis plays an important role in development of the lens, in shaping of the inner ear, in cardiac morphogenesis, in muscle development, in removal of interdigital webs, establishment of nervous and the immune systems. Apoptosis also helps in post-lactational mammary gland regression, ovarian follicular atresia and post-ovulatory regression, and in terminating an immune response by eliminating of activated immune cells. During bacterial or viral infection, apoptosis acts protectively by destroying the site of pathogen reproduction. Pathogens tries to evolve in several ways to inhibit apoptosis, e.g. by preventing cyt c release from mitochondria & caspase initiation and also by activating cell survival pathway. Alteration in the regulation of apoptosis can result in various pathologies like sepsis, stroke, myocardial infarction, ischemia, neurodegenerative diseases, diabetes, autoimmune diseases and cancer [14-17].

Autophagic cell death

Autophagic cell death is genetically regulated process for the

Table 1: Morphologic and Physiologic differences between pyroptosis and apoptosis cell death.

Morphologic and Physiologic characteristics	Pyroptosis	Apoptosis
Cell lysis	Present	Absent
Cell Swelling	Present	Absent
Pore formation	Present	Absent
Membrane blebbing	Absent	Present
DNA fragmentation	Present	Present
Nuclear condensation	Present	Present
Caspase 1	Activated	Not activated
Caspase 3	Not activated	Activated
Caspase 7	Activated	Activated
Release of cytochrome c	Absent	Present
Glycolysis enzymes	Inactivated	Inactivated
Outcome	Inflammation	No Inflammation

degradation of subcellular components, with the involvement of the enzymes ATG (Autophagy Related Gene)/Beclin protein. These proteins cause lysosomal enzyme degradation of intracellular components captured within a double-membrane vacuole termed the autophagosome. This catabolic process maintains energy for homeostasis and cell survival during starvation. Additionally, autophagic cell death has many diverse functions in cellular processes, such as cellular stress, differentiation, development, longevity and immune defense. Several interconnections exist between autophagy, apoptosis and necrosis. The presence of autophagic vacuoles in dying cells differentiates it with others. This type of cell death can be mediated under stress conditions and by chaperons [18,19].

Autophagic cell death follows a stepwise pathway including induction, nucleation and elongation. Induction acts through a protein kinase, mTOR (Mammalian Target of Rapamycin), which is important in controlling translation and cell-cycle progression. Nutrients and growth factors presence will activate mTOR, which inhibits autophagy. But deprivation of nutrient or growth factor, or treatment with rapamycin leads to inhibition of mTOR. This inhibition of mTOR activates ULK-Atg13-FIP200 (UNC-51 like kinase- Autophagy related gene 13-Family interacting protein of 200KD, a focal adhesion kinase) complex is activated, leading to the induction of autophagosome formation. After induction, vesicle nucleation begins, which is instigated by the congress of another complex, PI3KC3 (*Vps34* gene)-complex (Phosphatidylinositol 3 kinase catalytic subunit type 3). Beclin-1 (Atg6) serves as a platform for binding of various other proteins which positively regulate PI3KC3 activity. Anti-apoptotic Bcl-2 binds with Beclin-1 to prevent the autophagy process by abolishing autophagic signals. But in compromised state of cell, Bcl-2 becomes phosphorylated and releases Beclin-1 and thereby stimulating autophagy [7,20-23].

Vesicle nucleation progress to vesicle membrane elongation by involving two conjugation steps. In first conjugation step, vesicle curvature is formed by complex group of autophagy related genes (Atg12e-Atg5e-Atg16. In second conjugation step, LC3/Atg8 (microtubule associated protein light chain 3) is accelerated by binding to Phosphatidylethanolamine (PE) and to autophagic membranes. Lastly, the formed autophagosome fuses with a lysosome for degradation by the enzyme hydrolases. Cytoplasmic content of the cell during autophagosome process is not spilled into the extracellular space. Hence, autophagic cell death is also non-inflammatory like apoptosis (Figure 2). Various studies have established the role of autophagy during the infectious process. Autophagy protects organism from infectious disease by degrading intracellular bacteria, viruses, and protozoan pathogens. The role of autophagy in regulating inflammation has been demonstrated in Crohn's disease and sepsis. Crohn's disease is a type of chronic inflammation [24-30].

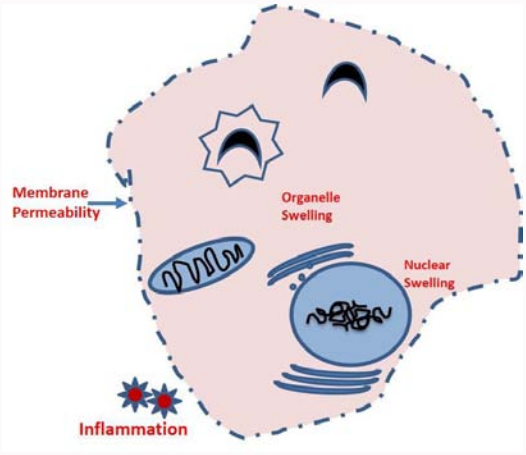

Figure 3: Morphological changes in necrosis.

Necrosis

Necrosis is considered an 'accidental' or primary form of cell death caused in response to physical and chemical insults. It is a passive process that does not require gene expression. It is also considered as irreversible cell injury involving many cells together with marked inflammatory responses. It is characterized by pyknosis, karyorrhexis, karyolysis, nuclear disappearance, cytoplasmic and organelle swelling, loss of cell membrane integrity and release of the cellular contents into the surrounding extracellular space (Robbins). The released intracellular contents are termed as Damage-Associated Molecular Patterns (DAMPs), which triggers inflammatory reactions. DAMPs stimulate nearby cells to express pro-inflammatory cytokines, chemokines, and adhesion molecules, *via* the Receptor for Advanced-Glycation End-Products (RAGE) and induces inflammation [31] (Figure 3).

Earlier, it was considered that this uncontrolled form of cell death lacks underlying signaling events but advancing evidence supports the existence of caspase-independent cell death pathways that functions in a strictly regulated developmental framework, as observed in interdigital cell death. If caspase activation is hampered, necrotic cell death proceeds instead, acting as a kind of back-up cell death pathway. Necrosis is induced by FADD (Fas-Associated Death Domain), a crucial adaptor protein in Fas- and TRAIL-R pathway. RIP1 (Receptor Interacting Protein 1) is also a crucial initiator of death receptor-mediated necrosis and the term necroptosis was introduced to designate programmed necrosis that depends on RIP1 [32-34].

Necroptosis is defined as cell death mediated through a pathway that depends on the receptor-interacting protein kinase (RIP) 1-RIP3 complex. Necroptosis is induced by a class of death receptors that includes Tumor Necrosis Factor Receptor (TNFR) 1, TNFR2, and Fas. TNFR1 and TNFR2 form complex I containing a death domain (e.g. TNF-α Receptor-Associated Death Domain (TRADD)), RIP1,

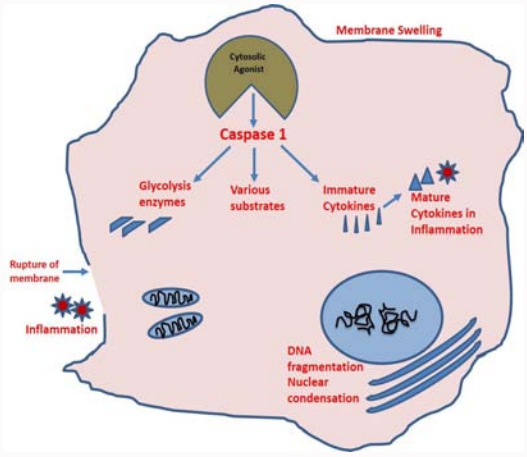

Figure 4: Inflammasome and caspase 1 dependent pathway in pyroptosis.

Fas-Associated Death Domain (FADD), and other factors & enzymes such as TNF-α receptor associated factor 2/5 (TRAF2/5) and inhibitor of apoptosis proteins (IAPs) cIAP1 and cIAP2 (36). Complex II is formed by the death domain containing protein FADD, caspase-8 and cFLIP. Activation of caspase-8 drives complex II into a pro-apoptosis state by cleaving RIP1 and RIP3. But, when the apoptosis pathway is inhibited, a complex "necrosome" is formed [35-37].

Accomplishment of necrotic cell death involves many mediators such as, Reactive Oxygen Species (ROS), calcium (Ca2+), calpains, cathepsins, phospholipases, and ceramide. If there is extensive DNA damage, it causes hyperactivation of poly-(ADP-ribose) polymerase-1 (PARP-1). Excessive PARP-1 activation leads to depletion of NAD+ by catalyzing the hydrolysis of NAD+ into nicotinamide and poly (ADP-ribose) (PAR), leading to ATP depletion, irreversible cellular energy failure, and necrotic cell death. Ultimately, PARP-1-mediated cell death requires the activation of RIP1 and TRAF2. ROS alteration leads to loss of the normal functions of proteins thereby enhancing their susceptibility to proteolytic degradation. Lipid peroxidation affects vital mitochondrial functions by destabilizes the plasma membrane and intracellular membranes of endoplasmic reticulum and lysosomes thereby leading to intracellular leakage of Ca2+ and lysosomal proteases. Reactive hydroxyl radicals are the potent inducers for lipid peroxidation. Increase Ca2+ in mitochondria, can activate phospholipases, proteases and neuronal Nitric Oxide Synthase (nNOS), all of which will contribute to the execution phase of necrotic cell death. Calpains get activated by elevated Ca2+ levels, which cleave the Na+/Ca2+ antiporter in the plasma membrane, resulting in a constant Ca2+ overload. Activated calpains contribute in the release of cathepsins in the cytosol through the lysosomal membrane permeability, as proposed by Yamashima et al. [38-40] and colleagues in the "calpain-cathepsin" hypothesis.

It is explained from earlier studies that necrosis can, in some conditions, standby for apoptosis to eliminate unwanted cells. For example, removal of interdigital cells during the development of digits by a caspase-independent necrotic-like process as seen in experimental animals Physiologically, necrosis is involved in signaling processes, such as ovulation, the death of chondrocytes during the longitudinal growth of bones, and cell turnover in the small and large intestines. It has an important mechanism for reducing T cell numbers after an immune response. Pathologically necrosis is observed during Ischemia/Reperfusion (I/R), which causes injury to organs, including heart, brain, liver, kidney, and intestine. It also contributes to excitotoxicity, which causes stroke, traumatic brain injury, and neurodegenerative disorders [32,41-44].

Pyroptosis

Another form of regulated cell death which is different from apoptosis and necrosis is recently recognized as 'Pyroptosis'. When specialized innate immunity in humans if compromised under critical situations with intracellular pathogens, then it is eliminated through pyroptosis. Significant advances have been made in the field of pyroptosis research due to detailed study of many pathogens system. Pyroptosis has been studied and researched in monocytes, macrophages and dendritic cells which are infected with microbial pathogens, such as Salmonella, Francisella and Legionella. All the result showed its unique dependent on caspase-1. Stimuli, such as DAMPs as in apoptosis & necrosis, can also induce pyroptosis, but in non-macrophage cells [45-47].

Firstly, the report of a caspase-1-dependent cell death was mentioned in mouse macrophages infected with the gram-negative bacteria *Shigella flexneri*. Shigella was the first reported to induce host cell death, which was initially described as apoptosis. Later, findings of other cell death process were further substantiated by reports of caspase-1-dependent cell death induction by *Salmonella typhimurium*. It was also confirmed that caspases-3, -6 and -7 remained inactive and cytochrome c release does not occur in these cells hence, it was established that the existence of a caspase-1-mediated cell death pathway is distinct from apoptosis. "Pyroptosis" term denotes as "pyro" means fire, which releases proinflammatory mediators, whereas "ptosis" denotes falling, a term used commonly to describe cell death [48-54] (Figure 4).

Caspase-1, is a member of the inflammatory caspases, and is present in the cytosol as an inactive zymogen, but is not involved in apoptosis. It is activated in a complex called the inflammasome. Inflammasomes are collection of protein complexes that recognize a diverse set of inflammation-induced by PAMPs (Pathogen Associated Molecular Pattern) and DAMPs (Damage Associated Molecular Pattern) which controls the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18 and is one of the drivers of pyroptosis (1). Assembly of inflammasome is induced by a variety of both exogenous and endogenous signals and several proteins, including Nod like Receptor (NLR) family i.e. *NLRP3* (NLR family pyrin domain containing 3), NLRC4 (NLR family Caspase Activation and Recruitment Domain (CARD) containing 3), AIM2 (Absent in Melaonoma 2 gene) and NLRP6 (NLR family pyrin domain containing 6). They act by inducing the formation of separate sized ion permeable pores in the plasma membrane which in turn results in increased osmotic pressure leading to water influx, cell swelling and ultimately cell lysis [55-60].

Regulations of inflammasomes are tightly regulated to avoid excess production of cytokines and it occurs at transcriptional or post transcriptional levels. Regulation of inflammasomes can be achieved through various paths. 1) *NLRP3* is expressed minimal in many cells and it requires signals like cytokines, Reactive Oxygen Species (ROS) or microbial ligands to express inflammasomes. The subcellular location and transferring of inflammasome components through ASC (Apoptosis associated speck-like protein containing CARD) becomes essential for the regulation of inflammasome activity. 2) It can occur through NLRC4 activation, which is dependent of ASC, initiating assembly of complexes with different components, whereas pyroptosis

is ASC independent. 3) Regulation can be achieved through induction of autophagy causing degradation of cell substances like proteins and organelles. Evidences have shown decrease inflammasome activation if cells show deficient autophagy. 4) Downregulation through cell to cell interaction and factors secreted leads to transcriptional and post transcriptional changes in inflammasome activity [61-65].

Experimental studies *in vivo* showed that inflammasomes participate in the antimicrobial innate immune response. Most widely researched inflammasome is the *NLRP3* inflammasome, which is shown to be involved in antibacterial, viral, fungal and parasitic immune responses. On infection, recognition occurs by means of Toll-Like Receptor 7 (*TLR7*) which induces transcription of the *NLRP3* inflammasome components which is followed by assembly of *NLRP3*. There is evidence that aberrant inflammasome activation also occurs by non-infectious agents which may be linked to the pathogenesis of diseases characterized by sterile inflammation. Level of caspase-1 activation after recognition of threat indicators, plays a role in the host response. Low level of caspase-1 initiate cell survival, control of intracellular bacterial growth and stimulating cytokine production in response to inflammation. Whereas high levels of caspases-1 leads to induction of pyroptosis and to several other inflammatory conditions [66,67].

Study conducted by Shao et al. [68] in 2007, highlighted an interesting fact of dual function of caspase-1 as an initiator and executioner caspase. As an initiator caspase-1 involved in cellular functions as maintenance of the intermediate filaments, microtubules and microfilaments (cytoskeleton), [69] ATP metabolism, detoxification, protein degradation and synthesis, signal transduction and cytokine production. Whereas as an executioner caspase-1 cleaved and inactivated a number of glycolysis enzymes, linking inactivation of biochemical pathways to the cell death. Morphological changes following pyroptosis present rapid membrane rupture and release of proinflammatory intracellular contents with initiated caspase-1. Caspase-1 dissolves cellular ionic gradient causing net increase in osmotic pressure, water influx, membrane swelling and eventually osmotic lysis with the release of inflammatory intracellular contents. (1) Previous studies have proved that pathophysiological process of injury and infectious diseases is associated with pyroptosis and by promoting the release of IL-1β, IL-18 and DAMPs, pyroptosis is increasingly regarded as an important mechanism of inflammatory and host defense responses. Cheng et al. [70] demonstrated that limited pyroptosis remains a quite stable state, while high level of pyroptosis induced the explosion of inflammation as observed in different stages of apical periodontitis with varying severity. Hence, pyroptosis releases more inflammatory molecules than the solely activation of caspase-1 [68-70].

The present article clears the fact that apoptosis cell death is mediated by caspases, with evident morphological changes. Necrosis occurs through physiochemical damage but cam also results due to programmed interplay of signaling events leading to membrane permeability. Autophagic cell death has resemblance to both apoptosis and necrosis but needs further investigation as it is genetically regulated cell death program. Pyroptosis is considered as a part of host defense system to fight against pathogens and it has distinct biochemical and morphological properties. Some of the differences between pyroptosis and apoptosis are outlined in (Table 1).

Conclusion

Evolving evidences suggest that apoptosis is not the only cell death program for removal of unwanted cells from the mammalian organisms instead involves other forms like autophagic, necrosis and pyroptosis cell death. As cell death is an important factor in host-pathogen interactions it is mandatory to understand the cross regulatory relationships, different forms of cell death, cellular pathways and their crucial role in inflammation process and pathophysiology of certain inflammatory conditions. Understanding the cellular and molecular pathways of cell death will lead to development of new therapeutic strategies that can either control the cell death or provide a basis for interventions in inflammatory conditions.

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Contribution Details

Dr. Bina Kashyap: Design, Definition of intellectual content, Manuscript preparation, Manuscript editing.

Dr. P Sridhar Reddy: Literature search, Data acquisition, Manuscript review.

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