Review Article

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DEATH TALES OF THE CELLS

Jyoti D Bhavthankar[1],Shubhangi D Mishra[2],Suresh R Barpande[3],Mandakini Mandale[4],Jayanti Humbe[5]

1.Associate Professor, Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Aurangabad
2.MDS student,Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Aurangabad
3.Professor, Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Aurangabad
4.Associate Professor, Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Aurangabad
5.Assistant Professor, Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Aurangabad.

ABSTRACT:

In all animals, regulated cell death plays key roles in a variety of biological processes ranging from embryogenesis to immunity. Too much or too little cell death underpins diverse pathologies, including cancer, autoimmunity, neurodegeneration and injury. Since eras, apoptosis has stayed as the mechanism most focused when it comes to the death of a cell, and most of the non apoptotic cell death mechanisms that have many rational roles behind various pathologies remain neglected. Researchers in the recent past have introduced many such novel cell death mechanisms and it is of interest to have an insight of what all are they. Here are mentioned such apoptotic and non apoptotic mechanisms with a brief idea of each of them

Key words : apoptosis, necrosis, necroptosis, pyroptosis, cancer, mitotic catastrophe, oncosis, NETosis, anoikis.

INTRODUCTION:

"Cell is the basic structural and functional unit of life." – this most widely accepted axiom signifies the importance of 'a cell' and thereby drives our interest towards its birth and death. A cell that was once born, is destined to die. Cells take birth, perform their assigned function, multiply and reproduce to let the functions be continually performed by their progeny and finally, die. In physiological healthy conditions, these cells die through a regulated programmed cell-death pathway and is crucial for all multicellular organisms. With an obvious significance of this, being the disposal of the senescent and damaged cells from the body, there are many other important biological processes ranging from embryogenesis to immunity where the death of cells is required. Too much or too little cell death underpins diverse pathologies like cancer, auto-immunity, neuro-degeneration and injury.

The cell death mechanisms can be broadly classified as active and passive. Passive cell death is the death of the cells due to external environment with excessive damage. On the other hand, active death of a cell comprises the suicidal pathways where the cell itself is responsible for its own demise. Since eras, the most studied and accepted pathway is apoptosis. However, recent researches have come up with many

*Corresponding Author Address: Dr Shubhangi Mishra Email: shubhsmishra38@gmail.com

non-apoptotic pathways of cell death like necroptosis, pyroptosis, mitotic catastrophe, anoikis, emperipolesis, etc. But does it really matter how a cell dies? Literature answers a resounding “yes” to this question and the reason being the fact that they exhibit differential occurrence in different pathological conditions. Also each of them renders vivid biochemical sites that can be targeted to modulate these mechanisms as a part of primary or adjuvant therapy.

In this commentary, we discuss the various cell death mechanisms in health and disease, their occurrence and roles, and the potential they carry as the targetable sites for therapies.

Apoptosis :

The word “apoptosis” is of Greek origin, meaning “dropping off” or “falling off” of petals from flowers or leaves from trees and was first used in a now-classic paper by Kerr, Wyllie, and Currie in 1972 to describe a morphologically distinct form of cell death. It is an active, inherently programmed phenomenon which can be initiated or inhibited by a variety of environmental stimuli, both physiological and pathological. There are four major players which are involved in triggering and influencing the apoptotic process. These are the caspases, Bcl-2 family of proteins, tumor necrosis factor receptor (TNF-R) superfamily, and adaptor proteins. [1]

Physiologically, all multicellular organisms use apoptosis during development, homeostasis, defense, metamorphosis, terminal differentiation, immune response, cellular response to growth factors and hormones. It plays an important role in the immune system, in removing self reactive T cells by negative selection. Lymphocytes can induce apoptosis in target cells: T cells, NK cells have been described to do so. Withdrawal of hormones results in atrophy of the hormone dependent tissue and apoptosis has been found to be responsible for this phenomenon in prostate, adrenal cortex, endometrium, and in mammary glands. Apoptotic cell death has also been observed during gut development, in epidermal skin cells and remodeling of cartilage and bones and antiviral defense. It may also be used to minimize the risk in cells frequently exposed to mutagenic chemicals or radiations.[2]

Apoptosis occurs following the induction of an intracellular genetically regulated cell death programme. A number of physiological and pathological stimuli including lack of nutrients, activation of cell surface death receptors, chemicals, ionizing radiation and direct physical injury can activate the apoptotic programme (Figure1). These stimuli activate different pathways leading to apoptosis but often converge on one common pathway involving the activation of caspases. Caspases are a group of enzymes that are involved in the regulation of apoptosis resulting in the classical apoptotic features.[3] Two distinct pathways; the intrinsic and the extrinsic, leading to activation of caspases have been identified. The

extrinsic pathway is initiated by activation of transmembrane death receptors.[4] The intrinsic pathway is activated by cellular stress and generally involves the release of mitochondrial proteins such as cytochrome c.[5,6]

During oral embryogenesis the regulation of the delicate balance between cell death and cell survival and the epithelial–mesenchymal interaction play an essential role in determining which cells are to be shed and which ones are to survive.[7] Molecules involved in regulating the development of oral soft and hard tissues include fibroblast growth factor[8], bone morphogenic proteins (BMP), sonic hedgehog (Shh), wingless type-1 (WNT-1) and TNF family.[9] The lining of oral mucosa is covered by a dynamic epithelium that is constantly renewed by proliferating basal cells. Basal keratinocytes differentiate and migrate through epithelial layers to the surface where they are shed-off as keratin squames. In this way keratinocytes are programmed to divide, differentiate and die by terminal differentiation. Therefore, for maintenance of epithelial structure and function, cell proliferation, terminal differentiation and spontaneous apoptosis have to be strictly regulated. The BCL-2 family of proteins appears to be involved in regulating terminal differentiation of keratinocytes. The antiapoptotic BCL-2 and BCL XL proteins are preferentially expressed in the basal and lower spinous layers, whereas the pro-apoptotic protein BAX is expressed in the more differentiated suprabasal cell layers.[10]

Likewise, the presence of apoptotic cells during a developing tooth has also been studied. At the early bud stage, apoptotic cells are seen in the budding dental epithelium beneath the oral ectoderm. At the late bud stage a streak of apoptotic cells is seen extending to the tip of the epithelial bud. No apoptosis is detected in the mesenchyme around the dental epithelium. Next, in the cap stage, apoptotic cells are seen on the periphery of the condensed dental mesenchyme. Later in the early bell stage apoptotic cells are evident in the secondary enamel knots as well as in stratum intermedium cells next to the enamel knots; while in the late bud stage these are evident in the presumed bud of the secondary tooth and in the disappearing secondary enamel knots.[11] Thus the selective removal of the cells during tooth development signify for the attainment of correct form, position and number of teeth. The proper disruption of the dental lamina has clinical significance because if clusters of epithelial cells from the dental lamina persist, they may form cysts over the developing tooth and delay eruption.

Apoptosis when more than required results simply in a tissue atrophy while when less than required, results in tissue hypertrophy. This was in simpler words. But in reality, this simple death mechanism has a lot to play in many of the disease processes. A disease is

identified by the area of cells affected by an abnormal apoptosis. For example, in case of oral aphthous ulcers, apoptotic bodies have been found in the prickle cell layer while in erythema multiforme, this apoptotic activity is seen more in the basal and parabasal keratinocytes. Similarly the basal keratinocyte apoptosis is seen in lesions of oral lichen planus and the bullae formed in epidermolysis bullosa.[12] A number of studies in the literature indicate that increased apoptosis or abnormal clearance of apoptotic material can contribute to autoimmune diseases.[13] Likewise, tissue destruction in periodontal conditions can also be attributed to the abnormal or increased apoptosis caused due to the periodontal pathogens. A. actinomycetemcomitans was shown to induce apoptosis of leucocytes by secretion of leukotoxin in a pathway involving casapase-1.[14]

In case of viral infections, viruses exert their effects on tissues by modulating the balance between cell death and cell proliferation. They can induce apoptosis in infected host cells by production of an array of viral products. Induction of apoptosis in infected cells permits escape of viruses, hence facilitating viral spread. Host cells respond to viral infection by initiating the suicide programme through inflammatory responses.[15] However, viruses have evolved mechanisms to overcome host defenses which include: blockage of apoptosis by viral BCL-2 (vBCL-2) homologues,[16] utilization of the phosphatidylinositol 3-kinase-Akt signaling pathway [17] or suppression of inducers of apoptosis such as p53. HSV induces apoptosis in activated T cells [18] and dendritic cells.[19] HSV induced apoptosis of dendritic cells could be reduced by blocking cell death receptors but not by the antiviral drug acyclovir. This may explain why acyclovir has limited effectiveness in the treatment of herpetic infections. Infection by VZV causes varicella (chickenpox) in sero-negative individuals and herpes zoster (shingles) in previously infected persons. VZV characteristically progresses along sensory nerves and remains quiescent in sensory ganglia during latency. In a recent study, it was shown that VZV-infected neurons were resistant to apoptosis compared with infected fibroblasts, suggesting that inhibition of apoptosis in neurons may play an important role in establishment of the latency stage by promoting survival of neurons.[20] An earlier study had shown that VZV-infected dendritic cells were resistant to apoptosis and were able to transmit the infection to T lymphocytes, suggesting a mechanism for transmission of VZV infection from mucosal surfaces to regional lymph nodes.[21] The HIV infection causes apoptosis of infected lymphocytes and increased spontaneous apoptosis of uninfected lymphocytes leading to massive CD4+ T-cell depletion in AIDS patients. Lymphocyte apoptosis in AIDS is induced by viral components such as gp120, tat, nef and cell surface death receptors.[22]

Since apoptosis helps maintaining a constant homeostasis of the body cells, a

defect in this mechanism results into uncontrolled and abnormal proliferation of cells; in short resulting into tumorigenesis. Cancer cells attain the ability to evade their inherent programmed cellular death alongwith the evasion of the apoptosis that might occur due to an immune response. Tumor cells may evade apoptosis by inactivation of apoptosis-inducing genes or by enhancement of the activity of antiapoptosis genes. The TP53 gene is important for induction of cell cycle arrest and apoptosis. The p53 protein appears to exert its effects at multiple stages of cancer progression, implying that there is a strong selection for tumor cells to inactive TP53.[23] Besides TP53 a number of apoptosis-inducing proteins, such as BAX and BAD, may be inactivated in tumors.[24] Tumors also increase the expression of proteins that inhibit apoptosis. BCLXL, an antiapoptosis protein was found to be overexpressed in oral cancer cells.[25]

Thus, with a vast literature covering this mechanism of programmed cell death, almost every physiological and pathological process can be rooted to “apoptosis”. The significance lies behind the fact of prognostic usage and therapeutically targetable elements of the mechanism. Assessing the levels of molecules playing role in apoptosis can relate to the degree of aggressiveness of a lesion. On the other hand, therapeutically, apoptosis can be ushered in or prevented depending on the disease process. The greatest application has been in the therapy for cancer wherein drugs like Oblimersen (a BCL-2 family antagonist) and Apomab, Amgen (the pro-apoptotic receptor agonists) are being tried extensively.

Necrosis :

Necrosis (from the Greek " death, the stage of dying, the act of killing " from "dead") is a form of cell injury which results in the premature death of cells in living tissue by autolysis. While apoptotic cell death has become increasingly well defined, our notions of necrotic cell death has become progressively more vague. At present, the most widely accepted way to define necrotic cell death is to show that the death was not mediated by apoptosis. Up until 1971, the term “necrosis” was used for all types of cell death. When Kerr(1971)et al. first observed a form of non pathologic cell death in certain tissues, they termed it shrinkage necrosis. As shrinkage necrosis became implicated in the control of organ homeostasis, it was renamed apoptosis. At present, the most widely accepted way to define necrotic cell death is to show that the death was not mediated by apoptosis. Morphologic description using light or electron microscopy remains the best way to define necrosis and contrast it with apoptosis. Apoptosis is characterized morphologically by pyknosis (deep staining of nuclear mass), nuclear fragmentation, and formation of condensed cell bodies (apoptotic bodies). This ordered morphology depends on the ability of the dying cell to engage in ATP-dependent processes

of self-degradation. In contrast, necrosis can be defined morphologically by electron-lucent cytoplasm, swelling of cellular organelles, and loss of plasma membrane integrity. These events can be reproduced experimentally by impairing a cell's ability to produce ATP. Because of these morphological and bioenergetic differences, apoptosis is now widely regarded to be analogous to an active or programmed form of cell death. In contrast, necrosis has come to be referred to as a form of cell death that is uncontrolled or pathological. The concept that necrosis is unprogrammed is reinforced by the fact that necrotic cell death can be caused by exposures of cells to supraphysiological conditions such as mechanical force, heat, or cold.[26]

Recent studies have demonstrated that in response to a given death stimulus, there is often a continuum of apoptosis and necrosis. Many insults induce apoptosis at lower doses and necrosis at higher doses. Even in response to a certain dose of death-inducing agent, features of both apoptosis and necrosis may coexist in the same cell. In addition, if not engulfed by neighboring cells or in cell culture, where phagocytosis does not usually happen, dead cells in the late stages of apoptosis may present necrotic features due to the loss of cellular energy and plasma membrane integrity. This process is called "apoptotic necrosis" or "secondary necrosis".[27]

Despite the idea that necrosis is an uncontrolled or default form of cell death, accumulating studies have suggested that this may not be true. Rather, it appears that necrotic cell death can be a regulated event that contributes to development and to the maintenance of organismal homeostasis. The genetic components of this programmed cell necrosis involve (1) gene products that function in the dying cell to induce an irreversible bioenergetic compromise that results in cell death, and (2) gene products that are selectively released into the extracellular environment to trigger a host response. The evolutionary advantage conferred by necrosis is that it allows cells to actively recruit a defensive or a reparative response to regions of multicellular organisms that have sustained damage or invasion. Programmed cell necrosis can be a consequence of extracellular signaling or can be initiated as a form of cellular suicide in response to intracellular perturbations. Cell suicide by necrosis appears to have evolved to allow multicellular organisms to have an early warning system to recognize and adapt to events that might compromise the integrity of the organism as a whole.

The core events of necrosis are bioenergetic failure and rapid loss of plasma membrane integrity. These can result from defined molecular events that occur in the dying cell, including increased mitochondrial ROS production, channel-mediated calcium uptake, activation of nonapoptotic proteases,

and/or enzymatic destruction of cofactors required for ATP production. In addition, these necrotic mediators are often induced in the dying cell simultaneously and potentiate each other's ability to initiate the demise of the cell.

The decline in function of the ATP-dependent ion pumps in the cytoplasmic membrane can lead to the opening of a so-called death channel in the cytoplasmic membrane that is selectively permeable to anions and inhibitable by glycine.[28] The opening of the death channel results in colloid osmotic forces and entry of cations that drive the cytoplasmic membrane swelling, and ultimately rupture.

Cellular stress resulting from nutrient starvation or a reduced oxygen supply often results in ATP depletion. The cells die by necrosis when their intracellular supply of metabolic substrates are depleted.[29] Necrosis is often observed in the internal regions of tumors where nutrient and oxygen supplies are limited. Cellular autophagy allows cells to maintain bioenergetics and viability by consuming their own intracellular macromolecules. However, the cells die by necrosis when their intracellular supply of metabolic substrates are depleted. Manipulating cell metabolism and ATP generation/ consumption can regulate cell fate. In healthy cells, the ATP levels are in the millimolar range, and as a result, no single biochemical reaction can instantly overwhelm the intracellular ATP pool. The mitochondrial respiration results in ATP generation through the electron transport chain. There lies a complex mechanism of the permeability pores in the mitochondrial membrane. Permeability transition (PT) pores open in the mitochondrial inner membrane in response to stimuli such as increased intracellular Ca2+, inorganic phosphate, alkaline pH, and ROS and mitochondria cannot produce ATP as long as the pores remain open. While the opening of the PT pore has been proposed to amplify apoptosis by mediating release of mitochondrial apoptogenic factors, its persistent opening leads to necrotic cell death.[30,31]

When mitochondrial respiration is inhibited, or under the circumstances where oxygen supply is limited, cells may switch from oxidative phosphorylation to glycolysis to generate ATP. Highly proliferating cells such as lymphocytes and tumor cells undergo net protein and lipid synthesis. As a result, they maintain ATP production almost exclusively through catabolizing glucose through a mixture of glycolysis and oxidative phosphorylation termed aerobic glycolysis . Inhibiting glycolysis in such cells induces necrosis. In addition, blocking glycolysis with 2-deoxyglucose can sensitize cells to necrotic death upon treatment with chemotherapeutic agents.

One efficient way to shut down glycolysis is by activating poly ADP ribose polymerase (PARP). In response to DNA damage, PARP is activated by binding to

DNA strand breaks, and catalyzes poly(ADP)-ribosylation of a variety of proteins by converting NAD into NAM and ADP-ribose.[32] Because cytosolic and mitochondrial NAD pools do not exchange freely across the mitochondrial inner membrane, PARP preferentially depletes the cytosolic NAD pool without affecting mitochondrial NAD. By depleting the cytosolic NAD pool, activation of PARP inhibits further glucose catabolism, preventing glucose-dependent ATP production. While activation of PARP induces necrosis , NAD replenishment rescues cells from PARP-mediated cell death.[33,34]

Just as in the other cellular responses, intracellular Ca^{2+} plays an important role in necrosis also. Ca^{2+} mediated necrosis has been characterized as the best form of programmed necrosis. increased cytosolic Ca2+ can initiate either apoptosis or necrosis. The outcome of cell death is probably determined by the concentration of cytoplasmic Ca2+. Whereas low to moderate Ca2+ (200–400 nM) triggers apoptosis, higher concentration of Ca2+ (>1 μM) is associated with necrosis. This may explain why Ca2+ released from the ER is mostly apoptotic, whereas Ca2+ influx through the plasma membrane is associated with necrosis. The mitochondrial metabolic status may also affect the sensitivity of mitochondria to Ca2+ poisoning and contribute to the determination of the death mode.[35]

The other molecules that play an important role in necrosis are the ROS. Cells in an aerobic environment are constantly generating ROS. Physiologic levels of ROS can regulate transcription, serve as signaling molecules, and defend against pathogen infection. Excessive production of ROS leads to oxidative stress, damage of intracellular molecules and organelles, and ultimately necrosis. Mitochondria are a major source of ROS that can initiate necrosis. Excess mitochondrial ROS can damage DNA by causing cleavage of DNA strands, DNA–protein cross-linking, and oxidation of purines.[38] This may lead to DNA-damage response, including activation of p53 and PARP. While activation of p53 may cause apoptosis and cell cycle arrest, hyperactivation of PARP leads to necrosis.[39] ROS also modify lipids, as the double bonds in polyunsaturated fatty acids are excellent targets for ROS attacks. Lipid oxidation can lead to the loss of integrity of both the plasma membrane and intracellular membranes such as that of lysosomes and the ER, leading to an intracellular leak of proteases or an influxofCa2+ and resulting in necrosis.

The physiological significance if such kind of cell death is still a matter of debate. The potential of necrosis to contribute to embryonic development has not been extensively investigated. However it has been suggested that apoptosis is not the only mechanism of death involved during embryogenesis, and that necrotic cell death may

sometimes compensate for the apoptotic deficient events.[41]

The older school of thoughts considers necrosis to be a purely pathological event and thus it is related more with the infectious and other pathological conditions. In case of infections, necrosis is seen as a response to the pathogenic toxins or the host tissue response. Recently,HIV-1 has been shown to kill CD4(+) T lymphocytes by necrosis rather than apoptosis.[42,43]

The significance of this kind of cell death has been reported mainly in cancer therapeutics. The development of resistance to apoptosis is an important step in carcinogenesis. Cancer biologists have begun to consider whether effective cancer therapeutics might induce cell death by activating necrosis. Approaches reported to be able to induce necrotic death in cancer cells include photodynamic treatment (PDT) and alkylating DNA-damaging agents. Several other chemicals or agents such as -lapachone, apoptolidin, and honokil also appear to induce cancer cell death through necrosis.[47,48] Thus programmed cell necrosis may be just as an important cell fate as apoptosis.

Necroptosis :

Contrary to the traditional belief, recent studies have led to the revelation that a subset of necrosis, known as necroptosis, is a form of regulated cell death.[49] The activation of necroptosis by ligands of death receptor family requires the kinase activity of RIP1.[50] Inhibition of RIP1 kinase by necrostatins, which are small molecule inhibitors of RIP1 kinase, blocks the initiation of necroptosis and allows cell survival. The execution of necroptosis involves the activation of receptor-interacting protein 3 (RIP3) by RIP1 kinase,[51,52,53] and mixed lineage kinase domain-like (MLKL).[54] The discovery of necroptosis overturned the traditional belief that necrosis is merely a passive process caused by overwhelming stress, and demonstrated the feasibility of targeting necroptosis for the treatment of human diseases characterized by necrotic cell death – such as ischemia-reperfusion injury and neurodegenerative diseases.

Activation of TNF receptor-1 can mediate NF-κB activation, apoptosis, or necroptosis. The different outcomes are determined by distinct TNF receptor-associated signaling complexes. Activation of NF-κB is mediated by TRAF-2, RIP-1, and other signaling molecules that lead to activation of IκB kinase and subsequent activation of NF-κB target genes. FADD and caspase-8 are the essential adapter proteins involved in apoptosis, which in hepatocytes requires a mitochondrial amplification loop through caspase-8-mediated cleavage of Bid. The subsequent translocation of Bax and Bak results in mitochondrial outer membrane permeabilization, cytochrome *c* release, and effector caspase-3 activation. Under conditions of impaired apoptosis, TNF receptor-1 can induce necroptosis, which involves RIP-1 and RIP-3 kinases. Among other effects, RIP-3 can increase the

production of reactive oxygen species (ROS) due to increased oxidative phosphorylation, resulting in intracellular calcium overload, mitochondrial membrane permeability transition (MPT), depletion of ATP, and necrosis.[55]

In health, necroptosis helps maintaining the adult tissue homeostasis. In the literature it has also been mentioned as the backup of apoptosis.[56]

In the states of disease, unlike apoptosis, necroptosis provides druggable targets and the most important of those being the RIP1 kinase. Thus acknowledging the role of necroptosis in various diseases like the ischemia reperfusion injury and the neurodegenerative disorders, many drugs are being studied and implicated. For example, necrosulfamide, is a drug that inhibits necroptosis and is thus being tried in neurodegenerative disorders. While on the other hand, in diseases like cancer, necroptosis if possibly brought about in the cancerous cells, shall help in preventing the progress of the disease. Thus necrostatins 1 and 3 are being thought upon as adjuvant therapeutic aids in cancer.[57]

Pyroptosis :

Pyroptosis is a more recently identified pathway of host cell death that is stimulated by a range of microbial infections (for example, Salmonella, Francisella and Legionella) and non-infectious stimuli, including host factors produced during myocardial infarction.[58] Caspase 1 was first recognized as a protease that processes the inactive precursors of interleukin 1β (IL-1β) and IL-18 into mature inflammatory cytokines, and was initially called interleukin IL-1β-converting enzyme.[59] However, caspase 1 activation can result not only in the production of activated inflammatory cytokines, but also rapid cell death characterized by plasma-membrane rupture and release of proinflammatory intracellular contents.[60,61] Caspase 1-dependent cell death is a programmed process of cellular self-destruction mediated by caspases, and therefore was not initially distinguished from apoptosis.[62,63,64] However, the mechanism, characteristics and outcome of caspase 1-dependent cell death are distinct from apoptosis. Thus, the term pyroptosis (from the Greek ‘pyro’, relating to fire or fever, and ‘ptosis’, meaning a falling), is used to described the inherently inflammatory process of caspase 1-dependent programmed cell death.[65] (figure 2)

Pyroptosis is morphologically and mechanistically distinct from other forms of cell death. Caspase 1 dependence is a defining feature of pyroptosis, and caspase 1 is the enzyme that mediates this process of cell death. Caspase 1 is not involved in apoptosis, and caspase 1-deficient mice have no defects in apoptosis and develop normally.[66,67] The apoptotic caspases, including caspase 3, caspase 6 and caspase 8, are

not involved in pyroptosis, and substrates of apoptotic caspases, including poly (ADP-ribose) polymerase and inhibitor of caspase-activated DNase (ICAD), do not undergo proteolysis during pyroptosis. Furthermore, loss of mitochondrial integrity and release of cytochrome c, which can activate apoptotic caspases, do not occur during pyroptosis.[68]

Since pyroptosis is seen only in disease states, it is necessary to curb or initiate the process whenever required according to the demand of the situation. Certain autophagy initiators are being used to reduce the inflammasome formation. Also miRNAs are the novel mediators to target pyroptosis.[69]

Ferroptosis :

It is a type of cell death which is initiated by the RAS selective lethal (RSL) compounds. Since it is an iron dependent form of non apoptotic cell death, it is known as ferroptosis. The distinctive morphological features of the cells having undergone ferroptosis is the appearance of mitochondria that are smaller than the normal with an increased membrane density.[70]

Ferroptosis inducers have been shown to inhibit the tumor growth in mouse models. Since it is an iron dependent mechanism, hematopoetic cell line tumors like in cases of diffuse large B cell lymphoma are said to be benefited more by inducing ferroptotic cell death. While in cases where ferroptosis has been shown to have deleterious effects like the neurodegenerative disorders, molecules like ferrostatins may be used to inhibit the same.[70]

Paraptosis :

Paraptosis is an alternative form of non-apoptotic cell death mechanism that may be induced by the insulin-like growth factor I receptor (among other inducers),is mediated by mitogen-activated protein kinases (MAPKs) and inhibited by AIP-1/Alix. The inhibition by AIP-1/Alix is specific for paraptosis since apoptosis was not inhibited.[71]

A striking similarity has been observed at the morphological level between paraptosis and the neuronal cell death observed in some neurodegeneration models which suggests that paraptosis may be a physiologically relevant process. In order to assess its potential occurrence during development and in neurodegeneration, it will be necessary to identify specific markers for paraptosis, the latter of which are currently unavailable.[72]

Chondroptosis :

This is a term that is applied to the apoptosis like death that takes place in chondrocytes. It is suggested that, chondrocytes undergo apoptosis but in a non classical manner but in a typical manner and hence is a separate term applied. The differences between the classical apoptosis and chondroptosis have been enlisted in the table.[73]

Mitotic catastrophe :

Mitotic catastrophe has been extensively used as a term to indicate cell death resulting from aberrant mitosis.[74] Functionally, mitotic catastrophe can be redefined mitotic as an apical mechanism that senses mitotic failure and responds to it by driving the cell to an irreversible fate, be it apoptosis, necrosis or senescence. According to this designation, mitotic catastrophe should be viewed as a bona fide oncosuppressive cascade that precedes and is distinct from, yet operates through, antiproliferative measures, including cell death and senescence.[75]

Failing mitoses are often associated with chromosomal breaks and deficient karyokinesis, which lead to the gross nuclear alterations (micronucleation and multi nucleation) that constitute the most prominent morphological traits of mitotic catastrophe. However, features of apoptosis and necrosis have also been observed in cells succumbing to mitotic failure,[76,77] raising the possibility that mitotic catastrophe might constitute a prelude to apoptotic or necrotic cell death rather than a bona fide cell death mechanism.[78] A heterogeneous group of stimuli and perturbations can trigger mitotic catastrophe. Some inducers of mitotic catastrophe directly affect the integrity of the genetic material (for example, DNA-damaging agents), whereas others interfere with the complex molecular machinery that ensures the faithful segregation of chromosomes (for example, microtubular poisons). Finally, some compounds trigger mitotic catastrophe via uncharacterized signaling pathways. For instance, hyperthermia and the consequent heat shock response have long been recognized as a cause of mitotic death and are being investigated as a possible means for radio sensitization,[79] yet the underlying molecular mechanisms remain unclear.

Malignant cells display highly heterogeneous chromosomal content (most often aneuploid), suggesting that during oncogenesis pre-cancerous and cancerous cells develop strategies to breach aneuploidy preventing mechanisms such as mitotic catastrophe. Thus, the avoidance of mitotic catastrophe may represent one of the gateways to malignant transformation.

Mitotic catastrophe-related factors are often mutated or epigenetically deregulated in tumours, correlating with aneuploidization and increased tumorigenicity. Mitotic catastrophe executioners, such as SAC components and TP53, are downregulated or inactivated by genetic or epigenetic events in several cancers.[80,81] Conversely, inhibitors of mitotic catastrophe, like survivin, are often overexpressed or hyperactivated.[82]

Cancer cells are often intrinsically more sensitive to mitotic catastrophe than their ‘normal’ counterparts,[83] implying the existence of a ‘therapeutic window’ for inducers of mitotic

catastrophe and suggesting that the activation of mitotic catastrophe might constitute a highly desirable therapeutic endpoint.

NETosis :

Neutrophils are the first line of defense of the immune system against infection. Among their weaponry, they have the ability to mix and extrude their DNA and bactericidal molecules creating NET-like structures in a unique type of cell death called NETosis. This process is important in order to control extracellular infections limiting collateral damage. Its aberrant function has been implicated in several human diseases including sepsis and autoimmune disease.

In the 2012 classification, NETosis is accepted for the first time as a specific cell death subroutine of granulocyte cells different from apoptosis and necrosis, based on the demonstration of its insensitivity to caspase inhibition and necrostatin, respectively.

There are two types of NETosis : the vital NETosis and the suicidal NETosis. In infectious diseases, vital NETosis allows PMNs to maintain conventional host defensive functions. Conventional neutrophil host response includes the recruitment cascade, emigration, chemotaxis, phagocytosis, and microbial killing. Also vital NETosis aids in containing local infections, such as gram-positive cellulitis, by allowing PMNs to rapidly release NETs and continue to chemotax and phagocytose live bacteria. Additionally, the live NET-releasing PMNs are able to maintain their membrane integrity, thereby imprisoning the captured bacteria. Intravascular NET release optimizes the capture of both bacteria and viruses within the blood stream. Intravascular NETosis may also contribute to immunothrombosis.[84]

Suicidal NETosis classically occurs following stimulation by phorbolmyristateacetate (PMA) through activation of protein kinase C and the raf–mitogen-activated protein kinase (MEK)–extracellular signal-regulated kinase (ERK) pathway. NADPH assists in the translocation of neutrophil elastase from cytosolic granules into the nucleus where it aids in chromatin breakdown via histone cleavage. MPO is required for chromatin and nuclear envelope breakdown and granular mixing within the NET vacuole. Following 120 minutes of intracellular NET formation, the neutrophil outer membrane ruptures, and the mature NET is extruded. By contrast, vital NETosis has been reported following both direct microbial exposure and lipopolysaccharide (LPS). Live S aureus induce rapid NET release (30 minutes) in human and mouse neutrophils in vitro and in vivo. For gram-negative bacteria, NETs are induced via Toll-like receptor (TLR) 4 activation of platelets followed by direct neutrophil-platelet interaction via CD11a, whereas both complement receptor 3 and TLR2 are required for vital NETosis following gram-positive infection. NETs are released via nuclear

budding and vesicular release of NETs. This mechanism spares the PMN outer membrane, thereby allowing the PMN to continue to function, even to the point of becoming anuclear.[85]

Apart from the role of NETosis in inflammation, it plays a deleterious role in cancer. It is suggested that platelet aggregation takes place in response to the high DNA content and the highly negatively charged chromatin of the NETs. These platelet aggregates help attract the tumor cells and thus help in metastasis.[86]

Thus therapeutically, in cancer, protein arginine deiminase inhibitor 4 (PAD4) may be used to target the NETs in order to limit metastasis. However, a body without or with fewer NETs shall be more prone to sepsis and thus this therapeutic implication is still under clinical trials.

Anoikis :

An important aspect of multicellularity is that cells only grow and differentiate when in the correct context within a tissue, and remove themselves by apoptosis when they are not. Cells sense their location through specific interactions with the extracellular matrix (ECM) as well as neighboring cells. Apoptosis in response to inappropriate cell/ECM interactions is termed anoikis, (Greek word meaning “loss of home” or “homelessness”) a name that in some way implies a special case of cell death initiated by signals not used in response to other proapoptotic insults.[87]

Integrin-mediated adhesion regulates all the same signaling pathways that control apoptosis in growth factor-mediated survival, DNA damage responses and death receptor mediated apoptosis, although to different extents. Which pathways regulate anoikis varies depending on cell type, with different integrins activating distinct signaling cascades. (figure 3)

Cancer cells in order to survive, must have the potential to evade this mechanism of anoikis. Transformed cells employ different strategies to compensate for, or circumvent, the anoikis signals and thus become anchorage independent**.** In general, these strategies follow three different patterns: adapting to the new surroundings, either by EMT or by integrin switching, to avoid anoikis; counteracting negative signaling by hyperactivation of survival or mitogenic pathways; or ‘hiding and waiting’ by entering into a dormant state through either autophagy or entosis, and then reactivating the cell cycle when conditions are favorable.[89]

The therapeutic significance of this type of cell death mechanism lies in the potential of the anti cancer drugs to induce anoikis. The molecular targetable sites of this mechanism may suggest the adjuvant drugs like quinazoline based α1 adrenoreceptor antagonists (Doxazocin

and Terazocin) to be used for the cure of cancer.[90]

Oncosis :

Unlike apoptosis which is characterized by cellular shrinkage, "oncosis" is a term used to designate the type of cell death which is specifically characterized by cellular swelling.[91]

It has been studied extensively in ischemic cell injuries and involves the progressive membrane injury relating 3 different stages. In stage 1 , the cell becomes committed to oncosis as a result of selective membrane injury with leak of ions and water due to ATP depletion and leading to cell swelling without generalized increase in cell membrane permeability. During stage 2, the cell is passing the point of loss of reversibility with the cell membrane becoming leaky indicating a non selective increase in membrane permeability. And stage 3 represents the eventual physical disruption of the cell membrane.[92]

Oncosis may result from toxic agents that interfere with ATP generation or processes that cause uncontrolled cellular energy consumption.[92]

CONCLUSION:

Does it matter how a cell die? The literature answers a resounding 'yes' to this question for many reasons. Every cell death mechanism has a distinct pathway of execution and a distinct time and place of occurrence. This clearly provides us with the targetable sites embedded within their execution pathways for either inducing or curbing a particular death mechanism. Acknowledging their role in various disease pathologies provides an insight as to what kind of therapy has to be implicated for better prognosis and cure. Literature embraces a vast knowledge of each of the above, and here we have tried to envelop a brief idea of each of them.

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FIGURES:

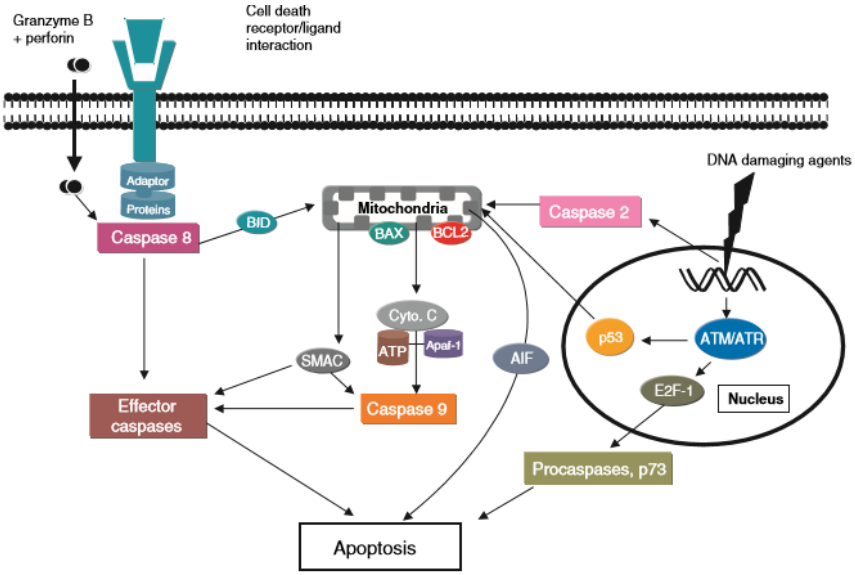

Figure 1 : Molecular mechanisms depicting the intrinsic and extrinsic pathways of apoptosis

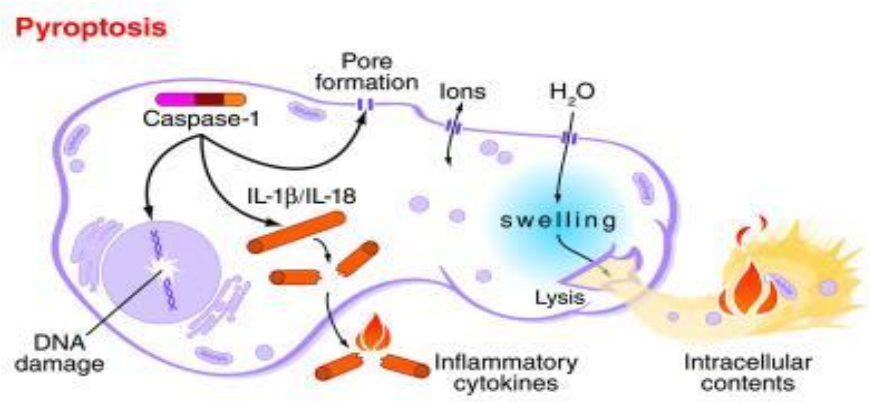

Figure 2 : Pyroptosis : When activated by a toxin or an infection, the enzyme caspase-1 initiates several reactions inside of the cell, some of which lead to DNA damage, others to the release of chemical distress signals called cytokines, and others to the formation in the cell membrane of tiny pores that let water flood in until the cell swells, bursts and spills its content

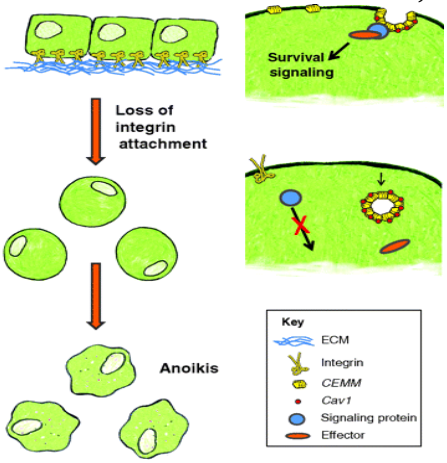

Figure 3: Anoikis : In adhered cells, cholesterol enriched membrane microdomains (CEMMs) at the plasma membrane allow correct activation and coupling of signaling molecules to their effectors (such as Rac–PAK and PI3K–Akt), which results in cell survival and growth. After cell detachment from the ECM, integrin signaling is shutdown and CEMMs are internalized in a Cav1-dependent manner, resulting in cell cycle arrest and anoikis.[88]

TABLES:

Table 1 : Differences between Pyroptosis and Apoptosis

Characteristic	**Pyroptosis**	**Apoptosis**
Inflammatory versus non-inflammatory	inflammatory	Non-inflammatory
Lytic versus non-lytic	Lytic	non-lytic
initiator caspase	caspase 1/4/5/11	caspase 2,8,9,10
effector caspases	none	caspase 3,6,7
DNA damage laddering TUNEL stain ICAD cleavage Chromatin condensation	 no yes no yes	 yes yes yes yes
nucleus intact	yes	no
plasma membrane pore formation	yes	no
PARP cleavage	no	yes
AnnexinV staining	tes	yes

Table 2 : differences between apoptosis, necrosis and paraptosis

	Apoptosis	Necrosis	Paraptosis
Nuclear fragmentation	+	-	-
Chromatin condensation	+	-	+/-

Vacuolation	-	+	+
Mitochondrial swelling	Sometimes	+	Late
DNA fragmentation	+	-	-
Inhibition by act D	+	-	+
PARP cleavage	+	+	-

Table 3 : Differences between classical apoptosis and chondroptosis

	Classical apoptosis	**Chondroptosis**
Nucleus	Chromatin condensation at periphery	Patchy condensation of chromatin throughout
Golgi apparatus	No increase	Increase in early stages
Endoplasmic reticulum	No changes	Increase in amount and expansion of lumen
Autophagic vacuoles	Not present	Frequently present
“blebbing” vs “budding”	Budding into apoptotic bodies	Blebbing of cytoplasmic material
Final elimination	Hetero-phagocytosis of apoptotic bodies	Auto-digestion of most cellular material
Function	Elimination of cells without inflammation	Auto-elimination in absence of phagocytes.