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A Comprehensive Review on Cell Death

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Abstract

A fundamental pathophysiological process, apoptosis is also a crucial stage in healthy growth and life. Despite the fact that a variety of triggers can cause cell death, the mode of cell death often follows distinct patterns. Necrosis is a non-physiological process that happens as a result of infection or injury. Apoptosis, also known as Type I cell death, and autophagy, often known as Type II cell death, are both types of planned cell death. Necrosis, which can take many various forms, is the death of cells brought on by outside forces like injury or infection. Necroptosis, a type of programmed necrosis, has recently been identified as an additional type of designed cell death. Necroptosis is thought to work as a cell-death fallback when apoptosis signaling is inhibited by endogenous or external elements like viruses or mutations. Cornification is a distinct process of terminal differentiation and programmed cell death that epidermal keratinocytes go through. The creation of the outermost skin barrier is a result of cornification. An overview of the various types of cell death and their mechanisms is provided in this review paper.

Keywords: Cell death; Apoptosis; Necrosis; Autophagy; Mechanisms.

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Introduction

Apoptosis is a vital and active process in multicellular animals that maintains tissue homeostasis and gets rid of potentially hazardous cells (Green and Llambi, 2015). Although some elements of the apoptosis concept had been explicitly articulated for many years prior, the name "apoptosis" (a-po-toe-sis) was first used to describe a physically distinct type of cell death in a now-classic study by Kerr, (1972) and Wyllie, (1980). It is the situation in which a biological cell stops functioning. This could be the result of a sickness, a localized damage, or the demise of the organism that the cells are a part of. It could also be the result of the natural process of old cells dying and being replaced by new ones. Apoptosis (or type I cell death), autophagic cell death (type II), and necrosis (type III) are the three major types of physically different cell death. All

three can be carried out by separate, and occasionally converging, signaling pathways that are activated in response to particular stimuli (Galluzzi et al. 2007). Cell shrinkage, membrane blabbing, and chromatin condensation (pyknosis) are signs of apoptosis (Kerr et al. 1972). According to Galluzzi et al. (2012), it can also be described as cell death coupled with the activation of caspase proteases. Large intracellular vesicles manifest and the autophagy machinery is activated during autophagic cell death. It should be noted that while though autophagy, the membrane engulfment subsequent catabolic breakdown of portions of the cytoplasm is a well-defined process, its role as a mechanism for active cell death is still up for debate. When a metabolic crisis occurs (such as low ATP levels and a lack of nutrients and amino acids), autophagy is primarily a survival mechanism that is activated. Protein clumps and damaged organelles, like mitochondria with low membrane potential. In most cases, autophagy, which is a stress response, goes hand in hand with cell death rather than contributing to it and merely denotes an unsuccessful attempt at survival (Shen et al. 2012). Early plasma membrane rupture and dilatation of cytoplasmic organelles, in particular mitochondria, are a traditional positive description of necrosis based on morphological criteria (Edinger et al. 2004; Kroemer et al. 2005). Necrosis is a type of cell damage that causes the autolysis the early death of cells in live tissue (Proskuryakov et al. 2003; Zappavigna et al. 2012). The present study will review the different mechanisms of different cell death and their effect (beneficial, detrimental or no effect) on multicellular organisms.

Methods

“Apoptosis’ or ‘Cell death’ were the basic term used in search of conducting and exploring from the internationally published articles, journals and scientific literature. When gathering data on cell death from different sources, these are the websites that should be highlighted in particular.

- ✓ Google Scholar https://scholar.google.com/
- ✓ ResearchGate https://www.researchgate.net/
- ✓ Google www.google.com
- ✓ BioOne https://bioone.org/
- ✓ GetCITED http://www.getcited.org/
- ✓ Academia https://www.academia.edu/

Owning to some limitation of the number of published studies, we included partial matches, scientific reports, conference papers, reviews, unpublished reports, opinion papers, thesis and other publications in the grey literature.

Results

1. Apoptosis

Multicellular organisms experience apoptosis, a type of planned cell death (Green & Douglas, 2011). The word "apoptosis" was first used by Kerr *et al.* (1972) to describe a type of cell death with certain morphological characteristics. Characteristic cell changes (morphology) and death

are caused by biochemical processes. These alterations include cell shrinkage, chromatin condensation (pyknosis), chromosomal DNA fragmentation, nuclear fragmentation (karyorrhexis), blebbing of the plasma membrane, and cell shrinkage. Apoptosis is a well-managed and regulated process that benefits an organism's life cycle. For instance, cells between the digits in a growing human embryo suffer apoptosis, causing the separation of fingers and toes. Apoptosis results in apoptotic bodies, which phagocytic cells can engulf and eliminate before the contents of the cell can leak out and harm neighboring cells (Alberts *et al.* 2008; JhonyStiban, 2015).

Physiological and pathological apoptosis can be used to discuss the causes of apoptosis. Cell deletion in populations of proliferating cells (such as the intestinal epithelium) and during menstruation are examples of physiological apoptosis. It also includes the removal of extra cells during embryogenesis and the elimination of potentially hazardous cells. However, pathological apoptosis targets the death of cancerous cells, virus-infected cells, and cells with DNA damage brought on by radiation, hypoxia, anticancer medications, etc.

Mechanism of Apoptosis

Caspases are activated during apoptosis, which controls all of the morphological modifications that distinguish this type of cell death. Cysteine proteases known as caspases have a preference for aspartic acid residues in their substrates. Caspases come in two varieties: effector caspases (caspases 3, 6 and 7) and initiator caspases (caspases 2, 8, 9, 10, 11, and 12). Binding to a certain oligomeric activator protein is required for initiator caspases to become active. These active initiator caspases then cleave proteins to activate effector caspases. The cell death program is then carried out by the active effector caspases by the proteolytic degradation of a variety of intracellular proteins.

i. Initiation Phase of Apoptosis

Apoptosis is strictly controlled by activation pathways since, once it starts, it invariably results in cell death (Alberts *et al.* 2015; Böhm&Schild, 2003). The intrinsic pathway, also known as the mitochondrial pathway, and the extrinsic pathway are the two activation mechanisms that are most clearly recognized (Alberts *et al.* 2015). The release of proteins from the intermembrane gap of mitochondria is required for the intrinsic route to function, which is triggered by intracellular signals produced when cells are under stress (Alberts *et al.* 2015). The extrinsic pathway is activated by extracellular ligands binding to cell-surface death receptors, which leads to the formation of the death-inducing signaling complex (DISC) (Alberts *et al.* 2015).

(a) Extrinsic Pathway of Apoptosis

The first pathway is known as the extrinsic pathway because it receives its initial signals from sources outside of the cell. Subsets of T-lymphocytes frequently initiate this route, along with other cells. FAS ligand is a surface molecule found on these lymphocytes. According to Dickins *et al.* (2012), this pathway is started when FAS ligand attaches to CD95 or DR4/DR5 on the surface of the targeted cells. A Death Inducing Signal Complex (DISC) is created as a result of FAS ligand interacting to the FAS receptor. According to Dickens *et al.* (2012), the FAS

Associated Death Domain (FADD) in this content binds to Procaspase-8 and this Procaspase-8 activates Caspase-8 with other Caspase. The Caspase Cascade, the subsequent stage of the extrinsic pathway, is a self-amplifying mechanism in which caspases activate one another. The second apoptotic pathway, also known as the intrinsic pathway, has a shared end point in the caspase cascade. Normal cells have the anti-apoptotic protein FLIP, and some viruses can prevent Procaspase-8 from activating during the extrinsic pathway (Micheau*et al.* 2001).

(b) Intrinsic Pathway of Apoptosis

The mitochondrial pathway is another name for the intrinsic pathway, and both pathways are started by signals coming from inside the cells. The intrinsic route is initiated by the release of cytochrome-C and a Secondary Mitochondrial Activator of Caspases (SMAC) (Eckelman*et al.* 2006). By preserving equilibrium between two sets of proteins in the mitochondrial membrane, this intrinsic mechanism is controlled. They are pro-apoptotic proteins like BAK and BAX and anti-apoptotic proteins like BCL-x and BCL-2. The anti-apoptotic protein binds to the pro-apoptotic protein in a healthy cell. Therefore preventing them from acting. BCL-x and BCL-2 are subsequently stopped in turn if a cell is injured or if it stops receiving survival signals. This occurs as a result of the activation of pro-apoptotic cells known as BAX and BAK inside of the mitochondrial membranes, which opens a permeability channel and allows mitochondrial substances like cytochrome-C to leak out into the cytoplasm from the mitochondria, where it binds to APAF-1 (Apoptosis Activating Factor) to form a substance known as an apoptosome. This Apoptosome initiates Caspase-9 activation (Chipuk*et al.* 2010; Eskes*et al.* 2000; Korsmeyer*et al.* 2000; Dewson*et al.* 2008, 2009; Goldstein *et al.* 2000; Munoz- Pinedo*et al.* 2006; Bratton *et al.* 2001; Bratton and Salvesen 2010; Zou *et al.* 1997; Malladi*et al.* 2009).

ii. Execution Phase of Apoptosis

Caspase-3, Caspase-6, and Caspase-7 are activated by Caspase-8 and Caspase-9. Apoptosis is actually brought on by execution caspases, which also target nuclear and matrix protein components and the cytoskeleton of the cell. Nuclear breakdown is what causes apoptosis to take place. Therefore, the caspases that are dominant during the execution phase also activate other enzymes like endonucleases, which have a propensity to degrade double-stranded DNA, a crucial trigger for the onset of apoptosis.

(a) Removal of Apoptotic Cells

Efferocytosis is the name given to the elimination of dead cells by nearby phagocytic cells (Vandivier*et al.* 2006). Dying cells that go through the final phases of apoptosis exhibit phagocytotic molecules on their cell surface, such as phosphatidylserine (Li *et al.* 2003). In the course of apoptosis, a protein known as scramblase redistributes phosphotidylserine from the inner leaflet surface of the plasma membrane to the extracellular surface. According to Savill*et al.* (2003), these chemicals designate the cell for phagocytosis by cells with the necessary receptors, such as macrophages. Phagocytes remove dying cells in a controlled manner without causing an inflammatory reaction (Krysko*et al.* 2009). Cellular RNA and DNA are divided and

sorted into various apoptotic entities during apoptosis; the division of RNA is started by nucleolar segregation (Halicka*et al.* 2000).

2. Autophagy

Lysosomes are used for the catabolic process of autophagy, which breaks down cellular materials. A number of cellular stresses, including food deprivation, DNA damage, and organelle destruction, can speed up autophagy, which is a low-level constitutive process. Although excessive autophagy can result in cell death (Esclatine*et al,* 2009; Klionsky, 2005), it functions as a protective mechanism that makes it easier to degrade extraneous or damaged cellular components. Autophagy's main function is to defend cells against stress situations like hunger. During times of hunger, autophagy breaks down cytoplasmic components to produce amino acids and fatty acids that can be used to build new proteins or are oxidized by mitochondria to make ATP for cell survival (Levine and Yuan, 2005). While necrosis and type I programmed cell death (apoptosis) are both caused by overly induced autophagy, type II programmed cell death (PCD) is caused by excessively induced autophagy and is separate from both of these processes (Chen et al., 2010; Levine and Yuan, 2005; Maiuri*et al,* 2007; Platini*et al,* 2010). In addition to helping the body cope with stress, autophagy also plays a role in immunity, defense against microbial invasion, senescence, lifespan extension, and normal development (Levine and Klionsky, 2004). According to Klionsky (2005) and Mizushima*et al.* (2008), autophagy plays a part in a variety of patho-physiologies, including cancer, myopathies, neurodegeneration, heart and liver illnesses, and gastrointestinal problems.

Autophagic cell death

Autophagic cell death is visually described as a kind of cell death that takes place in the absence of chromatin condensation but is accompanied by significant autophagic vacuolization of the cytoplasm (particularly by transmission electron microscopy). Cells that die with an autophagic shape have little to no connection with phagocytes, in contrast to apoptotic cells (whose clearance is ensured by engulfment and lysosomal breakdown) (Baehrecke, 2005; Clarke, 1990). Although the term "autophagic cell death" is a linguistic inducement to think that autophagy actually causes cell death, it actually just characterizes cell death with autophagy (Galluzzi*et al,* 2008; Levine and Yuan, 2005; Galluzzi*et al,* 2007).

Types of Autophagy

Autophagy is categorized into three primary categories: chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy (Klionsky, 2005). These categories are based on the various routes by which cargo is carried to the lysosome or vacuole. The primary mechanism, macroautophagy, is utilized to largely eliminate damaged cell organelles or extra proteins (Levine *et al,* 2011). The organelle that needs to be destroyed is first engulfed by the phagophore, which then forms a double membrane known as an autophagosome around it (Mizushima*et al,* 2002; *Esen et al,* 2012). The two organelles then combine as the autophagosome moves through the cell's cytoplasm to a lysosome (Mizushima*et al,* 2002).

Acidic lysosomal hydrolase in the lysosome breaks down the autophagosome's contents (Homma, 2011). Contrarily, microautophagy involves the lysosome's direct engulfment of cytoplasmic particles (Castro-Obregon and Susana, 2010). This happens either through cellular protrusion or invagination, which is the inward folding of the lysosomal membrane (Esen*et al,* 2012). CMA, or chaperone-mediated autophagy, is a very intricate and particular mechanism that depends on the recognition of the hsc70-containing complex (Česen*et al,* 2012; Bandyopadhyay*et al,* 2008). In order to bind to this chaperone and form the CMA-substrate/chaperone complex, a protein must have the recognition site for the hsc70 complex (Homma, 2011; Martinez *et al,* 2009). The CMA receptor will then be recognized and bound with by the protein that is attached to the lysosomal membrane, enabling this complex to enter the cell. The lysosomal hsc70 chaperone helps the substrate protein to unfold upon recognition and move across the lysosome membrane (Lee *et al,* 2012; Mizushima*et al,* 2002). Due to its one-by-one protein material translocation and extreme stipulation of what material penetrates the lysosomal barrier, CMA differs greatly from other forms of autophagy (Levine *et al,* 2011). Despite the fact that autophagy is typically thought of as being nonspecific, there are numerous instances of selective autophagy, such as mitophagy (for mitochondria), ribophagy (for ribosomes), pexophagy (for peroxisomes), and reticulophagy (for the endoplasmic reticulum, ER) (He and Klionsky, 2009).

Mechanism of Autophagy

The sequestration of cytoplasmic material into autophagosomes for bulk breakdown by lysosomes is a hallmark of macroautophagy. Transmission electron microscopy can identify autophagosomes from other forms of vesicles such endosomes, lysosomes, or apoptotic blebs since they are two-membraned by definition and contain degenerating cytoplasmic organelles or cytosol (Levine *et al,* 2004; Levine *et al,* 2008). When autophagosomes and lysosomes fuse, autolysosomes are created, where acidic lysosomal hydrolases destroy both the autophagosome inner membrane and its luminal cargo (Tasdemir*et al,* 2008). The autophagic route is finished at this catabolic stage. Initiation, nucleation, fusion of the autophagosome and lysosome, and hydrolysis are the four essential stages of autophagy. Genetically screened yeast revealed a number of autophagy regulatory molecules, including the key components of autophagy, the autophagy (Atg)-related proteins. The creation of the phagophore at the initiation stage requires the assembly and aggregation of the Atg1 complex, which consists of Atg1, Atg13, Atg17, Atg29, and Atg31 (Cheong *et al,* 2008; Kawamata*et al,* 2008). During the phase of nucleation, a complex made up of the class III PI-3 kinases VPS34, Atg6 (also known as Beclin1 in mammals), Atg14, and Vps15 regulates the production of phagophores at the ER and other membranes. He *et al,* (2007) and Molejon*et al,* (2013) suggest that the vesicle membrane proteins VMP1 and Atg9, which are found in the Golgi complex, autophagosomes, and endosomes, are involved in the transport of lipids to the isolation membrane. Two ubiquitin-like protein-conjugated systems, particularly Atg12 and Atg8, are necessary for the expansion and closure of the autophagosome (Ohsumi, 2001). Vesicle expansion and completion are mediated by two Atg8 and Atg12 ubiquitin-like (Ubl) conjugation systems. Atg12 is coupled to Atg5, whereas Atg8 is coupled to the lipid phosphatidylethanolamine (PE). Atg8-PE

(phosphatidylethanolamine) covalent structure is a typical hallmark of autophagy development and is linked to both the outer and inner membranes of the autophagosome. For the purpose of recycling Atg8, Atg4 can reversibly cleave the Atg8-PE covalent structure to yield Atg8. Following this, soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-like proteins mediate the fusion of the autophagosome and lysosome (Diao*et al,* 2017; Cheng *et al,* 2017; Itakura*et al,* 2012; Nair *et al,* 2011). Finally, different lysosomal enzymes hydrolyze different kinds of damaged organelles, proteins, lipids, and nucleic acids at low pH (Hamasaki *et al,* 2013, Mizushima*et al,* 2011).

3. Necrosis

It is now possible to improve upon the traditional positive definition of necrosis based on morphological criteria (early plasma membrane rupture and dilatation of cytoplasmic organelles, particularly mitochondria) (Kroemer et al., 2005; Edinger et al., 2004). The finding that inhibiting both autophagy and crucial apoptotic events can cause necrosis (Degenhardt et al., 2006) lends weight to the hypothesis that necrosis is a (or even the) default cell death mechanism. Additionally, a growing body of research suggests that necrotic cell death is just as well-regulated and programmed as caspase-dependent apoptosis (Zong& Thompson, 2006) and that it may be a significant cell death mode that is relevant to both pathology and physiology. This suggests the existence of caspase independent cell death pathways that can operate even in a strictly regulated developmental context (Chautan et al., 1999). If the traditional apoptosis machinery malfunctions, caspase-independent cell death can act as a fallback strategy (Fiers et al., 1999; Leist&Jaattela, 2001). According to Vercammen et al. (1998), Holler et al. (2000), and Kalai et al. (2002), cell death caused under such circumstances resembles necrosis rather than apoptosis and lacks the latter's characteristic traits. Necrotic cell death, then, results from significant interaction between a number of biochemical and molecular events at various cellular levels rather than from a single, well-described signaling cascade (Festjens et al., 2007). Necrosis may be completely unregulated or, on the other hand, may be programmed, depending on the situation. The ballooning of organelles and cells that leads to the rupture of the plasma membrane is the most striking morphological characteristic of planned necrosis. An imbalance in osmotic pressure is implied by the increase in cell volume and substantial intracellular vacuole development (Moquin& Chan, 2010). According to morphologic theory (McGee et al., 1992; Stevens & Lowe, 2001), the cell displays a number of alterations that reveal its developmental stage. Mild cytoplasmic swelling, organelle enlargement, ribosome loss, and rough endoplasmic reticulum blebbing from the plasma membrane of cytoplasmic fragments that comprise cytosol but do not include the big organelles (mitochondria, endoplasmic reticulum) can all be signs of it.

Types of Necrosis

According to Kumar et al. (2010), necrosis can take six different morphological forms: liquefactive necrosis, gangrenous necrosis, gaseous necrosis, fat necrosis, and fibrinous necrosis. According to Kumar et al. (2010), coagulative necrosis is characterized by the production of a gelatinous (gel-like) substance in dead tissues that preserves the tissue's architecture. Protein

denaturation leads to coagulation, which causes albumin to change into a solid, opaque state (Craft et al., 2010). Necrosis in this pattern is frequently observed in hypoxic (low-oxygen) settings, such as infarction. According to Craft et al. (2010), coagulative necrosis primarily affects organs like the kidney, heart, and adrenal glands. This type of necrosis is most frequently brought on by severe ischemia (McConnell, 2007). In contrast to coagulative necrosis, liquefactive necrosis (or colliquativenecrosis) is characterized by the breakdown of dead cells into a viscous liquid substance. This is common of bacterial infections, or occasionally fungal infections, as they can trigger an inflammatory reaction. Pus is the term used to describe the necrotic liquid mass, which is typically creamy yellow because it contains dead leukocytes (Kumar et al., 2010). Because the brain has little connective tissue and a high concentration of lipids and digestive enzymes, which allows cells to be easily eaten by their own enzymes, hypoxic infarcts in the brain manifest as this form of necrosis (Craft et al., 2010). A kind of coagulative necrosis that resembles mummified tissue is called gangrenous necrosis. It is a defining feature of gastrointestinal and lower limb ischemia. Liquid necrosis (wet gangrene) results from overlaying infection of dead tissues (Sattar, 2015). According to Stevens et al. (2002), activated lipases acting on fatty tissues like the pancreas can cause a specific necrosis of fat tissue known as fat necrosis. Acute pancreatitis results when pancreatic enzymes leak into the peritoneal cavity and liquefy the pancreatic membrane by converting triglyceride esters into fatty acids through the process of fat saponification. (Krishna et al., 2010). These lesions may bind to calcium, magnesium, or sodium to create enzymes that are a chalky white color (Craft et al., 2010). The calcium deposits may be substantial enough to be seen on radiographic examinations and have a distinct microscopical appearance (McConnell, 2007). Calcium deposits are visible to the naked eye as grittier white specks (McConnell, 2007).

Mechanism of Necrosis

Necroptosis, also known as planned necrosis, is a process that may be used to carry out this active necrosis (Krysko et al., 2008). It's interesting to note that TNF, FasL, and TRAIL (TNF-related apoptosis inducing ligand), which may also promote apoptosis, can also stimulate necroptosis. The serine/threonine kinases receptor interacting protein 1 (RIP1) and 3 (RIP3) mediate the main necrotic cell death pathway. Festjens et al. (2006) identified RIP1 as a critical death receptor-mediated necrosis initiator, while Cho, He, and Zhang (2009) identified RIP3 as a critical upstream activating kinase that controls RIP1-dependent necroptosis. For instance, TNF treatment causes the RIP1-RIP3 pro-necrotic complex to form, and RIP1 and RIP3 kinase activity are essential for stable complex formation and subsequent necrosis induction (Cho et al., 2009; Zhang et al., 2009). Recently, the RIP1 kinase activity was discovered to be the target of Necrostatin-1 (Degterev et al., 2008), which was first discovered as a small molecule inhibitor of necroptosis (Degterev et al., 2005). A key factor in determining whether cells die through apoptosis or necrosis is ATP levels. In contrast to the activities that precede apoptotic cell death, such as apoptosome production and caspase activation, necrosis is the final outcome of a bioenergetics catastrophe brought on by ATP depletion. In fact, adding glycolytic substrates can prevent hypoxia-induced necrosis in cells (Anundi et al., 1987; Leist et al., 1997). Therefore, it is expected that ATP regeneration during reperfusion of ischemic tissues will favor apoptotic cell

death over necrotic cell death. Additionally, when ATP synthase is blocked, cells that are stimulated to undergo apoptosis instead perish via necrosis (Formigli et al., 2000; Nieminen et al., 1994). Reactive oxygen species (ROS), calcium (Ca2+), calpains, cathepsins, phospholipases, and ceramide are only a few of the mediators that are involved in the execution stage of necrotic cell death (Brookes et al., 2004; Vanlangenakker et al., 2008).

Cornification

According to Kroemer et al. (2009), the epidermis experiences cornification, a very particular type of PCD that is morphologically and biochemically separate from apoptosis. It results in the development of corneocytes, which are dead keratinocytes containing a mixture of particular proteins (such as keratin, loricrin, SPR, and involucrin) and lipids (such as fatty acids and ceramides). These substances are essential for the cornified skin layer's function (mechanical resistance, elasticity, water repellence, and structural stability). 'Keratinization' or 'cornified envelope development' are terms that are less frequently used to describe cornification (Candi et al., 2005; Lippens et al., 2005). According to Counis et al. (1998) and Testa et al. (2004), it is commonly regarded as a terminal differentiation pathway comparable to those leading to other anucleated tissues (such as the lens epithelium and mature red blood cells). This is primarily because these processes show (often restricted) activation of the caspases and other components of the molecular machinery for cell death (Garrido and Kroemer, 2004; Galluzzi et al., 2008; Testa et al., 2004; Weber and Menko, 2005). However, unlike corneocytes, adult red blood and lens epithelial cells continue to be capable of dying from stress (Yan et al., 2006; Lang et al., 2005), hence only cornification should be taken into account as a true cell death program (Kroemer et al., 2009). According to a unique method of epithelial differentiation, cornification occurs at the molecular level when cells express all the enzymes and substrates needed to develop the epidermal barrier that isolates the body from its environment (Kroemer et al., 2009). This is accomplished by the extracellular release of specific lipids that are covalently attached to cornified envelope proteins, the action of crosslinking enzymes (such as transglutaminase types 1, 3, and 5) on a variety of substrates (such as loricrin, SPR, involucrin, and SP100), and the necessity of proteases for desquamation and impermeability.

Impacts of Abnormal Cell Death during Development

In multicellular organisms, active or programmed cell death is crucial for maintaining homeostasis as well as for the targeted removal of potentially hazardous or contaminated cells. Accordingly, dysregulation of the signaling pathways that initiate cell death can result in both degenerative diseases (too much cell death) and catastrophic diseases like cancer and autoimmune (too little cell death). Given the significance of cell death in development, it is reasonable to assume that genetic, viral, or teratogenic factors that have an impact on cell death programs will also have an effect on the embryogenic process. It would appear from animal models that mutations in the basic apoptotic pathways are fatal to the embryo. One such instance is the improper control of the post-mitochondrial apoptotic pathway, which causes an enormous overproduction of brain tissue and embryonic mortality. There is strong circumstantial evidence

that errors in typical cell death pathways have a role in a number of human congenital diseases, including syndactyly, failure of neural tube closure, cleft palate, congenital heart problems involving valve and cardiac blood vessel alignment, etc.

Conclusion

Caspase activation is thought to be a key component of the tightly controlled, energy-dependent apoptotic process, which is distinguished by distinct morphological and biochemical characteristics. The molecular mechanisms of action or activation of many of the important apoptotic proteins that are activated or inactivated in the apoptotic pathways have been found, but further study is needed to elucidate these proteins' molecular mechanisms of action. Understanding the apoptotic process' mechanical underpinnings is crucial since programmed cell death, which is brought on by a variety of physiological and pathological triggers, is a component of both health and illness. Apoptosis plays a significant role in the pathophysiology of many diseases, which makes it possible to intervene therapeutically at a variety of checkpoints. Understanding the molecular mechanisms of apoptosis and other forms of programmed cell death offers deeper understanding of the various disease processes and may therefore affect therapeutic approach. Additionally, a number of arguments can be made against the unambiguous separation of various cell types in the triad of necrosis, autophagy cell death, and apoptosis. Three different types of cell death, apoptosis, autophagy, and necrosis have each been investigated separately and are regarded as independent mechanisms. Here, the mechanism of cornification, a type of cell death distinct from necrosis and apoptosis, is also described. The complexity of cell death programs is implicated by the occurrence of numerous controlled cell death pathways, which also offers new therapeutic targets. It is necessary to conduct additional research to examine the connections between various cell death programs and to pinpoint the main molecular elements that control cell death under particular clinical circumstances.

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