International Journal of Science and Technology Research Archive

ISSN: 0799-6632 (Online)

Journal homepage: https://sciresjournals.com/ijstra/

(REVIEW ARTICLE)

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Is death a living being?

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International Journal of Science and Technology Research Archive, 2023, 05(02), 134–141

Publication history: Received on 28 October 2023; revised on 18 December 2023; accepted on 21 December 2023

Article DOI: https://doi.org/10.53771/ijstra.2023.5.2.0294

Abstract

The death process begins with the loss of function of one or more of the three classic vital organs: the heart, the brain, and/or the lungs. Failure to resuscitate the function of the affected primary organ leads to the cessation of the function of other organs. The cell carries death factors or elements such as caspases and some mitochondrial secretions - At the same time the mitochondria represent the basic source of energy and life in the cell. Death occurs only when activating the molecules and factors of cell annihilation. Apoptosis is a type of cell death mechanism, controlled by interactions between several molecules - and is responsible for removing unwanted cells from the body. Apoptosis can be induced by signals from inside the cell or by death signals coming from outside the cell via cosmic energy waves. Caspases are cysteine aspartate-specific proteases that are essential for the initiation and execution of apoptosis. As one of the initiator and executor caspases, caspase-2 is the most evolutionally conserved caspase, exerting both apoptotic and non-apoptotic functions. Caspases also have a role in inflammation, whereby they directly process proinflammatory cytokines such as pro-IL1β. These are signaling molecules that allow recruitment of immune cells to an infected cell or tissue. In addition to apoptosis, caspases play a role in necroptosis, pyroptosis, and autophagy, which are non-apoptotic cell death processes. Mitochondria coordinate cell stress responses, such as autophagy, and control nonapoptotic cell death routines, such as regulated necrosis. Mitochondrial permeabilization leads to release of these proteins, which then interfere with the IAP-inhibition of caspases, resulting in potentiation of cell death. Initiators of mitochondrial-driven inflammation include the release of mitochondrial dsRNA and mt DNA thereby initiating type I interferons. It is concluded that mitochondria not only power the metabolic cell activities with energy but also power the cell death with both energy and signaling molecules denoting that cell death is an active living being.

Keywords: Cell; Death; Apoptosis; Caspases; Mitochondrial

1 Introduction

Death is defined as the complete and permanent cessation of all vital functions, such as lack of blood pressure and cardiac activity, absence of reflex response to stimuli, and cessation of spontaneous breathing. However, since some clinicopathological conditions may mimic some death characteristics, the certainty of death is achieved through the observation of the following negative vital signs: loss of consciousness, loss of sensibility, absence of motility or muscular tonus, cessation of blood circulation, and ultimately, absence of cerebral activity. Once all these criteria are met, an individual is declared dead [1].

The death process begins with the loss of function of one or more of the three classic vital organs: the heart, the brain, and/or the lungs. Failure to resuscitate the function of the affected primary organ leads to the cessation of the function of other organs. For example, the unregulated activity of the heart "ventricular fibrillation" leads to a stop of cardiac circulation and failure of blood vessels, brain, and lungs, which in turn leads to loss of consciousness and stop of

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breathing within seconds. In contrast, pulseless electrical activity (PEA) emerges with collapse of the vascular system, which is a common version of decompensation but rarely discussed in resuscitation literature. The vascular system, therefore, should be viewed as a fourth vital system [2]. The key feature of life is a biological process that can control and regulate other processes, and it maintains that ability over time. This control can happen hierarchically and/or reciprocally, and it takes place in three-dimensional space. This implies that the information that a biological process must utilize is only about the control, but not about the content of those processes. Those other processes can be vastly more complex than the controlling process itself [3]. Getting rid of unnecessary or damaged cells is as important as cell vitality in living organisms, and is necessary to maintain homeostasis in tissues, organs, and the entire organism. Apoptosis can be induced by signals from inside the cell or by death signals coming from outside the cell via cosmic waves or energy. Any disruption in the apoptosis process can cause various types of diseases ranging from cancer to autoimmune diseases [4].

2 Discussion

Caspases are aspartate-specific cysteine proteases proteins found inside every living cell. Its function is to initiate and carry out the process of cell death. A growing number of studies have revealed the associations between dysregulated ncRNAs, and caspases involved in cell death in numerous human diseases. As one of the initiator and executor caspases, caspase-2 is the most evolutionally conserved caspase in mammals, exerting both apoptotic and non-apoptotic functions [5]- Caspases are essential for the initiation and execution of apoptosis. Mammalian caspases can be subdivided into three functional groups: initiator caspases (caspase 2, 8, 9, and 10), executioner caspases (caspase 3, 6, and 7), and inflammatory caspases (caspase 1, 4, 5, 11, and 12). Initiator caspases initiate the apoptosis signal while the executioner caspases carry out the mass proteolysis that leads to apoptosis. Inflammatory caspases do not function in apoptosis but are rather involved in inflammatory cytokine signaling and other types of cell death such as pyro ptosis. Initially synthesized as inactive pro-caspases, caspases become rapidly cleaved and activated in response to granzyme B, death receptors, and apoptosome stimuli. Caspases will then cleave a range of substrates, including downstream caspases, nuclear proteins, plasma membrane proteins, and mitochondrial proteins, ultimately leading to cell death. [6,7,8]. Caspases also have a role in inflammation, whereby it directly processes proinflammatory cytokines such as pro-IL1β. These are signaling molecules that allow recruitment of immune cells to an infected cell or tissue. There are other identified roles of caspases such as cell proliferation, tumor suppression, cell differentiation, neural development, and axon guidance and ageing [9,10]

Caspase deficiency has been identified as a cause of tumor development. Tumor growth can occur by a combination of factors, including a mutation in a cell cycle gene which removes the restraints on cell growth, combined with mutations in apoptotic proteins such as caspases that would respond by inducing cell death in abnormally growing cells. Conversely, over-activation of some caspases such as caspase-3 can lead to excessive programmed cell death. This is seen in several neurodegenerative diseases where neural cells are lost, such as Alzheimer's disease [10]. Caspases involved with processing inflammatory signals are also implicated in disease pathogenesis. Insufficient activation of these caspases can increase an organism's susceptibility to infection, as an appropriate immune response may not be activated [11] The integral role caspases play in cell death and disease has led to research on using caspases as a drug target. For example, inflammatory caspase-1 has been implicated in causing autoimmune diseases; drugs blocking the activation of Caspase-1 have been used to improve the health of patients. Additionally, scientists have used caspases as cancer therapy to kill unwanted cells in tumors [12,13]. Apoptosis, a type of cell death mechanism, is controlled by the interactions between several molecules and responsible for the elimination of unwanted cells from the body. Apoptosis can be triggered intrinsically or extrinsically through death signals from the outside of the cell. Any abnormality in apoptosis process can cause various types of diseases from cancer to auto-immune diseases. Different gene families such as caspases, inhibitor of apoptosis proteins (IAPs), B cell lymphoma (B cl)-2 family of genes, tumor necrosis factor (TNF), or p53 gene are involved and/or collaborate in the process of apoptosis [14]. Apoptosis also removes normal cells that are no longer needed, such as cells that produce antibodies after the antibody is no longer required. Programmed death can be induced in normal cells by external stimuli such as toxins, hormones, heat, radiation, and the absence of nutrients for the cell. It is estimated that a mass of cells approximately equal to body weight is removed each year (due to apoptosis). Given this range of critical situations in which apoptosis occurs, the possibility for therapeutic intervention is extraordinary [4,15].

A second family of proteins, the caspase proteolytic enzymes, were found to contributed to both the regulation by the BCL-2 family, and the execution of apoptosis after the death decision is confirmed. Generally, caspases function by the activation of other enzymes that dismantle the cellular cytoskeleton, and cellular organelles that degrade the nuclear DNA (deoxyribonucleic acid), from which there is no possibility of recovery. The cellular destruction occurs in place (*in situ*), and the cellular membrane system is reorganized to package the degraded components, including the digested genetic material, in membrane compartments. This packaging system prevents the materials from being

released generally within tissues. Macrophages and other scavenger cells then engulf the membrane packets and process them for reuse as the most basic cellular components. Thus, rather than functioning as immune cells, they should be considered more broadly as cellular transducers that interpret microenvironmental changes and actuate vital tissue responses. In some instances, neighboring cells may also engulf the degraded components [15,16]. Apoptosis can also be engaged through activation of death receptors (extrinsic pathway), such as the TNF and TRAIL receptor, at the plasma membrane. Complex formation at the death receptors allows for the activation and cleavage of caspase-8 which initiates cell death through cleavage and activation of caspase-3 and -7 or MOMP through the cleavage of pro-apoptotic BID into t BID. The involvement of the TRAIL/death receptor signaling pathway in the regulation of cancer invasion and metastasis is complex as both positive and negative roles have been reported. [17,18,19,20].

2.1 Mitochondrial Role

Mitochondria are ubiquitous double-membrane-bound organelles, regulate energy production, support cellular activities, harbor metabolic pathways, and, paradoxically, mediate cell fate. Evidence has shown mitochondria act as points of convergence for diverse cell death-inducing pathways that trigger the various mechanisms underlying apoptotic and nonapoptotic programmed cell death. Thus, dysfunctional cellular pathways eventually lead to various age-related diseases, such as neurodegenerative, cardiovascular, and metabolic diseases [21]. Through their many and varied metabolic functions, including mitochondria power life, paradoxically, mitochondria also have a central role in apoptotic cell death. Upon induction of mitochondrial apoptosis, mitochondrial outer membrane permeabilization (MOMP) usually commits a cell to die. Apoptotic signaling downstream of MOMP involves cytochrome *c* release from mitochondria and subsequent caspase activation. As such, targeting MOMP to manipulate cell death holds tremendous therapeutic potential across different diseases, including neurodegenerative diseases, autoimmune disorders, and cancer [22]. Numerous mitochondrial constituents and metabolic products can function as damage-associated molecular patterns (DAMPs) and promote inflammation when released into the cytosol or extracellular milieu [23]. Interestingly, t BID has recently been found to induce mitochondrial outer membrane permeabilization (MOMP) independently of BAX and BAK. Although mitochondrial apoptosis is immune silent, various pro-inflammatory pathways are activated by permeabilized mitochondria but silenced by caspase activity. Initiators of mitochondrial-driven inflammation include the release of mitochondrial dsRNA and mt DNA thereby initiating type I interferons. [17,24]. It is demonstrated that by activating NF-κB, MOMP can exert additional signaling functions besides triggering cell death. Moreover, they support a rationale for engaging caspase-independent cell death in cell-killing anti-cancer therapies [25]. The advances have introduced the identification of additional inflammasome platforms and pathways that regulate activation of inflammatory caspases; the discovery of gasdermin D as the effector of pyro ptosis and interleukin (IL)-1 and IL-18 secretion; and the existence of substantial crosstalk between inflammatory and apoptotic initiator caspases [26]. Caspases that participate in apoptosis are inhibited by proteins known as inhibitors of apoptosis (IAPs). In addition to apoptosis, caspases play a role in necroptosis, pyroptosis, and autophagy, which are non-apoptotic cell death processes. Dysregulation of caspases features prominently in many human diseases, including cancer, autoimmunity, and neurodegenerative disorders [27]. Overexpression of IAP proteins have been documented in various solid and hematological malignancies, rendering them resistant to standard chemotherapeutics and radiation therapy and conferring poor prognosis. This observation has urged their exploitation as therapeutic targets in cancer with promising pre-clinical outcomes [28] In addition, depletion of IAPs is associated with a NF-κ B response after MOMP. While apoptosis is a potent tumor suppressor mechanism, engaging apoptosis can have oncogenic effects if not executed properly [17].

2.2 Apoptosis-Mitochondria Interaction

Apoptosis operates as a key physiological mechanism that limits cell population expansion, either to maintain tissue homeostasis or to remove potentially harmful cells, such as those that have sustained DNA damage. Paradoxically, high-grade cancers are generally associated with high constitutive levels of apoptosis. Under sublethal apoptotic stress only a few selective mitochondria undergo MOMP, a process termed minority MOMP [29]. Emerging studies indicate that dysregulated NF-κB activity causes inflammation-related diseases as well as cancers, and NF-κB has been long proposed as the potential target for therapy of diseases [30]. It has been recently described that this selective mitochondrial permeabilization is dependent on mitochondrial fitness. BAX, a pro-apoptotic member of the Bcl-2 family, is a cytosolic protein that inserts into mitochondrial membranes upon induction of cell death. Dysfunctional mitochondria block BAX retro translocation thereby accumulating BAX on the mitochondria, making them more prone to MOMP under sublethal stress [31,32]. It was concluded that cytoplasmic accumulation of mitochondrial RNA is an intrinsic immune surveillance mechanism for cells to cope with mt DSBs, including breaks produced by genotoxic agents [33]. Both the adenine nucleotide translocase (ANT) and, more recently, the mitochondrial F_1F_0 (F)-ATP synthase dimers, monomers or c-subunit ring alone have been implicated in the mitochondrial permeability transition pore (mPTP) and rapid Ca^{2+} efflux [34]. Following sublethal apoptotic stress, cells rapidly accumulate DNA damage through caspase-activated DNase and the mitochondrial DNase Endo G. DNA damage acquired by sublethal caspase activity causes genomic

instability, cellular transformation, and increased tumorigenesis [17,35]. In addition, many of the pro-inflammatory pathways activated during cell death occur upon MOMP, the pivotal commitment points to cell death during mitochondrial apoptosis. Permeabilized mitochondria trigger inflammation, in part, through the release of mitochondrial-derived damage-associated molecular patterns (DAMPs). Caspases, while dispensable for cell death during mitochondrial apoptosis, inhibit activation of pro-inflammatory pathways after MOMP [17, 36]. Inhibitor of apoptosis proteins (IAPs) are E3 ubiquitin ligases that inhibit cell death pathways and are themselves inhibited by second mitochondria-derived activator of caspases (SMAC). SMAC mimetics small-molecule antagonists (SMs) of IAPs, are being evaluated as cancer therapies in clinical trials. IAPs are also crucial regulators of inflammatory pathways because they influence both the activation of inflammatory genes and the induction of cell death through the receptor-interacting serine-threonine protein kinases (RIPKs), nuclear factor κB (NF-κB)-inducing kinase, and mitogen-activated protein kinases (MAPKs). Several studies have revealed an anti-inflammatory potential of RIPK inhibitors that either block inflammatory signaling or block the form of inflammatory cell death known as necroptosis [37,38]. There are several endogenous inhibitors of death that protect cells from programmed death. For example, the release of "diablo" proteins from the mitochondria in healthy cells leads to the deactivation of a protein called "IAPS", the guard of the cell and the anti-programmed death, and the result is the death of the cell, and “SMAC” mitochondrial protein promotes cytochrome c-dependent caspase activation [39]. The mitochondrial pro-apoptotic protein SMAC/Diablo participates in apoptosis by negatively regulating IAPs and activating caspases, thus encouraging apoptosis. Unexpectedly, we found that SMAC/Diablo is overexpressed in cancer. This paradox was addressed by silencing SMAC/Diablo expression using specific siRNA (si -h SMAC) [40,41]. Mitochondria coordinate cell-wide stress responses, such as autophagy, and control nonapoptotic cell death routines, such as regulated necrosis. Mitochondrial permeabilization leads to release of these proteins, which then interfere with the IAP-inhibition of caspases, resulting in potentiation of cell death. Another endogenous inhibitor of IAPs is XAF1 [42,43,44]. Recent reports have demonstrated that MOMP in the absence of full-blown caspase activation can have unexpected and detrimental effects. It was identified that XAF1 (XIAP-associated factor) is a directly interacting protein of AKT1, which strongly binds the N-terminal region of AKT1 to block its K63-linked poly-ubiquitination and subsequent activation. AKT kinase is a key regulator in cell metabolism and survival, and its activation is strictly modulated [45,46.47].

It is suggested that mitochondria play a key role in regulating neurotransmitters responsible for communication between neurons and are involved in the production of neurotransmitters like dopamine, serotonin, and GABA, and they also help to regulate their levels in the brain. Additionally, mitochondria are involved in the stress response, and cortisol release, a hormone that can have a negative impact on mitochondrial function. Over time, this can lead to a decrease in energy production and an increase in oxidative stress, which can contribute to the development of mental health disorders [48]. Overall, the mind-mitochondria connection is an exciting area of research that has the potential to revolutionize our understanding of mental health. By improving our mitochondrial function through lifestyle interventions and supplements, we may be able to prevent and treat a wide range of mental health disorders.

In short, it is evident that mitochondria played dual role in apoptosis, meaning that it can activate apoptosis via pro-apoptotic protein SMAC/Diablo which participates in apoptosis by negatively regulating IAPs, and activating caspases, thus encouraging apoptosis. Alternatively, by using another mechanism, the mitochondrial E3 ubiquitin ligases inhibit cell death pathways thus inhibiting apoptosis. Interestingly, E3 ubiquitin ligases are themselves inhibited by second mitochondria-derived activator of caspases (SMAC).

2.3 Interrelation of Heat Shock Proteins and Apoptosis

Apoptotic stimuli induce the accumulation in the cells of a set of proteins known as stress or heat shock proteins (HSPs). HSPs are conserved proteins present in both prokaryotes and eukaryotes. These proteins play an essential role as molecular chaperones by assisting the correct folding of nascent and stress-accumulated misfolded proteins, and by preventing their aggregation. HSPs have a protective function, that is they allow the cells to survive to otherwise lethal conditions. Various mechanisms have been proposed to account for the cytoprotective functions of HSPs. Several of these proteins have demonstrated to directly interact with components of the cell signaling pathways, for example those of the tightly regulated caspase dependent programmed cell death machinery, upstream, downstream and at the mitochondrial level. HSPs can also affect caspase-independent apoptosis-like process by interacting with apoptogenic factors such as apoptosis-inducing factor (AIF) or by acting at the lysosome level [49]. Considerable evidence has now accumulated indicating that the intracellular mechanisms that are activated in response to different stresses including the DNA damage response, the unfolded protein response, mitochondrial stress signaling and autophagy, as well as the mechanisms ensuring the proliferative inactivation or elimination of terminally damaged cells such as cell senescence and regulated cell death; all are coupled with the generation of signals that elicit microenvironmental and/or systemic responses. These signals, which involve changes in the surface of stressed cells and/or the secretion of soluble factors or micro vesicles, generally support systemic homeostasis but can also contribute to maladaptation and disease [50].

HSP depletion results in increased Cell Senescence (SC), while overexpression of HSP decreases CS in cancer, fibroblasts, and stem cell lines. As reports addressing the role of HSP in CS are lacking, more studies are highly needed to make valid conclusions on the role of HSP in CS and related pathological phenotypes in humans. A deep understanding of the role of HSP in CS can point to possible targets for senescence induction in cancer cells or senescent cell elimination in age [51,52].

It was found that the cellular-stress response can mediate cellular protection through expression of heat-shock protein (Hsp) 70, which can interfere with the process of apoptotic cell death. Stress-induced apoptosis proceeds through a defined biochemical process that involves cytochrome *c*, Apaf-1 and caspase proteases. Using a cell-free system, Hsp70 prevents cytochrome *c*/d ATP-mediated caspase activation but allows the formation of Apaf-1 oligomers. Hsp70 binds to Apaf-1 but not to procaspase-9 and prevents recruitment of caspases to the apoptosome complex. Therefore, Hsp70 suppresses apoptosis by directly associating with Apaf-1 and blocking the assembly of a functional apoptosome. Induction of heat shock proteins (HSPs) following cellular damage can prevent apoptosis induced by both the intrinsic and the extrinsic pathways. The intrinsic pathway is characterized by mitochondrial outer membrane permeabilization (MOMP), cytochrome c release, apoptosome assembly, and caspase activation. HSPs promote cell survival by preventing MOMP or apoptosome formation as well as via regulation of Akt and JNK activities [53,54]. Engagement of the TNF death receptors induces the extrinsic pathway that is characterized by Fas-associated death domain-dependent (FADD-dependent) caspase-8 activation or induction of NF-kappa B to promote cellular survival. HSPs can directly suppress proapoptotic signaling events or stabilizing elements of the NF-kappa B pathway to promote cellular survival [55, 56].

Abbreviations.

- BAX = Bcl-2 Associated X-protein. BAK= Bcl-2 Associated Kinase.
- Bid is an abundant pro-apoptotic protein of the Bcl-2 family that is crucial for death receptor-mediated apoptosis in many cell systems.
- NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells.
- XAF = Xyloglucan endotransglucosylase/hydrolase Activating Factor
- SMAC = second mitochondria-derived activator of caspases.
- Apaf 1 = Apoptotic protease activating factor 1.

3 Conclusion

- The cell carries death factors or elements such as caspases and some mitochondrial secretions - At the same time mitochondria represent the basic source of energy and life in the cell. Death occurs only when stimulating and activating the molecules and factors of cell annihilation - Mitochondria coordinate cell stress responses, such as autophagy, and control nonapoptotic cell death routines, such as regulated necrosis. Mitochondrial permeabilization leads to release of these proteins, which then interfere with the IAP-inhibition of caspases, resulting in potentiation of cell death. Initiators of mitochondrial-driven inflammation include the release of mitochondrial dsRNA and mt DNA thereby initiating type I interferons. It is evident that mitochondria not only power the metabolic cell activities with energy but also power the cell death with both energy and signaling molecules denoting that cell death is an active living being and here we can understand the God saying (who created death and life) Surat Almulk, verse 2. This means that death and life are particulate molecules and elements supplemented with a specific signaling energy waves that all are created by our God.
- The death signals coming from outside the cell through the cosmic waves or energy then interact with the genes of the DNA carried by dozens of nucleic acids “messenger RNAs”. These carriers of the messages lastly deliver them to the targeted cell organelles in order to activate the caspases molecules “death factors” and from here we understand the Almighty’s saying (Even if death comes to one of you, Our messengers take him to death, and they do not fail) Surat Al-Anaam, verse 61. The messengers in the plural form do not mean the angels, because the angel of death is only one and obviously specializes in observing and recording death operations on the universal level and not on the individual level.
- We note that the mitochondria play a pivotal role in supplying the cell with energy to accomplish and direct the process of death, which means that death is a vital process that takes place only in the presence of energy or in other words; it is a creature.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no known competing financial interests that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest.

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