Multidisciplinary Sciences Reports

Review

NEURODEGENERATION PROCESSES GO FAR BEYOND NECROSIS AND APOPTOSIS!

1 Rogério de Freitas Lacerda rogerio.lacerda@ufac.br

2 Abigail Gonçalves da Silva abigailgoncalves79@gmail.com

3 Isabela Cristina Sena Romano isabelacsromano@gmail.com

1 Centro de Ciências Biológicas e da Natureza – CCBN, Universidade Federal do Acre – UFAC, Rio Branco, Acre, Brazil
2 Programa de Pós-Graduação em Ciências da Saúde na Amazônia Ocidental, Universidade Federal do Acre – UFAC, Rio Branco, Acre, Brazil
3 Egressa do Programa de Pós-graduação em Neurociências, Universidade Federal de Minas Gerais - UFMG, Belo Horizonte, Minas Gerais, Brazil.

ABSTRACT

Neural plasticity is a consequence of a delicate balance between the processes of neurodegeneration and neurogenesis. When neurodegeneration overcomes neurogenesis, neurodegenerative diseases occur, which affect cognitive functions such as memory, language, and executive functions. Neurodegeneration, the process of neuronal cell death, presents several aspects that were categorized according to their macroscopic and/or morphological characteristics. The concept of apoptosis, autophagy, and necrosis is still widely used today. On the other hand, more in-depth forms emerge in the clinical and academia, describing the cascade of cell death events through biochemical approaches, and the essential (causal) and accessory (correlative) aspects of the cell death process. New concepts were introduced, addressed in the modules of signal translation involving issues such as the initiation, execution, and propagation of cell death, as well as the pathophysiological relevance of each of the main types. Currently, twelve types of cell death are already defined, not only apoptosis, necrosis, and autophagy. In this review, we will address the main mechanisms of cell death, with special emphasis on the participation of caspases and other proteins in these mechanisms. We will discuss some types of cell death such as extrinsic and intrinsic apoptosis, necrosis, necroptosis, and autophagy-dependent cell death. We hope to elucidate key points in molecular systems, including the receptors involved in cell death and their role in neurodegeneration, and showing that neurodegeneration has characteristics beyond morphological (apoptosis and necrosis).

Keywords: Neurodegeneration. Cell death. Apoptosis. Necrosis.

DOI: https://doi.org/10.54038/ms.v1i1.2

Subject: July 08, 2021 - Accepted: July 30, 2021

GENERAL ASPECTS

One of the important issues in neurobiology is to understand the molecular mechanisms underlying neurodegenerative diseases, or neuronal loss, associated with behavioral and cognitive changes seen in various diseases of the central nervous system (CNS). During the neuronal plasticity[1] process, two opposite phenomena occur, known as neurogenesis[2] and neurodegeneration [3], which under physiological conditions are in a dynamic balance. Some stimuli or insults can lead to dysfunctions that culminate in too much cell death, resulting in imbalance, and consequent superposition of neurodegeneration on neurogenesis.

The occurrence of this imbalance, with a predominance of loss of neurons and/or a decrease in neurogenesis, displaces the balance and causes damage that characterizes a series of diseases known as neurodegenerative diseases. This fact can cause cell loss in important regions of the Central Nervous System (CNS), leading to deficits in cognitive processes. Neuronal death is the main pathological feature of neurodegeneration in conditions such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, and Wernicke-Korsakoff Syndrome (WKS: Wernicke-Korsakoff Syndrome) (1).

Some of the mechanisms that lead to cell death, such as apoptosis and necrosis, understood as independent, have characteristics in common and can participate in many health or disease conditions (2,3). The cell death process is regulated and the understanding of each of the pathways and interphases of the molecular systems that are part of this process is essential for the development of rational intervention strategies, in the case of neurodegenerative diseases or physiological aging itself (4–7).

[1] Plasticity (Neuroplasticity): ability of the nervous system to modify its structure and function as a result of experiences - environmental stimuli. (63).
[2] Neurogenesis: process of formation of new neurons in the brain, originating from neural stem cells. (64)
[3] Neurodegeneration: progressive loss of structure or function of neurons, culminating in cell death. (65)

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

NEURODEGENERATION

Cell Death Mechanisms

Cell death manifests itself with macroscopic morphological changes. The mechanisms by which dead cells and their fragments are discarded have historically been used to classify cell death in three different ways: (1) type I cell death or apoptosis, exhibiting cytoplasmic shrinkage, chromatin condensation (pyognosis), nuclear fragmentation (karyorexia), “bubbles” in the plasma membrane, culminating in the formation of small intact vesicles (commonly known as apoptotic bodies) that are efficiently absorbed by cells with phagocytic activity and degraded within lysosomes; (2) type II cell death or autophagy, manifesting as extensive cytoplasmic vacuolization and culminating, similarly to type I, with phagocytic uptake and consequent lysosomal degradation; and (3) type III cell death or necrosis, not showing distinct characteristics of type I or II cell death, but ending with the elimination of cells debris in the absence of phagocytic and lysosomal involvement.

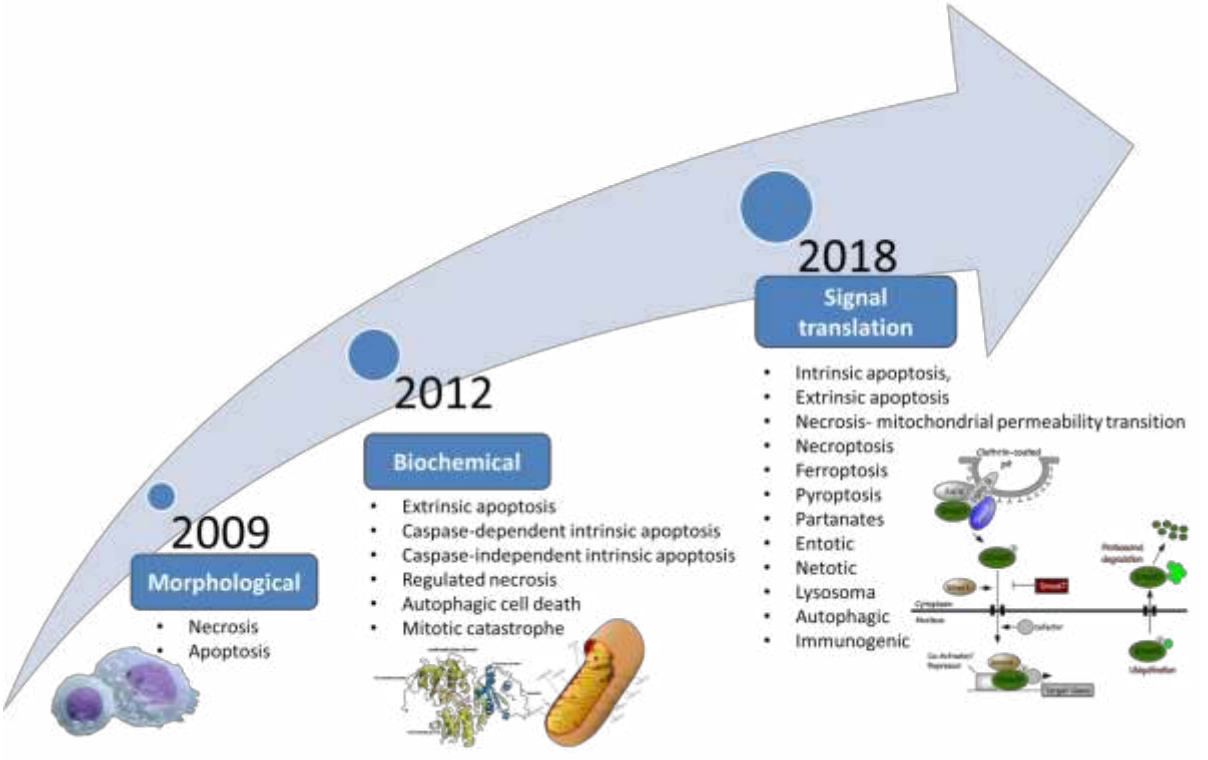
Furthermore, while apoptosis and autophagy do not involve inflammation, necrosis signals inflammatory processes initiation. This morphological classification is still widely used, regardless of multiple limitations and caveats. Despite being considered independent mechanisms, these can co-participate in cell death that occurs both in the physiological and pathological state (8–10).

To create an adequate classification of the different types of cell death, in 2005 the NCCD: Nomenclature Committee on Cell Death was created. In 2009, apoptosis, necrosis, and mitotic catastrophe were the terms used by the NCCD to classify cell death, this classification is based on the characteristics and morphological changes. In 2012, a classification based on the biochemical characteristics of the events was made available, and new terms were included, such as extrinsic apoptosis, caspase-dependent intrinsic apoptosis, caspase-independent intrinsic apoptosis, regulated necrosis, autophagic cell death, and mitotic catastrophe. In addition, other types were added, such as anoikis, entosis, partanatos, pyroptosis, NETosis, and cornification (9). As the field continued to expand and new mechanisms, with multiple pathways, of cell death, are being evidenced, in 2018 the NCCD proposed a new classification of types of cell death, distinguishing essential (causal) aspects from accessory aspects (correlative) of the cell death process.

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

The main focus has been placed on the signal translation modules involved in the initiation, execution, and propagation of cell death, as well as the pathophysiological relevance of each of the main types of regulated cell death (RCD: Regulated Cell Death). According to (8) new terms were added (twelve in all) for the types of cell death: intrinsic apoptosis, extrinsic apoptosis, necrosis - mitochondrial permeability transition (MPT), necroptosis, ferroptosis, pyroptosis, partanates, entotic, NETotic, lysosomal, autophagic, and immunogenic **(Figure 1)**. Below we provide details on some of these categories of cell death.

Figure 1 - Evolution of classification and different types of cell death.



The process of regulated cell death (RCD: Regular Cell Death) is involved in two diametrically opposite scenarios. On the one hand, RCD can occur in the absence of any exogenous environmental disturbance, thus operating as an embedded effect of developmental logical physiological programs or tissue turnover/renewal. These completely physiological forms of RCD are generally referred to as programmed cell death (PCD: Programmed Cell Death). On the other hand, RCD can originate from disturbances in the intracellular or extracellular microenvironment, when such disturbances are too intense or prolonged that the

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

Adaptive Responses cannot “buffer” with the cellular stress induced by them and restore homeostasis. In the CNS, DAMPS (Damage-associated molecular pattern) or alarmins, such as cytochrome C (Cyt C), mitochondrial transcription factor A (TFAM), and cardiolipin, have been studied as important components in brain disorders, as in neurodegenerative diseases, e.g. Parkinson's D. and Alzheimer's D (11–13).

APOPTOSE

Apoptosis refers to a type of RCD, regulated by genes. When apoptosis occurs, apoptotic cells retain plasma membrane integrity and metabolic activity as the process progresses to completion, allowing for rapid clearance by macrophages or other cells with phagocytic activity (a process known as efferocytosis) (14). Apoptosis and consequent efferocytosis are not always immunologically silent, as previously thought. *In vitro*, end-stage apoptosis is usually followed by the complete breakdown of the plasma membrane and the acquisition of a necrotic morphotype (secondary necrosis) (15).

In most cases, apoptosis can be triggered in two ways: i) intrinsic stimulation through the mitochondrial signaling pathway; or ii) extrinsic stimulation through the activation of two types of receptors, *Death Receptors* (DR)s present on the cell surface, including TNFα receptors, or activation of dependence receptors, which have as a ligand some types of neurotrophins (5,6). Both intrinsic and extrinsic apoptosis, activation of cysteine-aspartate-proteases (caspases) (EC 3.4.22) is required and these pathways are known to be caspase-dependent, according to the 2012 classification by the NCCD. However, evidence shows that apoptosis can occur even after inhibition of caspases, evidencing the existence of other mechanisms of apoptosis, as considered in the 2018 classification (5).

INTRINSIC APOPTOSIS

Intrinsic apoptosis is a form of RCD initiated by a variety of microenvironmental disturbances, including (but not limited to) growth factor removal, DNA damage, endoplasmic reticulum (ER) stress, reactive species oxygen (ROS) overload, replication stress, changes in microtubules, or mitotic defects (8).

The critical step for intrinsic apoptosis is mitochondrial outer membrane permeabilization (MOMP) (TAIT; GREEN, 2010), which is controlled by pro-apoptotic and anti-apoptotic components of the BCL2 (B-Cell Lymphoma Protein 2, Apoptosis

Regulator) protein family, a group of proteins that share one to four domains of BCL2 homology (ie, BH1, BH2, BH3, and BH4) (16). The pro-apoptotic components of the BCL2, BAK, and BAX protein Family are activated via transcription or post-translation, when specific organelles or cell compartments suffer disturbances in homeostasis, in fact operating as cellular transducers of stress signaling (17).

The current view is that activated BAX and BAK form homodimers or heterodimers, resulting in the assembly of a lipid pore that alters mitochondrial permeability and causes deep rearrangements of the mitochondrial ultrastructure (18,19).

The permeabilization of the mitochondrial outer membrane (MOMP) promotes the cytosolic release of apoptogenic factors that normally reside in the mitochondrial intermembrane space (20). These mitochondrial proteins include somatic cytochrome C (CYCS), which operates in the mitochondrial respiratory chain, mitochondrial caspase activator proteins (SMAC/DIABLO - second mitochondrial activators of caspases), apoptosis-inducing factor (AIF), endonuclease G, and high-temperature protein A2. The release of CYCS and SMAC into the cytosol is favored by mitochondrial crest remodeling, which is based on the oligomerization and activation of mitochondrial OPA1, such as dinamine-GTPase (21), which are GTPases responsible for the recycling of synaptic vesicles. These processes cause an increase in the production of reactive oxygen species, activating an amplification mechanism of apoptotic signals (9).

The cytosolic pool of CYCS binds to apoptotic peptidase activating factor 1 (APAF1) and to pro-caspase 9 (ProC9), in an ATP-dependent manner, to constitute the responsible supramolecular complex known as the apoptosome. by activating CASP9 (22–24). This activation occurs through the binding of ProC9 to the caspase recruitment domain (CARD) of the APAF-1 protein and, once in its active form (CASP9), it must remain attached to the apoptosome to maintain substantial catalytic activity. Then, the CASP9 primer cleaves and activates caspases from the execution phase of apoptosis, such as Caspase-3 (CASP3) and Caspase-7 (CASP7), through proteolysis that rearranges protein loops critical in the formation of active sites (25). When enabled, execution caspases can cleave and activate other execution caspases in a feedback system during this phase (amplification of execution of apoptosis). CASP3 favors DNA fragmentation by catalyzing the proteolytic inactivation of the DNA fragmenting factor alpha subunit. CASP3 and CASP7

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

facilitate, without being indispensable, RCD (26–28).

On the other hand, there are also members of the BCL2 family of proteins that act as anti-apoptotic, decreasing the MOMP. These anti-apoptotic proteins, like pro-apoptotic ones, also contain the four BH domains and are usually inserted into the outer membrane of the mitochondria or the ER membrane. Anti-apoptotic members of the BCL2 family promote cell survival by (1) regulating Ca2+ homeostasis in the ER (29,30); (2) promotion of bioenergetic metabolism in the interaction with F1FO-ATP synthase (31); and (3) contribution to the regulation of homeostasis – redox (32). Most members of the pro-survival BCL2 family inhibit BAX and BAK, preventing their oligomerization and pore-forming activity, either directly after physical sequestration in OMM, or indirectly after sequestration of BH3-protein activators **(Figure 2- A)**.

Extrinsic Apoptosis

The extrinsic pathway involves the activation of two types of receptors present in the cell plasma membrane, known as (i) **cell death receptors or apoptosis signaling receptors**, and represented by two groups **(Figure 2 - A)** (ii) **Dependency Receptors**, **(Figure 2 - B)** whose activation occurs when the levels of its specific ligand fall below a specific threshold (8).

(i) Cell death receptors include Fas cell surface death receptor (FAS); also known as CD95 or APO-1, and TNF receptor, a member of the superfamily 1A (TNFRSF1A; better known as TNFR1), 10A (TNFRSF10A; better known as TRAILR1 or DR4), and 10B (TNFRSF10B; better known as TRAILR2 or DR5). Activation of death receptors triggers activation of caspases-8, which in turn activates caspase-3/7 culminating in apoptosis (33–36). As a general rule, the binding and activation of death receptors induce the formation of a death-inducing signaling complex (DISC), "complex I" and "complex II", which operate as molecular platforms to regulate the activation and functions of CASP8 (or CASP10, in a limited number of situations). The CASP8 gene encodes CASP8 which is synthesized as a zymogen and is the first caspase activated in the extrinsic pathway, which occurs after the formation of the DISC complex (37).

The molecular mechanisms that regulate the activity of CASP8 after death receptor stimulation have been extensively investigated. In particular, CASP8 maturation and activation involve a cascade of events initiated by the connection of

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

proCASP8 to FAS, via Fas-associated via death domain (FADD) in the DISC. This interaction allows the assembly of a linear filament of CASP8 molecules (depending on its DED: death effector domain) that facilitates homodimerization and consequent activation by autoproteolytic cleavage.

A key role in this scenario is mediated by c-FLIP, which is a compound of the CASP8 family, which functions as a regulator of CASP8. Evidence indicates that c-FLIP short (c-FLIPS: small) and long (c-FLIP: long) variants inhibit and activate CASP8, respectively, modulating CASP8 oligomerization. Activated CASP8 cleaves c-FLIPL and the heterodimeric complexes of CASP8 with c-FLIPS (but not c-FLIPS) are endowed with limited enzymatic activity, which favors the oligomerization of CASP8 and its consequent activation. The c-FLIPL and CASP8 isoforms appear to be recruited into the DISC "platform" at comparable levels, supporting the notion that high levels of c-FLIPL expression inhibit, rather than activate, extrinsic apoptosis (38,39) possibly, for interrupting CASP8 maturation **(Figure 2 - A).**

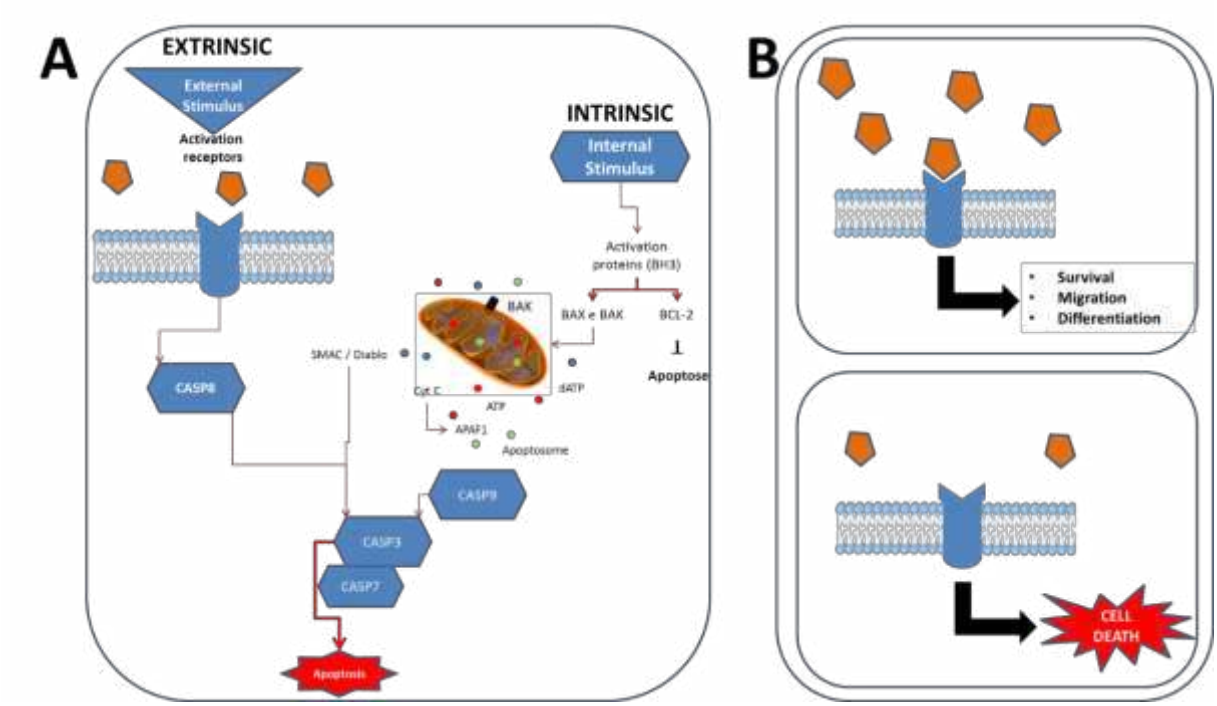
(ii) Dependence Receptors were first described in 1993. They play fundamental roles in different processes, such as development, oncogenesis, and neurodegeneration. The family of "addiction receptors" is composed of approximately 20 members, including (1) netrin 1 receptor (NTN1), DCC netrin receptor 1 (DCC: deleted in colorectal cancer), netrin A receptor unc-5 (UNC5A), UNC5B, UNC5C and UNC5D; (2) the neurotrophic receptor tyrosine kinase 3 (NTRK3); and (3) the "sonic hedgehog" (SHH) receptor. The classic view of transmembrane receptors is that they are activated when they bind to their respective ligands but are relatively inactive when not bound. In contrast, dependence receptors mediate apoptosis in the absence of their ligands, but when the concentration of ligands increases and these binds and activate these receptors, the consequence is the maintenance of homeostasis and cell survival **(Figure 2 - B)** (40).

Growing evidence supports the view that dependence receptors also play crucial roles in the neurodegeneration process. Data on the role of the p75NTR receptor in the central nervous system indicate that p75NTR knockout mice showed increased basal brain cholinergic markers, as well as cell hypertrophy, increased number of cholinergic fibers, and increased long-term potentiation (LTP) in the hippocampus. These results suggest that activation of p75NTR inhibits septohippocampal cholinergic function. Furthermore, mice expressing the Swedish mutant ß-amyloid precursor protein (APP) are a model for Alzheimer's disease, and

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

those *know out* for p75NTR performed better in memory tests than those that were from wild-type to p75NTR.

Figure 2: A) Extrinsic and intrinsic pathways of apoptosis. B) Dependence receptor.



Collaborative work between the laboratories of Bredesen and Mehlen showed that APP is a dependence receptor (41), with atrophic ligand (netrin-1) and a single caspase cleavage site (Asp664) necessary for apoptosis induction; caspase cleavage generates the proapoptotic peptides Jcasp and C31. In addition, amyloid β peptide also binds to APP, being an "antistrophic ligand" that competes with netrin-1 for interaction with APP, as well as competing with other trophic ligands for their respective receptors. This effect identifies β amyloid peptide as the first "antitrophin" and suggests that its accumulation may trigger a specific pro-death state, an antistrophic state-resulting in the synaptic loss, neuritic retraction, and neuronal death that characterizes Alzheimer's disease (40–45).

NECROSIS - TRANSITION OF MITOCHONDRIAL PERMEABILITY

Necrosis can be recognized early and defined through pathomorphological characteristics, which occur when cells or the body are confronted with intense external aggression. It is unscheduled cell death, generating more damaging processes to adjacent cells and/or to the organism as a whole. Various causes,

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

including trauma, can lead to an alteration of the internal environmental osmotic pressure, disrupting the balance of an organism's internal homeostasis and leading to necrosis. Many reactions occur, including loss of cell membrane integrity, cell membrane swelling (due to cell tonification and Na/K pump dysfunction), and mitochondrial dysfunction. Due to the rupture of the cell membrane, a large number of intracellular elements leak out, which can cause and aggravate inflammation of the surrounding tissues (4,8). Some processes are very similar to necrosis, such as those characterized by necroptosis, described below; the transition process of mitochondrial permeability and the death process called Partanatos. All of these are grouped under the name of regulated necrosis activated by the receptor-interacting protein, RIP-kinase-3 (RIPK-3) (8,9).

The transition process of mitochondrial permeability, for example, is initiated by intracellular disturbances of oxidative species or an increase in the level of cytosolic calcium. The abrupt drop in impermeability to small solutes across the inner membrane of the mitochondria results in rapid dissipation of the membrane potential, osmotic breakage of both the inner and outer membrane of the mitochondrion, and the beginning of the cell death process (8). At the biochemical level, the opening of pores such as transient permeability complexes (PTPC) by interactions with pro and anti-apoptotic peptides of the BCL2 family, such as BAX, BAK, and BID such as BCL2 and BCL-XI, mentioned above.

The involvement of channels such as the VDAC (voltage-dependent anion channel) type channel can still be observed, a protein that has an action on the transport of macro and micro components through the outer membrane of the mitochondria, responsible for the transport of ions, cellular metabolites such as NAD+ /NADH, ADP/ATP, succinate, citrate, and ions, such as Ca2+, between the cytosol and mitochondria, which together with proteins present in the membrane of the endoplasmic reticulum can raise the level of mitochondrial calcium ion and thus trigger the death process cell phone (8,46–49).

NECROPTOSIS

Other cell death processes permeate the mechanisms of apoptosis and necrosis and can also coexist in a certain physiological or pathological state (3,50). In recent decades, a new, more alternative form of necrosis, called necroptosis, has been considered an alternative pathway to cell death (51). Necroptosis is distinguished from necrotic passive cell death, in that it follows cellular programming,

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

involving the protein kinases RIPK1 and RIPK3, which interact with TNF-R1 receptors (36,52). Initialization by the receptor generates the formation of complex I contain the TRADD proteins (TNF-Receptor Associated via Death Domain); cIAPs (Cellular Inhibitor of Apoptosis Proteins), TRAF2 (TNF receptor-associated factor 2), and RIPK1 (receptor-interacting kinase 1). The polyubiquitination of RIPK1 at residues k11, k48, and k63 recruits the IkB kinase (IKK) leading to the activation of the transcription factor NFkB together with the activation of a pro-inflammatory process, suppressing the cell from the cell death process (53).

Through a mechanism that compromises polyubiquitination through TNF alpha-induced protein 3 (TNFAIP3; better known as A20), RIPK1 dissociates from the TNF-R1 receptor and forms a cytosolic IIb complex with FADD, caspase-8, and RIPK3. When caspase-8 activity is high, it cleaves the protein kinases RIPK1 and RIPK3 promoting apoptosis. However, this cysteine protease, caspase 8, can be inhibited, thus lowering its activity by forming a complex constituted by caspase-8 and cFLIP protein. With low activity or even its absence, the phosphorylated RIPK1 protein recruits the MLKL (Mixed lineage kinase domain-like) protein, forming the necrosome. Once phosphorylated, the MLKL protein translocates from the cytosol to the membrane, leading to the process of necroptosis (8,36,54).

AUTOPHAGY DEPENDENT CELL DEATH

Autophagic cell death is a type of RCD that depends on the autophagic machinery or its components (55). This cell death process, also called type II programmed cell death, according to the NCCD, is characterized by the formation of double-membrane vesicles that will contain organelles or other intracellular materials, called autophagosomes. These fuse with lysosomes so they can be degraded and recycled. The importance of the double membrane is given, because, after fusion with the lysosomes, everything inside the outer layer will be degraded, including the inner membrane itself (56,57). The formation of autophagosomes is controlled by atg proteins or proteins related to autophagy, translated from the ATG gene (AuTophaGy related Genes, gene-related to autophagy) (57).

The causes of autophagy are diverse and range from cellular stress caused by hypoxia, radiation, treatment, and action of chemicals to nutritional deprivation. The duration and severity of the stressor must still be considered. The autophagy process has a mechanism distinct from other types of cell death, acting as a mediator of the

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

physiological process of cell death or in the absence of apoptotic factors, such as BAX and BAK proteins and caspases themselves (9). This cell death process can also act concomitantly with other pathways, favoring and helping other processes. For example, we have ferroptosis promoted by the autophagic degradation of ferritin; the extrinsic apoptosis that through the autophagic degradation of the tyrosine phosphatase protein can be favored and still; the favoring of necroptosis by the autophagic degradation of c-IAP1 and c-IAP2 (inhibitor of apoptosis proteins) (8).

Physiological cell death mechanisms, such as autophagic, are important in the CNS, as after mitotic division there is an accumulation of defective proteins and organelles that must be degraded and recycled. Despite the lack of knowledge on the formation of autophagosomes in the neuronal cell, there is a problem in the distortion of any mechanism, which can lead to neurodegeneration and diseases such as Alzheimer's, Huntington's, and amyotrophic lateral sclerosis if the process has problems in regulation (58–62).

There are other types of cell death, according to (8), which can be summarized as **Entotica**: A type of RCD that originates from actomyosin-dependent cell internalization (entosis) and is performed by lysosomes. **Ferroptosis**: It is a form of RCD initiated by specific disorders of the intracellular microenvironment, such as severe lipid peroxidation, which depends on the generation of ROS and the availability of iron. The mechanism by which dead cells and their fragments are taken up by phagocytes and eliminated. **Immunogenic cell death** a form of RCD that is sufficient to activate an adaptive immune response in immunocompetent hosts. **Lysosome-dependent cell death**: A type of RCD demarcated by primary lysosomal membrane permeabilization (LMP) and precipitated by cathepsins, with optional involvement of MOMP and caspases. **NETotic**: A ROS-dependent, hematopoietic-derived cell-restricted RCD modality associated with NET extrusion. **Partanates**: A modality of RCD initiated by PARP1 hyperactivation and precipitated by a consequent bioenergetic catastrophe associated with MIF-dependent AIF-dependent DNA degradation of the mitochondria. **Pyroptosis:** A type of RCD that critically depends on the formation of pores in the plasma membrane by members of the gasdermin protein family, often (but not always) as a consequence of the activation of caspase by an inflammatory process. All no less important, but with specific action characteristics.

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

CONCLUSION AND FINAL CONSIDERATIONS

In summary, a large body of evidence suggests that the action of caspases or other proteins in neurodegenerative processes may or may not be essential and that blocking by genetic means or with specific pharmacological inhibitors generally delays (but does not prevent) apoptosis *in vitro* and *in vivo* (at least in the mammalian system), since cells can switch to other types of RCD. These data show that the cell death process encompasses countless physiological parameters, with molecular alterations that include enzymes, proteins, peptides, ions, and that restriction and division only according to morphological criteria can mask countless relationships and among themselves and common points.

CONFLICT OF INTEREST

The authors have no other conflicts of interest.

REFERENCES

1. Liu D, Ke Z, Luo J. Thiamine Deficiency and Neurodegeneration: The Interplay Among Oxidative Stress, Endoplasmic Reticulum Stress, and Autophagy. Mol Neurobiol. Molecular Neurobiology; 2017;54(7):5440–8.
2. Kristiansen M, Ham J. Programmed cell death during neuronal development: the sympathetic neuron model. Cell Death Differ [Internet]. Nature Publishing Group; 2014;21(7):1025–35. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4207485&tool=pmcentrez&rendertype=abstract
3. La Rovere RML, Roest G, Bultynck G, Parys JB. Intracelular Ca2+ signaling and Ca2+ microdomains in the control of cell survival, apopotosis and autophagy. 2016.
4. Solá S, Pedro T, Ferreira H, Rodrigues CMP. Conceitos gerais Necrose ou apoptose : quando e por quê ? 2001.
5. Grivicich I, Regner A, da Rocha AB. Morte Celular por Apoptose. Rev Bras Cancrol [Internet]. 2007;53(3):335–43. Available from: http://www1.inca.gov.br/rbc/n_53/v03/pdf/revisao4.pdf
6. Saikumar P, Dong Z, Mikhailov V, Denton M, Weinberg JM, Venkatachalam MA. Apoptosis: definition, mechanisms, and relevance to disease. Am J Med [Internet]. 1999;107(5):489–506. Available from:

http://www.sciencedirect.com/science/article/pii/S0002934399002594

7. Nijhawan D, Honarpour N, Wang X. Apoptosis in neural development and disease. Annu Rev Neurosci. 2000;23(May 2006):73–87.
8. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 2018.
9. Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny M V., et al. Molecular definitions of cell death subroutines: Recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ. 2012;19(1):107–20.
10. Shi R, Fu Y, Zhao D, Boczek T, Wang W, Guo F. Cell death modulation by transient receptor potential melastatin channels TRPM2 and TRPM7 and their underlying molecular mechanisms. Biochem Pharmacol. England; 2021 Jun;190:114664.
11. Bajwa E, Pointer CB, Klegeris A. The role of mitochondrial damage-associated molecular patterns in chronic neuroinflammation. Mediators Inflamm. 2019;2019.
12. Chaudhry SR, Hafez A, Jahromi BR, Kinfe TM, Lamprecht A, Niemelä M, et al. Role of damage associated molecular pattern molecules (DAMPs) in aneurysmal subarachnoid hemorrhage (aSAH). Int J Mol Sci. 2018;19(7).
13. Wilkins HM, Weidling IW, Ji Y, Swerdlow RH. Mitochondria-derived damage-associated molecular patterns in neurodegeneration. Front Immunol. 2017;8(APR):1–12.
14. Green DR, Oguin TH, Martinez J. The clearance of dying cells: Table for two. Cell Death Differ. Nature Publishing Group; 2016;23(6):915–26.
15. Berghe T Vanden, Vanlangenakker N, Parthoens E, Deckers W, Devos M, Festjens N, et al. Necroptosis, necrosis and secondary necrosis converge on similar cellular disintegration features. Cell Death Differ. Nature Publishing Group; 2010;17(6):922–30.
16. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nat Rev Mol Cell Biol [Internet]. 2014;15(1):49–63. Available from: https://doi.org/10.1038/nrm3722
17. Villunger A, Michalak EM, Coultas L, Müllauer F, Böck G, Ausserlechner MJ, et

al. p53- and Drug-Induced Apoptotic Responses Mediated by BH3-Only Proteins Puma and Noxa. Science (80-) [Internet]. American Association for the Advancement of Science; 2003;302(5647):1036–8. Available from: https://science.sciencemag.org/content/302/5647/1036

18. Dewson G, Kluck RM. Mechanisms by which Bak and Bax permeabilise mitochondria during apoptosis. J Cell Sci. 2009;16:2801–7.
19. Shamas-din A, Brahmbhatt H, Leber B, Andrews DW. BH3-only proteins : Orchestrators of apoptosis. BBA - Mol Cell Res [Internet]. Elsevier B.V.; 2011;1813(4):508–20. Available from: http://dx.doi.org/10.1016/j.bbamcr.2010.11.024
20. Tait SWG, Green DR. Mitochondria and cell death: outer membrane permeabilization and beyond. Nat Rev Mol Cell Biol [Internet]. 2010;11(9):621–32. Available from: https://doi.org/10.1038/nrm2952
21. Frezza C, Cipolat S, Martins de Brito O, Micaroni M, Beznoussenko G V., Rudka T, et al. OPA1 Controls Apoptotic Cristae Remodeling Independently from Mitochondrial Fusion. Cell. 2006;126(1):177–89.
22. Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri ES, et al. Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. Cell. 1997;91(4):479–89.
23. Riedl SJ, Salvesen GS. The apoptosome : signalling platform of cell death. Nat Rev Immunol. 2007;8(May):405–13.
24. Ferraro E, Fuoco C, Strappazzon F, Cecconi F. Apoptosome Structure and Regulation. In: Cecconi F, D'Amelio M, editors. Apoptosome: An up-and-coming therapeutical tool [Internet]. Dordrecht: Springer Netherlands; 2010. p. 27–39. Available from: https://doi.org/10.1007/978-90-481-3415-1_2
25. Cavalcante GC, Schaan AP, Cabral GF, Santana-Da-Silva MN, Pinto P, Vidal AF, et al. A cell's fate: An overview of the molecular biology and genetics of apoptosis. Int J Mol Sci. 2019;20(17):1–20.
26. Zhivotovsky B, Samali A, Gahm A, Orrenius S. Caspases : their intracellular localization and translocation during apoptosis. 1999;644–51.
27. Li P, Zhou L, Zhao T, Liu X, Zhang P. Caspase-9: structure, mechanisms, and clinical application. 2017;8(14):23996–4008.
28. Kuida K. Caspase-9. 2000;32:121–4.
29. Rong Y, Distelhorst CW. Bcl-2 Protein Family Members: Versatile Regulators

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

of Calcium Signaling in Cell Survival and Apoptosis. Annu Rev Physiol [Internet]. 2008;70(1):73–91. Available from: https://doi.org/10.1146/annurev.physiol.70.021507.105852

30. Monaco G, Decrock E, Arbel N, Van Vliet AR, La Rovere RM, De Smedt H, et al. The BH4 domain of anti-apoptotic Bcl-XL, but not that of the related Bcl-2, limits the voltage-dependent anion channel 1 (VDAC1)-mediated transfer of pro-apoptotic Ca2+ signals to mitochondria. J Biol Chem. 2015;290(14):9150–61.
31. Alavian KN, Li H, Collis L, Bonanni L, Zeng L, Sacchetti S, et al. Bcl-xL regulates metabolic efficiency of neurons through interaction with the mitochondrial F1 FO ATP synthase. Physiol Behav. 2012;176(3):139–48.
32. Velaithan R, Kang J, Hirpara JL, Loh T, Goh BC, Le Bras M, et al. The small GTPase Rac1 is a novel binding partner of Bcl-2 and stabilizes its antiapoptotic activity. Blood. 2011;117(23):6214–26.
33. Linkermann A, Green DR. Necroptosis. N Engl J Med [Internet]. 2014;370(5):455–65. Available from: http://www.nejm.org/doi/10.1056/NEJMra1310050
34. Oberst A. Death in the fast lane: what's next for necroptosis? FEBS J. 2016;283:2616–25.
35. Nagata S, Tanaka M. Programmed cell death and the immune system. Nat Rev Immunol [Internet]. 2017;17(5):333–40. Available from: http://www.nature.com/doifinder/10.1038/nri.2016.153
36. Fuchslocher Chico J, Saggau C, Adam D. Proteolytic control of regulated necrosis. Biochim Biophys Acta - Mol Cell Res [Internet]. Elsevier; 2017;1864(11):2147–61. Available from: http://dx.doi.org/10.1016/j.bbamcr.2017.05.025
37. Strasser A, Jost PJ, Nagata S. Review The Many Roles of FAS Receptor Signaling in the Immune System. Immunity [Internet]. Elsevier Inc.; 2009;30(2):180–92. Available from: http://dx.doi.org/10.1016/j.immuni.2009.01.001
38. Chang DW, Xing Z, Pan Y, Algeciras-Schimnich A, Barnhart BC, Yaish-Ohad S, et al. C-FLIPL is a dual function regulator for caspase-8 activation and CD95-mediated apoptosis. EMBO J. 2002;21(14):3704–14.
39. Gilot D, Serandour AL, Ilyin GP, Lagadic-Gossmann D, Loyer P, Corlu A, et al.

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

A role for caspase-8 and c-FLIPL in proliferation and cell-cycle progression of primary hepatocytes. Carcinogenesis. 2005;26(12):2086–94.

40. Goldschneider D, Mehlen P. Dependence receptors: A new paradigm in cell signaling and cancer therapy. Oncogene. Nature Publishing Group; 2010;29(13):1865–82.
41. Lourenço F, Galvan V, Fombonne J, Corset V, Liambi F, Muller U, et al. Netrin-1 interacts with amyloid precursor protein and regulates amyloid-β production. Cell Death Differ. 2009;16(1):665–663.
42. Pathway ANA--independent I, Rao R V, Castro-obregon S, Frankowski H, Schuler M, Stoka V, et al. Coupling Endoplasmic Reticulum Stress to the Cell Death Program. J Biol Chem. 2002;277(24):21836–42.
43. Mehlen P, Thibert C. Dependence receptors: between life and death. Cell Mol Life Sci. Switzerland; 2004 Aug;61(15):1854–66.
44. Mehlen P, Rabizadeh S, Snipas SJ, Assa-Munt N, Salvesen GS, Bredesen DE. The DCC gene product induces apoptosis by a mechanism requiring receptor proteolysis. Nature. England; 1998 Oct;395(6704):801–4.
45. Forcet C, Ye X, Granger L, Corset V, Shin H, Bredesen DE, et al. The dependence receptor DCC (deleted in colorectal cancer) defines an alternative mechanism for caspase activation. Proc Natl Acad Sci U S A. 2001;98(6):3416–21.
46. Shoshan-Barmatz V, Zakar M, Rosenthal K, Abu-Hamad S. Key regions of VDAC1 functioning in apoptosis induction and regulation by hexokinase. Biochim Biophys Acta - Bioenerg [Internet]. Elsevier B.V.; 2009;1787(5):421–30. Available from: http://dx.doi.org/10.1016/j.bbabio.2008.11.009
47. Shoshan-Barmatz V, De Pinto V, Zweckstetter M, Raviv Z, Keinan N, Arbel N. VDAC, a multi-functional mitochondrial protein regulating cell life and death. Mol Aspects Med [Internet]. 2010;31(3):227–85. Available from: http://dx.doi.org/10.1016/j.mam.2010.03.002
48. Tan W, Colombini M. VDAC closure increases calcium ion flux. Biochim Biophys Acta - Biomembr. 2007;1768(10):2510–5.
49. Bathori. G, Csordas G, Garcia-Perez C, Davies E, Hajnoczky G. Ca2+-dependent control of the permeability properties of the mitochondrial outer membrane and voltage-dependent anion-selective channel (VDAC). J Biol Chem. 2006;281(25):17347–58.

DOI: https://doi.org/10.54038/ms.v1i1.2
Subject: July 08, 2021 - Accepted: July 30, 2021

50. Wallach D, Kang T, Kovalenko A. Concepts of tissue injury and cell death in inflammation: a historical perspective. Nat Rev | Immunol. 2014.
51. Degterev A, Huang Z, Boyce M, Li Y, Jagtap P, Mizushima N, et al. Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. Nat Chem Biol [Internet]. 2005;1(2):112–9. Available from: https://doi.org/10.1038/nchembio711
52. Newton K, Wickliffe KE, Dugger DL, Maltzman A, Roose-Girma M, Dohse M, et al. Cleavage of RIPK1 by caspase-8 is crucial for limiting apoptosis and necroptosis. Nature [Internet]. Springer US; 2019;574(7778):428–31. Available from: http://dx.doi.org/10.1038/s41586-019-1548-x
53. Wang L, Du F, Wang X. TNF-α Induces Two Distinct Caspase-8 Activation Pathways. Cell. 2008;133(4):693–703.
54. Ashkenazi A, Salvesen G. Regulated Cell Death: Signaling and Mechanisms. Annu Reveiw cell Dev Biol. 2014;337–56.
55. Mcarthur K, Kile BT. Apoptotic Caspases: Multiple or Mistaken Identities? Trends Cell Biol [Internet]. Elsevier Ltd; 2018;28(6):475–93. Available from: http://dx.doi.org/10.1016/j.tcb.2018.02.003
56. Mizushima N, Ohsumi Y, Yoshimori T. Autophagosome formation in mammalian cells. Cell Struct Funct. 2002;27(6):421–9.
57. Tooze SA, Yoshimori T. The origin of the autophagosomal membrane. Nat Cell Biol [Internet]. 2010;12(9):831–5. Available from: https://doi.org/10.1038/ncb0910-831
58. Komatsu M, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature [Internet]. 2006;441(7095):880–4. Available from: https://doi.org/10.1038/nature04723
59. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, et al. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature [Internet]. 2006;441(7095):885–9. Available from: https://doi.org/10.1038/nature04724
60. Rubinsztein DC, DiFiglia M, Heintz N, Nixon RA, Qin ZH, Ravikumar B, et al. Autophagy and its possible roles in nervous system diseases, damage and repair. Autophagy. 2005;1(1):11–22.
61. Kesidou E, Lagoudaki R, Touloumi O, Poulatsidou KN, Simeonidou C.

Autophagy and neurodegenerative disorders. Neural Regen Res. 2013;8(24):2275–83.

62. Mariño G, Madeo F, Kroemer G. Autophagy for tissue homeostasis and neuroprotection. Curr Opin Cell Biol [Internet]. 2011;23(2):198–206. Available from: http://www.sciencedirect.com/science/article/pii/S0955067410001729
63. Turrigiano GG, Nelson SB. Hebb and homeostasis in neuronal plasticity. Curr Opin Neurobiol. 2000;10(3):358–64.
64. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci [Internet]. 1999;2(3):266–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10195220%255Cnhttp://www.nature.com/neuro/journal/v2/n3/pdf/nn0399_266.pdf
65. Rubinsztein DC. The roles of intracellular protein-degradation pathways in neurodegeneration. Nature. 2006;443(7113):780–6.