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# Cellular Stress Promotes Cellular Suicide: Review Article

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## ABSTRACT

The focus of this overview was to elucidate the different kinds of stresses that influence cell survival, growth, and cellular functions, in addition to cellular quiescence and cellular suicide, as well as how the cell tries to respond to these stressful stimuli. A cell's cycle is a sequence of developments that enables a cell to replicate every component of itself, divide into two nearly identical new cells, and endow each with the information and resources it needs to repeat the process. For tissue homeostasis, the ideal stabilization of proliferation of cells, demise of cells, and the proportion of positive to negative signals determines if the cell is alive or dead. Cells could indeed cope with adverse conditions in an assortment of ways, from triggering long-term survival strategies to establishing the demise of cells, which ultimately expel dead cells. The kind, intensity, and time frame of the stress, plus the kind of cell, all play a significant role in determining whether cells mount a defensive or destructive response to stress. This review will talk about the consequences of cellular responses to stress and discuss a range of stressful situations and the degree to which the animal's cells' react to multiple exhausting factors ranging from the physiologically programmed advancement of cells to cellular senescence and/or a variety of pathological disorders.

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## INTRODUCTION

Cellular stress is a response to alterations or variances in extracellular circumstances that harm macromolecule function and structure **(Poljšak and Milisav, 2012)**. Stress, if either endogenous or exogenous, can sabotage a stable state throughout organelles found in cells, which makes a significant contribution to cell malfunction and has an impact on longevity **(Li *et al.*, 2021).** As a result, to deal with constant stimulation from both within and outside, organisms must have distinctive pathways for signalling between cells (**Kirkwood and Austad, 2000**). Based on the intensity, frequency, and length of the anxious stimuli, cells either re-establish cellular homeostasis or adopt an abnormal situation in the new environment. Various stressors induce multiple cellular reactions, such as cell repair pathways and cell responses that lead to temporary adaptation to certain stress factors, such as autophagy, cell death, or others **(Poljšak and Milisav, 2012)**.

## 1.Various sorts of stressors

### 1.1. Stress of the heat

Heat stress (HS), or hyperthermia, is a well-studied exterior of stress that has a detrimental impact on virtually all of the cell's parts as well as numerous metabolic/signaling and signalling pathways (**Morimoto, 2011**). Heat stress causes cellular senescence-like cell cycle arrest; therefore, one of the most intriguing aspects of HS is cellular division phase selectivity. Recently, HS has been shown to induce diverse consequences of DNA damage in both phases (I mean G1 in addition to G2), as well as limiting DNA replication in the non-S phase as a result of broken double-strands of DNA in the non-S phase (**Velichko *et al.*, 2015**). Although it was recently enacted that intense HS may trigger the demise of cells through necrotic processes or apoptosis during mitosis and others that have been skipped, the fateful cell judgement drives by critical sublethal HS have been overlooked (**Velichko *et al.*, 2013**).

Also, denaturing proteins, incorrect folding, and misaggregation are all triggered by HS, bringing about deactivation and functionlessness. Denaturing proteins, incorrect folding, and misaggregation are all triggered by HS, bringing about deactivation and function lessness. As a result, proteins are very sensitive molecules that are negatively impacted by hyperthermia, so heat shock is a prototypical

proteotoxic sort of cellular stress that leads to disrupting the homeostasis within cells and forces the establishment of the heat shock rejoinder heat shock response (HSR), which limits the damage to cellular organelles and stops cellular propagation and growth until the stress reason is eliminated and the breakage has been repaired (**Richter *et al*., 2010**). Heat shock proteins (HSPs) are the main HSR key regulators; therefore, under standard and extreme conditions, molecular chaperones have responsibility for unfolded, folded, alongside, or fold-back proteins (**Whitley *et al*., 1999**). According to comparable molecular mass, HSPs can be divided into two families: first of all, chaperones with mass molecules that vary from 8–28 kDa comprise the small-sized, ATP-independent HSPs (**Bakthisaran *et al*., 2015**). The second are chaperones with masses of molecules that vary between 40 - 105 kDa comprise the large, ATP-dependent HSPs; the last (second family) consists of the chaperone family members of 70 and 90 kDa, likewise, the stress-induced form of HSP70 encompasses the (70 kDa) category; and the 90-kilo-Dalton group is produced up of two chief isoforms: the induced form of HSP90 and the constant form, which is declared HSP90β (**Sreedhar *et al*., 2004**).

HSP40s, also known as J-proteins, serve as regulators of co-chaperones by interacting with HSP70 through their J domain. (**Walsh *et al*., 2004**). HSPs tie in an ATP-dependent pattern in which to aid in the repair of hampered proteins generated in cells suffering from stressors and thus avoid pervasive gathering in cells and internal components such as the membrane of the cell; however, the proteins that have been misfolded are conveyed by HSPs to ATP-dependent chaperones, resulting in assistance in appropriate folding by binding HSP with a co-chaperone; therefore, the mechanisms of chaperones restrain the process known as apoptosis by turning on a set of enzymes. (**Almalki *et al*., 2021**).

## 1.2. Genotoxic stress

The safeguarding of genetic information is essential for an organism's cellular activities throughout all organizational levels. As a result, DNA deterioration becomes particularly risky and necessitates complicated genetic machinery accountable for ensuring homeostasis via repairing DNA. A variety of pivotal governing factors involve multiple checkpoints in the cell cycle, as does the definitive outcome of whether to animate the death of the cells in a programmed manner in cells with irreparable DNA impairment **(Swift and Golsteyn, 2014).** A variety of factors that damage DNA cause genotoxic stress, such as exogenously ionizing rays and radiation from ultraviolet rays, alkylating compounds, X-rays, and others, but the most common source of endogenous stress is the kind of species of oxygen that are reactive, which form as an unavoidable by-product of energy fabrication in cellular mitochondria via sugar phosphate oxidation **(Coates *et al*., 2005).** Endogenous DNA damage is more common than exogenous damage. Remarkably, both endogenous and exogenous sources cause DNA lesions that are similar in nature; among them are double-strand breaks, a basic site, helix-distorting adducts, inter- and intra-strand cross-links, and modified bases. These abnormalities, if not right, can cause chromosomal aberrations, transversions, base transitions, or frameshift mutations **(Lopez Bergami and Zeev, 2011).**

The cellular response to genotoxic distress can be modelled as a transduction signalling cascade that is predictable as a response to damaging DNA. The fundamental proteins that discriminate between destruction of DNA and impairment of replication are known as sensor proteins; they subsequently send a signal to transducer proteins, which are mostly protein kinases that are evoked via phosphorylation. Finally, the signal is transmitted to a slew of effector proteins, which carry out many processes in cells, notably the repair of DNA, checkpoints of the cell cycle, senescence of cells, and impairment of replication are known as sensor proteins; subsequently send a signal to transducer proteins, which are mostly protein kinases that are evoked via phosphorylation, finally, the signal is transmitted to a slew of effector proteins, which carry out a many processes in cells, notably repairing process of DNA, checkpoints of the cell cycle, senescence of cell, and apoptotic process **(Coates *et al*., 2005).**

## 1.3. Oxidative stress

The occurrence of this stress is elicited through an imbalance between synthesis as well as the accumulation of reactive species (RS) at a cellular level and the biological system's proficiency to remove these reactive substances. Although these ROS are typically produced as responses to utilization of oxygen and can perform physiological processes, for example, sending signals and threats from the environment such as ultraviolet radiation, radiation from ionizing, contaminants, and toxic metals, as well as xenobiotics, can also produce them, as well as causing tissue and cell deterioration **(Pizzino *et al*., 2017).** Radicals that include superoxide, hydroxyl, hydrogen peroxide, and singlet oxygen molecules are examples of reactive substances that are typically produced by biological mechanisms as byproducts of metabolism **(Navarro-Yepes *et al*., 2014).** When these radicals end up agitated, they begin to ellect for the most vital biologic molecules, for instance, lipids and proteins, alongside nucleic acids **(Wu *et al*., 2013).** Also, RS are usually generated by mitochondrial cells under

either normative or pathological conditions, and their synthesis is primarily reliant on enzymatic and nonenzymatic reactions. Enzymatically, this includes the chain of respiration, prostaglandin creation, a process of phagocytosis, and the pathway of cytochrome P450 (**Halliwell and Gutterridge, 2015).** Nonenzymatic reactions, especially if the oxygen interacts with biological substances or while the cells are confronted with ionizing radiation **(Valko *et al*., 2007).** The impact of free radicals upon cells varies given the sort of free radical species and their concentration; therefore, radicals at low concentrations are able to enhance , whereas **(Martindale and Holbrook, 2002).**

### 1.4. Hypotoxic stress

Hypoxia is a situation that occurs when there is insufficient oxygen demand for the body's tissues. A hypoxic condition occurs when the oxygen entering a cell does not match the oxygen requirements of the same cell. This leads to an imbalance between oxygen supply and energy demand in a living cell as a result of physiological and pathophysiological systems **(Datta and Dougherty, 2018).** A normal cell is subjected to hypoxic stress as a result of normal physiological variations during foetal development, wound healing, adjusting to high altitude, inflammation, and so on (**Semenza, 2000).** To generate energy, aerobic organisms require oxygen (O2). As a result, oxygen lack capacity causes serious stress in cells; a lack of oxygen is also related to an abnormal buildup of free radicals, which brings about extra stresses on the cell's proteins and their DNA **(Peciuliene *et al*., 2022).** Cells initiate a variety of adaptive mechanisms in low $O_2$ (hypoxic) circumstances to balance the availability of $O_2$ with the demands for metabolism, bioenergy, and redox, causing cells to transiently stop moving through the cell sequence, reducing reliance on energy and cellular programmed death while secreting proangiogenic and longevity elements **(Majmunder *et al*., 2010).** were previously known as erythropoietin production regulators, but they are now acknowledged as crucial transcriptional response modulators to hypoxia. Furthermore, aside from their resiliency in cell stress reactions, this demonstrated that hypoxia-inducible factors play a vital role in each pathogenic and physiological process. **(Ziello *et al*., 2007).**

### 1.5. Nutrient stress

Nutrient availability is critical for metabolic homeostasis and cellular function; glucose is among the most vital nutrients, and both a lack and an abundance of it can induce cellular stress **(Wang *et al*., 2012).** Fundamental metabolic mechanisms are highly conserved among many eukaryotes, which include yeast and mammals, and utilize either glycolytic digestion and/or mitochondrial energies in response to signals from outside the cell, cell-based prerequisites, and the energy expenditure or circadian phase **(Sahar and Sassone-Corsi, 2009).** In some types of cells, such as liver, muscle, and adipocytes, extra carbon is able to be preserved as lipid or glycogen; however, in the disordered state of cell development and/or proliferating, the majority of cells fail to absorb extra nutrients. For that reason, growth factor signalling is mainly responsible for nutrient uptake in metazoan cells; consequently, excessive or insufficient intake of nutrients triggered by signals of growth factors can have a significant impact on cellular bioenergetic fitness **(Wellen and Thompson, 2010).** The amount of free radicals yielded by mitochondria is a strong indicator of growth factor-regulated nutrient uptake; when this radical assembly outpaces that requisite for typical physiological reactions such as cell signaling, proliferation, and differentiation, cells experience stress that leads to cellular death or metabolic disorders consisting of diabetes and tumors **(Hamanaka and Chandel, 2010).**

## 2. Stress responses in cell cycle

Stress causes mammalian cells to activate processes that facilitate cellular activities and thus preserve biological and microenvironmental stability **(Galluzzi *et al*., 2018).** There are three fundamental kinds of responses: stressors can activate cellular repair mechanisms or cause temporary adaptation. 2. cellular senescence or ageing 3. cause cell death. The majority of the responses are designed to restore cells' normal physiology; however, they can consume a significant amount of resources in the process (**Galluzzi *et al*., 2018).**

### 2.1. Activation of cellular repair or temporary cellular adaptation

To maintain cell homeostasis under a variety of different environmental and physiological circumstances, these cells have modified different stressful response pathways for signaling.

#### 2.1.1. Responses to heat shock

This sort of response is a cellular defensive procedure stimulated next to various stressors, including elevated temperature or infections, in which chaperon proteins help stop the cellular stress response by folding and refolding proteins and initiating autophagy **(Richter *et al*., 2010).** Proteins that cause heat shock are produced in high quantities instantaneously upon detecting stress, such as elevated temperature or hypoxia (i.e., temperature elevations of 3-5 degrees Celsius above usual). Many stimuli, including oxidative stress and heavy metals, have since been discovered to activate this response. This ubiquitously conserved cellular stress response

is coordinated by heat shock factor 1 **(Anckar and Sistonen, 2011).** In vertebrates, there are four major isoforms that encode the factors that cause heat shock (HSF1, HSF2, HSF3, as well as HSF4). The most important factor for heat shock response stimulation is HSF1, but these variables include: HSF1-HSF2 as well as HSF4 are all currently identified in vertebrate species, but HSF3 has only been found in avian species. HSF2 regulates feminine fertility and sperm production, while HSF4 regulates the growth of the eye lens **(Dutta *et al*., 2022).** HSF1 is composed of 529 sequences of amino acids and has four critical functional and structural domains, including a regulatory domain, an oligomerization domain, a DNA binding domain, and an additional transactivation domain **(Neudegger *et al*., 2016).**

According to typical growth circumstances, monomeric HSF1 occurs in the cytoplasm in an inactive state in interaction with several regulating proteins, including HSP27, HSP70, and HSP90, which are also downregulated by these molecular chaperones **(Neef *et al*., 2014).** Hsp90 is upregulated and functions as a molecular chaperone intracellularly, suppressing the premature folding of nascent polypeptides, but on the other hand, both types of Hsp70 and Hsp27 have been demonstrated to safeguard cells from cell death initiation by a broad sort of stress and suicide of a cell style, such as apoptosis and necrosis, by inhibiting suicide mechanisms and indirect means by over-all survival actions **(Fulda *et al*., 2010).** The monomeric form of HSF1 is distributed in different situations of stress, enabling modifications that aid in translocation in the nucleus and conversion to an effective binding portion of DNA or adding up a phosphate group via the phosphorylation process, and adding or subtracting an acetyl group are illustrations of after-translational adjustments that are essential for HSF1's initialization and attenuation cycles **(Dai, 2018).** HSF1 unites with the promoters of its intended genetic material, among which are proteins that are evoked during heat shock through a conserved pentameric pattern **(Anckar and Sistonen, 2011).**

### 2.1.2. Oxidative stress response

Occurrence of stress caused by oxidation, antioxidants in the cell work together to combat an oxidizing agent's impacts and reestablish redox stability; therefore, each living organism has evolved to withstand oxidative damage, with variations in superoxide anion or hydrogen peroxide levels triggering on or off genes that encode protective enzymes, factor transcription, and structures of proteins **(Dalton *et al*., 1999).** Reactive radicals are also thought to act as second messengers independent of oxidative stresses, cell proliferation, necrosis, and apoptosis, even though numerous findings have guided the recommendation that cells can detect reactive species and activate specific responses **(Scandalios, 2002).** ROS have also been shown to initiate programmatic cellular death, forcing cells to switch to a different mechanism of cell death generally, but specifically under oxidative stress, two mechanisms handle the conversion of apoptotic cells to necrotic cells: In caspase inactivation or a decline in the content of ATP inside the cells, the caspase enzymes have an active location for cysteine nucleophiles that are susceptible to alkylation, nitrosylation, and oxidation **(Chandra *et al*., 2000).** The majority of researchers noticed that oxidation also has a tendency to boost the expression of these inducing HSPs, especially HSP27 **(Swindell *et al*., 2007).**

### 2.1.3. DNA damage response

The crucial defect that triggers the responsiveness of damaged DNA, such as breaks of double and/or single strands of DNA due to impairment of DNA function, is a common indication of activity in cellular stressful conditions caused by radiation, chemotherapeutic therapy, or UV light exposure (**Roos and Kaina, 2006**). DNA damage to mammalian cells is often triggered by several causes to oversee the integrity of the genomes; therefore, three primary parts of damaged DNA response mechanisms are the sensors, the transducers signaling, and the effectors (some of which perform overlapping responsibilities): ATR (ATM-Rad3-related) as well as ATM (ataxia telangiectasia mutated) are kinases that serve as the centre of the sensors for and cause DNA to reply to any defect (**Liang *et al*., 2009**). At the level of transducers, DNA deterioration causes cell cycle checkpoints to be stimulated, as well as the mechanisms for repairing DNA with regard to genetic anomalies; if the response fails, a similar mechanism eventually stimulates the senescence of cells or regulated cell death, which both have an impact on the control of systematic and microenvironmental equilibrium (**Chang *et al*., 2017**).

At this level, checkpoint kinases were used to stimulate multiple signal transduction processes, the most important of which are ATM-Chk2 along with ATR-Chk1, which must be activated for effective combination of the checkpoints and repair of DNA steps; however, they can indeed regulate other physiological performances, including apoptosis or cell senescence (**Smith *et al*., 2010**), and both kinases transmit indicators from the sequence flow of the sensors to the effectors (**Zhou and Bartek, 2004**). The damaging response of genetic material effectors includes proteins associated with repairing DNA, controlling gene transcription, copying the genetic

material, cell-cycle monitoring, and the process of apoptosis, like CDC25, p53, and several DNA-repairing enzymes (**Zou and Elledge, 2003**). Most of the above effectors are ChK1/ChK2 or ATM/ATR, but the most important of them is p53, which is essential for arresting the cells through the direct response due to DNA damage (**Rodier *et al*., 2007**). ATM/ATR and yet another PIKK-related protein, DNA-PK, can both phosphorylate and stabilize p53. ChK2, which acts as the substrate of ATM in reaction to damaged DNA, can also phosphorylate p53 (**Bakkenist and Kastan, 2004**).

### 2.1.4. Response to unfolded proteins (unfolded protein response, UPR)

To fix the folding of the proteins, glycosylation, oligomerization, and disulfide bond creation are all part of the posttranslational mechanisms of the secretory and membrane-associated proteins; therefore, all the cellular pathways for checking the cellular surroundings are required for mature protein production and secretion (**Fulda *et al*., 2010**). There are 2 pathways for responding to unfolded proteins: once cells are subjected to conditions such as poverty of the supplying glucose, limitation of glycosylation of proteins , disruption of $Ca^{2+}$ equilibrium, and lack of oxygen, this leads to the accumulation of unfolding proteins in the endoplasmic reticulum (ER), also called endoplasmic reticulum stress, and this pathway is considered a more prevalent pathway. The second way is the occurrence of unfolded proteins in the mitochondria. These 2 ways turn on a coordinated and effective collection of routes leading to an event referred to as "unfolded protein response" (**Ron and Walter, 2007**). In mammalian cells, the UPR is complicated and operates over three major receptors positioned in the transmembrane of the endoplasmic reticulum: type I transmembrane protein inositol requiring 1 (IRE1α); eukaryotic initiation factor 2α (eIF2α) kinase (PERK); and activating transcription factor 6 (ATF6) (**Cao and Kaufman, 2012)**.

## 2.2. Cellular senescence

Hayflick and Moorhead's (1961) exploration of cellular senescence, an activity that controls cell fate and can be recognized as an indicator of ageing, and when the experiments are done, the researcher and colleagues find In vitro, human diploid cells of the fibroblast are subjected to strain to cease splitting up. **(Hayflick and Moorhead, 1961)**. Cellular senescence is a sustainable halt in the cycling of the cell that can be stimulated in ordinary cells by a variety of internal stimuli and/or external triggers, in addition to biological signals such as gradual short telomere length, telomeric organization alters and signals from mitogenic processes, radiance, reactive oxidants, and stress that cause gene damage, epigenetic modification, chromatin disorder, disrupted proteostasis, malfunctioning of mitochondria, inflammatory conditions, and possibly signaling from damaged tissue , chemotherapy medications, and nutritional deficiencies **(Mikuła-Pietrasik *et al*., 2020).** Ageing of the cells is thought to be a self-motivated process with numerous steps for the period of which the characteristics of ageing cells vary and adapt based on the environment **(Kumari and Jat, 2021)**.

The ordinary cessation of cell division is initiated by biological clues or various kinds of stressors; therefore, cells may react to the stressor factor by eliciting repair, the death of a cell, or premature senescence, depending on the cell sort and the severity and starting point of the stimuli that cause stress **(Galluzzi *et al*., 2018).** Stop dividing of the cells due to developing of age differs from a further sort of growing arbitrary halt recognized as quiescence in that it takes place in the first phase (G1) and potentially in the second phase (G2) of the normal cycle of the cell, although the quiescence occurs in the phase G0 **(Di Leonardo *et al*., 1994).** Senescence of the cells has the ability to impair repairing of the tissue and renewal, accelerating advancing age. As a result, removing cells that are senescent may assist in minimising the effects of ageing tissue and increasing life expectancy. Also, senescence may serve as an effective against cancer way, blocking the growth of malignant cells and having a plan for both positive and negative impacts on the health of the organism. Some researchers have approved that are senescent may assist in minimizing the effects of aging tissue and increasing life expectancy, also senescence may serve as an effective against cancer way, blocking the growth of malignant cells and having a plan for both positive and negative impacts on the health of the organism, while some researchers approved that the signalling of p53, p21, and p16 is crucial in the regulation of the senescence process **(Kumari and Jat, 2021).**

In rejoinder to damage the genetic material (DNA) induced by telomere breakage and oxidant or detection of tumour cells, p53/p21WAF1/CIP1 is initiated; therefore, the fundamental DNA damage response (DDR) signalling provokes cellular senescence by chronically activating p53, and the range of strategies for inhibiting p53-mediated signalling can prevent the advance of senescence in the cell **(Beauséjour *et al*., 2003).** While $p^{16INK4A}$/pRB Pathway: When pRB is dephosphorylated, it unites with E2Fs, creating a complex of the RB-E2F, such that these complexes attach to the promoter part of E2F genes and prevent transcriptional genes that relate to the cell cycle from being inhibited by cyclinE-CDK2

hyperphosphorylation of RB, which consequently leads to the liberation of E2Fs, boosting transcription of the genes that relate to the phase of synthesis (S-phase), and thus the cycle of the cells is in progress **(Zhang *et al*., 2000).** Interdependence between the RB and mitogenic AKT signalling pathways has been proposed to play an important role by converting quietness cells to senescence cells by controlling the multiple activities of the factors in transcription, for instance FOXO3a, Forkhead, and FOXM1 **(Imai *et al*., 2014).**

Cellular senescence is an end and steady condition of growth block; therefore, these cells are not able to multiply even after optimum growing circumstances and mitogenic stimulation **(Di Micco *et al*., 2021).** The cells that are prone to senescence are more resistant to apoptosis due to the raised manifestation of cell survival and the presence of BCL-2 proteins that inhibit apoptosis, despite the existence of external stress **(Yosef *et al*., 2016).** The genetic pathways governing the option between apoptosis and senescence are unidentified, and cell fate may be influenced by the strength and period of the original sign, in addition to the origin of the impairment and the cell type **(Childs *et al*., 2014).** Since senescence and apoptosis systems focus on vital parts such as p53 upregulation, the inability of senescent cells to respond to the process of apoptosis is probably dependent on p53 quantities and function **(Kirschner *et al*., 2015).**

## 2.3.Cellular death

Cell death takes place when a living cell ceases to function, either as a consequence of the normal old cell's death and then being substituted with another one, such as programmable cell death, or as an effect of stressors; so, there are two types: necrosis is a nonphysiological process that happens as a consequence of a pathological condition, whereas Type I of the cell death is considered apoptosis and Type II of the cell death is considered autophagy, which are distinct physiologically-programmed cell death processes **(Kierszenbaum and Tres, 2019).** Under stress, cells in biological tissues drop dead through programmed cell death and necrosis based on the excitation of molecular mechanisms inside the dead cell that either transform the survival of cells or send suicide signals that effectively damage the cells, which are sentenced to numerous extracellular circumstances (pH, oxidizing agents, heat, as well as cleansers) or factors from inside the cells (DNA break and excess $Ca^{2+}$); then, these factors activate different sorts of organelle signalling paths, allowing cells to maintain correct function of the DNA, folding of the proteins, energizing, ionic status, and equilibrium of the redox, and thus avoid damage **(Belizário *et al*., 2015).**

### 3.1. Necrosis

The morphology of necrosis has characteristics that are characterized by an upsurge in the volume of cells (oncosis), oedema of organelle components, which leads to shattering of the cell's membrane, and eventually degenerative conditions of the components inside the cell, while, previously, necrotic manner was assumed to be an uncontrollable style of cell dying that occurs in the cells, and yet findings are intensifying that the dying cells which are suffered from necrosis is delicately coordinated by a setup of transduction routes and catalytic method and with the help of two receptors: the first one is death domain receptors but the second named as Toll like receptors, for example, have been establish to induce necrosis process, specifically when the inhibitors of caspase enzyme are existing **(Kroemer *et al*., 2009).** Since the necrosis process is common in ischemia, trauma, and potentially a few aspects of degeneration that occur in the nerve, additional organic molecule recognition and genetic description are clinically meaningful impacts **(Golstien and Kroemer, 2007).**

### 3.2. Programming the death of the cell

The death that occurs in the cell in response to occurrences within the cell, including apoptosis and/or autophagy, carried out in a biological mechanism that usually affords benefit through an organism's life span is acknowledged as programmed cell death (PCD). PCD pieces are critical for the animal's growing tissues **(Engelberg-Kulka *et al*., 2006).**

### 3.2.1. Autophagy

Autophagy is enabled by autophagy proteins to trigger the formation of structures known as autophagosomes. Autophagosomes transport debris cell fragments to a lysosome in the cell. The job of a lysosome is to metabolize or dissolve other cell components. Lysosomes ingest junk from some components of cells and then discharge the reused parts that remain. These raw products are utilized by the cells to create new components **(Yang and Klionsky, 2010).** Autophagy arises at a normal rate throughout developmental stages in addition to under stressful circumstances; likewise, it is commonly thought of as a cell preservation system since it eliminates harmful or archaic proteins and ancient organelles and utilizes the secondary products that are used for fuel and metabolites in anabolic reactions **(Mizushima *et al*., 2008)** Furthermore, autophagy is activated by stressful circumstances like starvation, a lack of growth factors, and infectious agents, besides extracellular influences like hormones and cytokines, which can also influence autophagy, whereas insulin and insulin-like growth factor 1 restrict autophagy **(Jung *et al*., 2020).** Autophagy's primary function is

to encourage cell survival after stress or nutrient deficiency by reprocessing critical biological parts. In fact, inhibiting autophagy,whether genetically or chemically, enhances cell death under stress conditions **(Kroemer *et al*., 2009).** The forms of self-degradation are macroautophagy and microautophagy, beside chaperone-mediated autophagy (CMA); microautophagy is the immediate transfer of cytosolic cargo parts into the lysosome via membrane invaginations, but CMA is characterized by the partial translocation of proteins with the KFERQ-like motif (a pentapeptide in the protein sequence that is required for the subsequent targeting and degradation of chaperone-mediated autophagy substrates in lysosomes) throughout the lysosomal membrane **(Denton and Kumar, 2019).**

### 3.2.2. Necroptosis

Is a controlled cellular death process that in appearance looks resemble necrosis and relies on the kinase endeavour of the receptor-interacting protein 3 (RIP3) and upregulation of the bonded lineage kinase domain-like protein (MLKL), which at first largely relies on the activation of the RIP1 kinase as well as can be induced throughout pathological situations, typically as consequences of activation of the death receptor in particular biological cellular instances **(Dionísio *et al*., 2020).** TNF receptors trigger necroptosis after caspases are chemically repressed **(Galluzzi *et al*., 2012).** It is marked morphologically by an upsurge in the cell mass of the cells, oedema of organelle structures, permeabilization of the plasmatic membrane, collapse in the cell, and expulsion of cellular constituents; and due to the production of inflammatory cytokines, damage-correlated molecular modality, and pathogen-linked molecular mechanisms, necroptotic cells enhance an extremely inflammatory response **(Sanguiliano *et al*., 2014).** Cells undergo controlled necroptosis upon extraneous or intrinsic lines getting started by TNF, TLR (toll-like receptors), along with NLR (NOD-like receptors) agonists, interferons, and contaminants such as viruses and bacteria **(Berghe *et al*., 2014).**

### 3.2.3. Anoikis

It refers to the apoptosis induction in the cells as a consequence of their impairment of adherence to the matrix of outside cell matter and their surroundings; therefore, this phenomenon was dubbed 'anoikis,' derived from the Greek words meaning homelessness, and it's crucial in avoiding unregulated cell translocation and attachment, leading to abnormal growth; moreover, in a few cellular stresses, like hypoxia, that have been recognized to be associated with certain actions, anoikis are governed primarily by contact with the extracellular and neighbouring cells **(Gilmore, 2005)**. Anoikis has some essential properties to begin with: First, extracellular matrix (ECM) receptors of the integrin family are necessary for cells to inhibit anoikis; second, overexpression of Bcl-2 inhibited anoikis, suggesting a need for mitochondrial membrane permeabilization to arise. And finally, not every type of cell is potentially vulnerable to anoikis. "For example", epithelial and endothelial cells were discovered to be more responsive than fibroblasts, with the latter ready to sustain themselves without ECM if serum growth factors exist **(Gilmore, 2005).**

### 3.2.4. Ferroptosis

Is an emerging form of programmable demise of the cell that is unique in that there is substantial oxidation of lipids and iron buildup when the death of the cells is starting; therefore, the severity of ferroptosis is iron-dependent **(Li *et al*., 2020).** Dixon first suggested the notion of ferroptosis in 2012, while employing erastin to destroy RAS-mutant cancer cells (RAS is a protein that works as an oncogene) **(Dixon *et al*., 2012).** In terms of morphological features and their task, ferroptosis differs from other physiological and pathological processes like necrosis, apoptosis, and autophagy by reason of the fact that it lacks the morphological features of usual necrosis, like cytoplasmic expanding, organelle swelling, and cell membrane explosion, as well as the features of classical apoptotic processes, like condensate of chromatin, shrinking of the cell, and the emergence of bodies that are apoptotic and cytoskeleton decomposition (Xie ***et al*., 2016).**

In comparison to autophagy, ferroptosis doesn't lead to the development of traditional tight bilayer membrane structures (autophagic vacuoles); therefore, ferroptosis is illustrious from other sorts of cell dying because the mitochondrial diminution coincides with higher membrane masses and the decrease or disappearance of the cisternae of mitochondria **(Yang and Stockwell, 2008).** Biochemically, there is a depletion of intracellular glutathione (GSH) and oxidizing agents of the lipids that cannot be broken down by the distillation procedure that is catalysed through an enzyme called glutathione peroxidase 4 (GPX4), and along with $Fe^{2+}$, oxidized fats are oxidized in a Fenton-like manner, producing big quantities of reactive species and facilitating the ferroptotic process **(Friedmann Angeli *et al*., 2014).** A wide range of compounds that initiate ferroptosis are classified into four types: The first one is erastin, an early-stage ferroptosis activator that leads to diminished glutathione by speedily suppressing the Cystine/Glutamate Antiporter System (Xc). On the other hand, erastin has another specific objective: anion channels that are voltage-based result

in the loss of normal mitochondrial functions **(Li *et al*., 2020).** Ras-selective Letha 3 (RSL3) and diphenyleneiodonium chloride 7 (DPI7) are in the second type because they effectively limit GPX4 function and cause ferroptosis **(Yang *et al*., 2014).** Ferroptosis-inducing agents (FIN56), which have two techniques for triggering ferroptosis, are included in the three types: First, FIN56 enhances GPX4 degenerative changes. The second step, FIN56, ties to the squalene synthase, reducing antioxidant-producing ubiquinone coenzyme Q10; this reaction promotes the cell's responsiveness to FIN56-provoked ferroptosis **(Liang *et al*., 2019).** The last type comprises $FINO_2$, an organic peroxide with several similarities to artemisinin that produces ferroptosis via a combination of GPX4 deactivation and oxygenation of adjustable iron **(Gaschler *et al*., 2018).**

### 3.2.5. Eryptosis

Erythrocyte suicide is marked by red blood cell compression, blebbing, and phospholipid jostling of the membrane itself via an enhanced $Ca^{2+}$ reservoir in the cytosol to perform function, which causes eryptosis **(Lanfg and Qadri, 2012).** An upsurge in cytosolic $Ca^{2+}$ action causes eryptosis by reactivating the enzyme (cysteine endopeptidase calpain), which catalyzes proteolysis in the cytoskeletal of the cell, subsequently triggering blebbing; then $Ca^{2+}$ stimulates sensitive efflux of the $K^+$ and $Cl^-$ and thus increases the polarity of the membrane; at this point, the KCl rose outside of the cell and attracted osmotically obliged water, resulting in cell shrink **(Lang *et al*., 2010)**. Ceramide increases the $Ca^{2+}$ sensibility of red blood cells to stimulate eryptosis by releasing platelet activating factor and elevating the expression of their receptors on erythrocytes to enhance ceramide formation following osmotic erythrocyte shrinkage **(Lang *et al*., 2015).** A state of shock causes disturbance of the osmolarity, oxidative stress, dwindling of energy, the condition of having a body temperature greatly above normal, and cadmium poisoning triggers eryptosis, as well as a wide range of substances, such as some neurotransmitters like nitric oxide and catecholamines, aromatic substances like thymol, which inhibit eryptosis, and erythropoietin, which helps to prevent eryptosis by suppressing $Ca^{2+}$ permeability **(Repsold and Joubert, 2018).** Undue eryptosis causes the susceptibility of sundry red blood cells to phagocytosis by macrophages, leading to the occurrence of an acute type of anaemia **(Lang *et al*., 2017).**

### 3.2.6. NETosis

It is a distinct style of cell dissolution that occurs in neutrophils caused by an early pathogenic trigger that results in the expulsion to the extracellular of its chromatin and granular and the assembly of, for example, antiviral proteins **(Gillot *et al*., 2021).** When neutrophils go through the NETosis mechanism, the nuclear and then granular membranes break up into small parts, the chromatin relives the condensation, and it spreads within the cytoplasm, where it combines with a sort of protein in the cytoplasm, which guides the disruption of its membrane and the liberation of granular protein-decorated chromatin throughout the extracellular environment; There are 2 pathways for NETosis: conventional suicidal NETosis and the non-suicidal pathway **(Yang *et al*., 2016).** The preliminary approach involves fastening ligand adhesion to receptors of the neutrophil toll-like or cytokine receptors as well as IgG-Fc and/or complement **(Garcia-Romo *et al*., 2011).** While the non-suicidal pathway (also called vital NETosis) takes about 30 minutes to occur and is triggered through platelet activators, microbial organisms, and proteins associated with complement, after this step of activation, calcium influxes into neutrophils; as a result, the electrostatic forces that link between the histone and DNA fall apart, resulting in chromatin losing its condensation; these chromatins, along with histones and granules, are transported away from the neutrophil by vesicles **(Huang *et al*., 2022).**

### 3.2.7. Paraptosis

According to reports, a number of mechanisms, such as the expression of the Insulin Growth Factor 1 Receptor (IGF1R), proteasome suppression, stress inside the ER, the development of reactive oxygen species (ROS), and the entry of calcium into the mitochondria, can cause paraptosis.

Is a caspase-independent that differs from apoptosis in the acronym "para" means "in relation to," therefore the paraptosis and the apoptosis are related to each other in some features but differ in chemical and physicochemical characterization, morphology, in addition to response to apoptotic inhibitors; therefore, they are independent of caspase, while Sperandio and colleagues at work appear to have coined the idiomatic paraptosis when they used a receptor of the growth factor 1 that resembles insulin to incite die off in fibroblasts during embryonic status in mice (Sperandio ***et al*., 2000).** The cells that undergo paraptosis lack apoptotic features such as nuclear fragmentation, figuration of the apoptotic body, and chromatin intensification; rather, the formation of vacuoles in the cytosol as well as from the endoplasmic reticulum was observed, and there was also mitochondrial swelling, but no autophagic vaculation was seen. Also, paraptosis has some of the same morphological characteristics as necrosis, such as the generation of vacuoles in the cytoplasm and

mitochondrial bulge, as well as the ineffectiveness of caspase restrainers **(Khalili and Radosevich, 2018).**

**(h) Pyroptosis**: "Pyro" is Greek meaning fire and "ptosis" for fall; therefore, the term pyroptosis can be translated as "fiery falling," and it refers to the explosion of pro-inflamed signals from cells that are dying, stimulated by a variety of triggers like cancer, and it is critical for bacterium infection control. It is noteworthy that it differs from paraptosis in that it is dependent on caspase pathways **(Bergsbaken *et al*., 2009).** Pyroptosis is different from other forms of programable dying in that it involves swift lysis of the membrane of a cell, ripping, and the emission of proinflammatory molecules from inside the cell. This stark dissimilarity is similar to apoptosis **(Albert, 2004).**

**3.2.8.** Even though some elements of the apoptosis idea had been clarified many years prior, the transliteration of the usual cell death programme to "fall" was done by the Romanians and was initially employed by Kerr, Wyllie, and Currie in a paper in 1972 to identify a distinguishable style of normal cell dying **(Kerr *et al*., 1972).** Apoptotic manner is a normal biological course that takes place throughout growth, maturation, and ageing as a physiologically stable strategy for preserving instances numbers of the cells in body tissue; it can also arise as a defensive response, for instance, in defence mechanisms responses if cells are hurt due to disorder or even toxic and hazardous agents. While there are numerous physiological and pathological triggers and circumstances that may lead to apoptosis, it's not like each and every cell is reacting to apoptosis in retaliation to a similar trigger (Norbury **and Hickson, 2001).** The varied morphological alterations that manifest throughout apoptosis can be distinguished under a light microscope. You can find out cell retraction and condensate of chromatin, known as pyknosis," which is the most unique characteristic of apoptosis over the initial phases, as well as the cytoplasm turning denser and the organelles becoming more pressed. All characterization of apoptosis is visible on histologic examination in odd cells or tiny collections of cells and seems to be a spherical or oval mass with bushy purple chromatin pieces in the nucleus and dusky eosinophilic stain in the cytoplasm **(Elmore, 2007).**

Apoptosis pathways are extremely intricate and technologically advanced and encompass a reliant energy sequence of molecular incidents. According to current investigation, there are two fundamental cell dying ways: the external way in nature, also known as the death receptor way, and the intrinsically known (mitochondrial way). Current evidence confirms that these two ways are related **(Igney and Krammer, 2002).** As apoptosis is occasionally provoked with the perforin/granzyme way by doing DNA damage that occurs in the single-strand using granzyme B or as granzyme A way that initiates the death of cells simultaneously in an independent caspase way **(Martinvalent *et al*., 2005).** Apoptosis is as important in normal biological processes as its analogue, the replication process known as (mitosis); it plays a complementary but contrasting part in the control of different cellular communities to mitosis and cell growth; approximately, around billions of cells exist every single day in the bodies of animals just to repopulate those that die due to the apoptotic process, and this percentage can skyrocket once there is a rise in cellular death due to natural growth, getting older, or ailments **(Renehan *et al*., 2001).**

Also, **Abdullah and Tawfeeq, (2022)** found that caspase-3 levels increased after exposure to toxic substances like gossypol because it induces apoptosis in the rat ovary. Additionally, the nanoparticles will increase apoptotic cells in multiple organs when delivered without regard to dose or time frame **(Al-hamadany, and Azubaidy, 2023).** Activation of apoptosis has positive effects at times, and according to **Maty's 2021** results, increasing the body's antioxidant levels by adding either synthetic or natural antioxidants to poultry dietary intake will turn on apoptosis as a defence mechanism.

## CONCLUSION

By extrapolating the article's topic and throughout the contemporary international research and the research conducted locally, we have included that the loss of a delicate equilibrium between the mitotic and apoptotic processes can be perilous. When apoptosis arises inadvertently, the body eliminates effectively functioning cells. On the other hand, this review discusses a range of stressful situations and the degree to which the animal's cells' react to multiple exhausting factors, as well as how the cell cycle tends either physiologically to programmed death or pathologically to forced death.

## Conflict of interests

There aren't any conflicts of interest among the writers at this point or anywhere else.

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