CHAPTER 06

Cellular Crossroads: Oxidative Stress, Inflammation and Apoptosis in Molecular Biology

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SUMMARY

Oxidative stress (OS), inflammation and apoptosis are the fundamental molecular players in cellular biology that regulate the homeostatic balance in biological systems. Inflammation and apoptosis are part of the immune system, which counters any harmful stimulus produced either from outside or inside the body. OS is induced as a result of excessive free radical production in the body that disrupts the normal physiological condition of the body leading to various diseases. The stimulation of OS further activates inflammation and apoptosis which further damages the cells. Alzheimer's disease, cancer, Parkinson's disease, cardiovascular disorders, organ damage and neuronal damage are some major disorders that result from the uncontrolled induction of these biological molecules. Therefore, OS is the major culprit behind all these disorders. However, these molecular pathways are of great importance due to the therapeutic implications that can be taken, via targeting these routes, to combat various human disorders, most importantly cancer. Further research is required to understand and develop the pharmacological methods that can target these pathways. This chapter will cover all the aspects of the sources, functions and molecular routes of OS, inflammation, and apoptosis. Furthermore, we will discuss how these key molecular players are crosslinked with each other.

INTRODUCTION

The intricate network of cellular processes within a biological system is regulated by continuously controlled mechanisms. Oxidative stress (OS), apoptosis and inflammation are the key molecular players in cellular biology. Various studies have demonstrated that these molecular phenomena can play a pivotal role in numerous diseases including cancer (Caliri et al., 2021) as well as multiple organ damages such as testicular dysfunction (Akbar & Ijaz, 2024), kidney damage (Hayat et al., 2024) and hepatotoxicity (Kucukler et al., 2020). OS is a condition in which the homeostatic balance among oxidants and antioxidants is impaired (Kośmider et al., 2023). It can also be defined as the relative abundance of reactive oxygen species (ROS) in comparison to the antioxidants which is further associated with diabetes, cardiovascular anomalies, neurodegenerative diseases and various other pathologic circumstances (Sies, 2015). Moreover, the overproduction of ROS leads to membrane dysfunction and also damages DNA and protein molecules. ROS directly oxidizes the biomolecules and disturbs their normal functioning, which is the major reason for the instigation of OS (Jomova et al., 2023). Nonetheless, when the level of ROS transcends a certain limit, it becomes deleterious for the cell as well as the organism (Pizzino et al., 2017).

Inflammation is a defensive mechanism of the body in which the immune system of the body produces a biological reaction against a detrimental stimulus. Tissue damage, toxins, toxic compounds and microbial infections (viral or bacterial) are some factors that can induce inflammation. Although, inflammation is an adaptive response of the body towards any harmful stimulus that may threaten the homeostatic balance of the body but this response is executed at the expenditure of normal cellular functions (Medzhitov, 2010). Inflammation is associated with various neurodegenerative conditions such as sclerosis, Alzheimer's disease and Parkinson's disease (Glass et al., 2010). Inflammation has also been reported to induce glomerulonephritis (inflammation of the glomerulus in the kidney), inflammatory bowel disease in the intestine as well as sepsis (van Hoeve & Hoffman, 2022). However, Apoptosis is a natural physiological mechanism of programmed cell death that aids in the eradication of redundant cells or cells that are seriously injured (Boada-Romero et al., 2020). Apoptosis is indispensable in normal cell renewal, appropriate embryonic development and the functioning of the immune system. Various diseases including Parkinson's disease, stress, Alzheimer's disease, toxins along with uncontrolled cell proliferation and DNA damage may instigate apoptosis (Lopez & Tait, 2015).

In this chapter, we will discuss the interplay of OS, inflammation and apoptosis in different biological conditions. We will further discuss their sources, functions as well as the effects induced by these factors and how one factor controls the other factors.

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OXIDATIVE STRESS

The term OS with its association with biological systems initially appeared in the 1970's. It can be described as the imbalance between the production of reactive oxygen species (ROS) and the ability of specific antioxidants to quench them (Korovesis et al., 2023). The quantification of OS has shown that it was found upsurged in aging people as well as individuals with unhealthy lifestyles such as eating unhygienic food, alcohol consumption, smoking as well as genetic susceptibility (Jomova et al., 2023). OS can be induced externally as well as internally. External causes of OS are chemical compounds including alcohol, environmental toxicants, smoking and UV radiation. Whereas, internal factors include enzymes as well as peroxisomes specifically xanthine oxidase, a detoxifying enzyme, and NADPH [nicotine amine dinucleotide (Sosa et al., 2013)].

The ROS is generated from oxygen in the form of free radicals due to continuous cell metabolism. Whereas free radicals are chemical structures that contain at least one unpaired electron in their outer-most shell which makes them highly reactive elements (Jomova et al., 2023). Reactive species are classified into four types based on the key atom involved. These reactive molecules can either be reactive chloride species (RCS), ROS, reactive nitrogen species (RNS) as well as reactive sulfur species (RSS). However, the most commonly producing reactive specie among them is ROS (Sosa et al., 2013). ROS is constantly produced in the mitochondria as a byproduct of cellular respiration and is regarded as the principal source of oxidative damage in all aerobic organisms. In addition to this, other source from where ROS is generated continuously are viral infections and chronic diseases (Georgakilas et al., 2010). A certain level of ROS is crucial inside the body for the normal functioning of important physiological processes, modulation of important transcription factors as well as redox homeostasis. However, when the level of ROS surpasses a certain limit, it becomes harmful to the cells, tissues, organs and ultimately the organism (Pizzino et al., 2017). Therefore, when the equilibrium between anti-oxidants and pro-oxidants is disturbed, OS is triggered which damages the intracellular molecules such as proteins, DNA, RNA and lipids. Thus, the upsurged level of ROS exterminates the cellular defense (antioxidants) as well as damages the neighboring cells (Sosa et al., 2013).

Anti-oxidants are a front-line of protection that guard the macromolecules i.e., DNA, proteins and lipids from OS via diminishing the ROS level. Antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), glutathione S-transferase (GST), glutathione reductase (GSR) together with glutathione peroxidase (GPx) regulate the OS via reducing the level of ROS (Papas et al., 2019). SOD is an important free radical scavenging enzyme that transforms O_2^- into H_2O_2 (Bromfield, 2016). SOD has three variants i.e., cytosolic SOD1, mitochondrial SOD2 and extracellular SOD3. SOD1 and SOD2 have been reported to safeguard the body against tumor formation (Dubois-Deruy et al., 2020). Furthermore, GPx promotes H_2O_2 degradation by transforming reduced glutathione to glutathione disulfide (GSSG) (Schjenken & Robertson, 2014). GPx and SOD also protect the tissues from carcinogenic elements and inhibit tumor production. During these reactions, reduced GSH is responsible for the donation of electrons (Birben et al., 2012). Moreover, GST converts GSH to xenobiotic substrates, therefore, playing a key part in detoxification (Hayes et al., 2005).

Nuclear factor erythroid 2-related factor (Nrf-2) is a critical transcription factor that is activated by the cell in order to increase its antioxidant defense mechanism against OS. The activation of Nrf-2 elevates the expressions of antioxidant genes (Salim, 2017). Therefore, Nrf-2 is an effective pharmacological target for treating various disorders including neurodegenerative diseases as well as OS. While in the case of chronic disorder, the levels of the antioxidant enzymes are decreased due to the disturbance in oxidant-antioxidant balance that leads to excessive generation of ROS (Elsayed et al., 2022). This in turn, induces OS as well as lipid peroxidation (LPO), which is evidenced by the increased level of malondialdehyde (MDA), a LPO marker. Therefore, a rise in the level of ROS and OS plays an integral part in prompting multi-organ damage (Forman & Zhang, 2021).

The excessive generation of ROS may instigate damage in fundamental biological molecules i.e., DNA, lipids and proteins. ROS reacts with the biomolecules and disturbs the normal formation and repair mechanism of DNA. OS results in alternations in the bases of DNA that may cause insertions, deletions, point mutations as well as chromosomal translocations, consequently activating oncogene or inactivating tumor suppressor genes (Hussain et al., 2016). 8-hydroxy-deoxy-guanosine, and 8-oxoguanine are some indices of OS induced DNA damage. 8-hydroxydeoxyguanosine, a foremost oxidative DNA damage product, is an oxidized form of guanine. It can bring transverse mutations i.e., G:C to T:A or A:T to C:C due to its base pair with cytosine as well as adenine (Bardelčíková et al., 2023).

A cellular environment rich in ROS primarily affects proteins. The excessive production of reactive sulfur radicals from thiol groups (–SH) as well as carbonyl groups such as ketones and aldehydes may also damage proteins. ROS can induce modifications in the structure of proteins that result in loss of protein function (Sosa et al., 2013). ROS can either directly or indirectly react with carbohydrates, lipids and proteins, ultimately bringing about protein damage. ROS attacks peptide bonds and their side chains also. Hydroxyl free radical (OH-1) generation can further remove a hydrogen atom from the polypeptide framework of protein resulting in the formation of carbon centred radicals. When the protein is damaged by ROS, the activity of enzymes that take part in the repair mechanism of DNA is reduced. The impairment of membrane transport proteins as a result of ROS can consequently generate cellular potassium which will instigate a cascade of alterations inside the cell leading to further damage (Klaunig, 2018).

The OS also damages lipid molecules present in the body. OS targets phospholipid membranes of cells and causes LPO, a key characteristic of OS that encourages the death of cells (Bardelčíková et al., 2023). LPO mainly occurs when ROS reacts with lipids especially polyunsaturated fatty acids

[PUFAs (Klaunig, 2018)]. The cell membrane contains high concentration of polyunsaturated lipids, making it particularly vulnerable to oxidation by ROS (Sosa et al., 2013). LPO induced by ROS resultantly escalates the permeability of the plasma membrane which in turn causes the death of cells. ROS reacts with PUFAs present in the plasma membrane and yields lipoperoxyl radical (LOO•), which as a result, further reacts with a lipid molecule to form a lipid free radical as well as a lipid hydroperoxide (LOOH). LOOH is an unstable molecule, so it produces alkoxy and peroxyl radicals, which then generate secondary products. The free radicals formed during LPO have limited effects because they have a very short life span, but the products obtained from the breakdown of these lipid peroxides act as second messengers of OS, due to their extended half-life as well as their ability to transport from the point of their generation (Barrera, 2012). MDA is the end product of LPO, it reacts with DNA to form a complex of MDA-DNA. These complexes exhibit pro-mutagenic activities and also provoke mutations in tumor suppressor genes in human tumors (Ayala et al., 2014). OS is a common source of a variety of diseases as well as disorders such as neurological disorders, cancer, pulmonary diseases, cardiovascular disorders and a variety of other ailments (Jomova et al., 2023). Some of the disorders induced by OS are given in Table 1.

INFLAMMATION

Inflammation is an integral component of the defense system of the body. It is a vital, innate and non-specific immune response in which the breakdown of tissues as well as the cleaning of cellular, extra-cellular and pathogenic waste occur. It plays an integral part in the recognition and elimination of hazardous foreign stimuli by the immune system and initiates the therapeutic mechanism (Zhang et al., 2019). Inflammation can either be acute or chronic. Acute inflammation is the non-specific and first line of protection of the body against any hazard. Moreover, the preliminary response of the body against any trauma or infection is known as acute inflammatory response. Harmful compounds, trauma or microbial invasion damages the tissues which instigates acute inflammation. Acute inflammation quickly becomes severe and normally lasts for a few days. Whereas, steady, prolonged inflammation lasting for an extended timeframe from several months to years is referred as chronic inflammation. Chronic inflammation, if not timely treated, can cause abnormal changes in tissues as well as organs.

Table 1. Various disorders and damages induced as a result of OS.

Disease/ disorder	Damages Induced by OS	References
Male infertility	Damages seminiferous tubules and spermatozoa	Hamza et al., 2023
Cancer	Encourages mutation and activates hypoxia-inducible factor (HIF) which promotes tumorigenesis	Pisoschi et al., 2021
Parkinson disease	Disintegrate dopaminergic neurons	Wei et al., 2018
Alzheimer's disease	Involved in neurodegeneration as well as elevates the accretion of β-amyloid (protein fragments located in the brain of patients with Alzheimer's disease)	Cheignon et al., 2018
Articular damage	Causes the death of chondrocytes	Phull et al., 2018
Cardiovascular disorders	Elevates blood pressure along with endothelial dysfunction, contractile dysfunction, mitochondrial dysfunction, cardiac fibrosis, cardiomyocyte hypertrophy and heart failure	Santillo et al., 2015

Inflammation is characterized by swelling, fever, redness, pain and tissue dysfunction at the tissue level, which is induced due to immunological, vascular as well as inflammatory responses of cells towards any injury or infection. The modifications in vascular permeability, recruitment as well as accretion of leukocytes along with the unleashing of inflammation regulators are some critical events that occur during the mechanism of inflammation (Takeuchi & Akira, 2010). In case of tissue damage, leukocyte chemotaxis is activated, by the body via chemical signaling cascades, from the site of their general circulation to the specific site of injury. These leukocytes trigger the inflammatory response by producing cytokines (Jabbour et al., 2009). During the inflammatory response, vasodilation escalates the transport of protective molecules via blood to the damaged site. Vascular permeability is enhanced which permits the liberation of antibodies in the local environment where it can target the invader microbes. Furthermore, leukocytes move to the damaged site and try to ingest as well as destroy the pathogens (Rock & Kono, 2008).

The inflammatory mechanism is a coordinated process of signaling pathways stimulation that controls the levels of inflammatory regulators in the cells. Pathogen-associated molecular patterns (PAMP) are microscopic structures that can initiate the inflammatory response via activating the pattern-recognition receptors (PRR) present in immune as well as non-immune cells (Gudkov & Komarova, 2016). NOD-like receptors, C-type lectin receptors (CLR), retinoic acid-inducible gene (RIG)-I-like receptors plus Toll-like receptors (TLR) are some classes of PRR families (Takeuchi & Akira, 2010). In mammals, the inflammatory response is activated by the TLR family which activates signaling cascades inside the cell resulting in the transportation of transcription factors like NF-κB along with activator protein-1 (Czerkies & Kwiatkowska, 2014). The inflammatory factors begin the intracellular signaling pathways which in turn instigates inflammatory regulators including cytokines, in particular, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These cytokines control inflammation via interacting with TLR, IL-6 receptor (IL-6R), TNF receptor (TNFR) as well as IL-1 receptor (IL-1R). The activation of receptors initiates multiple key pathways involved in inflammation i.e., Janus kinase-signal transducer and activator of transcription (JAK-STAT), mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B [NF-κB (Zhao et al., 2021)].

NF-κB transcription factor is pivotal in the inflammatory, apoptotic as well as immune response. Inhibitors of NF-κB

(IκB) kinase (IKK) modulate the activation of NF-κB pathway via a process regarded as IκB phosphorylation. IκB is degraded following phosphorylation by the proteasome, allowing NF-κB to be released and translocate to the nucleus for the activation of gene transcription (Hayden & Ghosh, 2012). While on the other hand, MAPK are protein kinases that mediate the cellular reaction to different types of stimuli such as heat shock, osmotic stress, mitogens as well as inflammatory cytokines. MAPK signaling pathway consists of 3 parts: a MAPK, a MAPK kinase (MAPKK) as well as a MAPKK kinase (MAPKKK). The phosphorylation of MAPKKKs triggers the MAPKKs, which as a result, phosphorylates and stimulates MAPKs. Activated MAPKs further activate the related transcription factors, which instigate the inflammatory response (Zhao et al., 2021).

JAK-STAT is another signaling pathway by which the extra-cellular factors can regulate the expressions of genes. It involves a wide array of growth factors, cytokines, and interferons along with many other related molecules including growth hormone as well as leptin (O'Shea et al., 2015). The receptor linked JAKs are stimulated via ligands which undergo reciprocal phosphorylation, this creates the docking sites for cytoplasmic transcription factors, STATs. Before being transferred to the nucleus, the STATs present in the cytoplasm undergo phosphorylation followed by dimerization. An essential part of STAT dimerization and DNA binding is tyrosine phosphorylation. Hence, JAK-STAT signaling pathways precisely translate extracellular signals into transcriptional responses. For instance, the interaction between IL-6 family members and the receptor's plasma membrane initiates the activation of JAK-STAT proteins. Following activation, STAT proteins are translocated to the nucleus, where they bind to specific target gene promoter regions, thereby exerting regulatory control over the transcription of inflammatory genes (Boengler et al., 2008).

Proinflammatory cytokines are mostly generated by activated macrophages and are associated with the escalation of inflammatory response (Zhang & An, 2007). Important proinflammatory cytokines are interleukin-1 (IL-1), IL-6 as well as tumor necrosis factor-α (TNF-α). IL-1 family has eleven members i.e., IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-37, the IL-1 receptor antagonist (IL-1Ra), IL-36Ra and IL-1Hy2 (Boraschi et al., 2011). From these, IL-1β is a potential proinflammatory cytokine that is recognized as an endogenous pyrogen. IL-1β is liberated by monocytes as well as macrophages and non-immune cells in response to infection, injury, inflammation and invasion. IL-1β expression is increased following the damage in the central nervous system and peripheral nerve. It also elevates the manufacturing of prostaglandin E2 and substance P in glial and neuronal cells (Turner et al., 2014). Whereas, the IL-6 family belongs to pleiotropic cytokines which contain members of IL-6 as well as IL-11. Various cells express IL-6 i.e., T-cells, mononuclear phagocytes, B-cells, fibroblasts, liver cells, bone marrow cells, keratinocytes and endothelial cells. IL-6 plays a critical role in haematopoiesis, maturation of B-cells for producing antibodies, activation of T-cells, control of Th2 (T helper 2) and Treg phenotypes, activation and control of neuronal neuropeptides expression and also in protein secretions by the liver [coordinated with IL-1 (Smith & Maizels, 2014)]. Furthermore, intrathecal infusion of IL-6 triggers thermal hyperalgesia as well as tactile allodynia in nerve-injured and intact rats, correspondingly (Zhang & An, 2007). TNF-α is a member of the TNF superfamily of type II transmembrane proteins. There are thirty receptors and nineteen ligands that are associated with TNF-α. These receptors and ligands facilitate the functionality of TNF-α in cellular immunity, inflammation, apoptosis and differentiation. Macrophages are the primary source of TNF-α, while other sources include different cells such as T-cells, monocytes, mast cells, keratinocytes, neurons and fibroblasts (Lobito et al., 2011). TNF-α is fundamental in protection from viral, bacterial and parasitic infections. Furthermore, it activates B-cell proliferation as well as immunoglobin production and also prevents cardiac hypertrophy (Bradley, 2008).

Inflammation is regarded as one of the foremost causes of diseases. According to an estimation, fifteen percent of human cancers are linked to chronic inflammation (He & Karin, 2011). Chronic inflammation induced tissue damage has been seen in many organs and organ systems such as the pancreas, heart, kidney, brain, liver, lungs, gastrointestinal tract as well as reproductive system. Hypertension, dyslipidaemias, smoking, diabetes, excessive consumption of food and infections like influenza or genetic and autoimmune disorders including rheumatoid arthritis and lupus are some key risk factors involved in inflammation (Fig 1). The endothelial dysfunction induced due to inflammation is the main cause of the development of various chronic disorders linked with inflammation including renal damage, atherosclerosis and cardiovascular disorders, cancer and diabetes (Turner et al., 2014). Furthermore, inflammation is also involved in chronic renal injury, non-alcoholic fatty liver disease as well as neurodegeneration (Daiber et al., 2017).

APOPTOSIS

Apoptosis is a natural physiological process of programmed cell death that aids in the elimination of cells from the body that are unnecessary or that have suffered from irreversible damage (Boada-Romero et al., 2020). It is crucial in the development of embryos as well as in the tissue homeostasis of adults. It occurs in a programmed manner along with some constructional changes such as chromatin condensation, cytoplasmic membrane blabbing and cell contraction. Apoptotic malfunctioning contributes significantly to cancer pathogenesis and is recognized as a key player in most of the types of cancer (Bagheri-Mohammadi, 2021). Various studies have discussed the role of apoptosis in the autoimmune system and highlighted the significance of apoptosis in regulating the immune response and the development of B- and T-cells. It has a pivotal role in the protection against pathogens as well as the removal of tumor cells (Mita et al., 2006).

Apoptosis occurs via two pathways i.e., intrinsic (mitochondrial) or extrinsic (death receptor), depending upon the nature of the stimuli. These pathways are linked with one another and therefore, affect one another. During both pathways, the initial process is similar which comprises the activation of apical caspases i.e., caspase-9 and caspase-8.

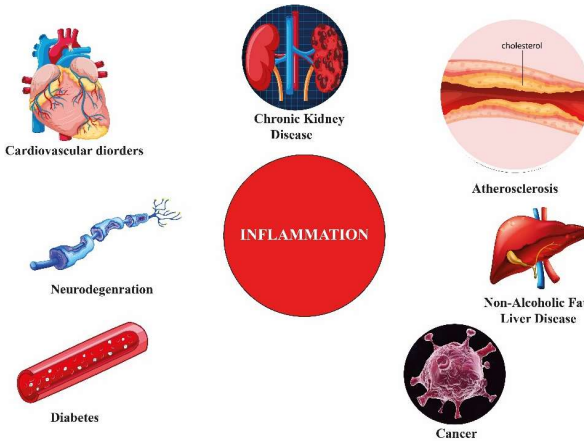

Fig 1. Illustration of inflammation induced damages and diseases in different parts of the body

These apical caspases further trigger the downstream effector caspases (caspase-3 and caspase-7), provoking the death of cells (Wu & Bratton, 2013). The extrinsic pathway is started by specific proteins found at the cell surface called death receptors (Gupta et al., 2023). When a death ligand binds with the death receptor the extrinsic pathway is instigated. The death receptors comprise TNF receptor 1 (TNFR1), Fas as well as their ligands, i.e., TNF and Fas ligands, respectively. When death receptors bind with TNF-related apoptosis initiating ligand (TRAIL or Apo2L), the extrinsic pathway is stimulated. This binding reaction then forms a death-instigating signaling complex. The extrinsic pathway is also activated when Fas ligand binds with cell surface bound Fas receptors. This forms a Fas-associated death domain (FADD) which stimulates a series of reactions within the cell leading to apoptosis. These pro-apoptotic receptors of cell death contain a protein-protein interaction domain which is regarded as the death domain. During the terminal step of the extrinsic pathway, the caspases self-amplify activation of one another in the 'caspase cascade' (Jan, 2019).

The intrinsic pathway is activated independently in cells. The situations leading to the activation of intrinsic pathway are DNA injury, collection of misfolded or unfolded proteins, deficiency of factors needed for survival, hormones, cytokines, and growth factors, hypoxia as well as ROS. The forces initiating the intrinsic route can be produced from outside or inside the cell i.e., OS, chemotherapeutic agents and exposure to radiation (Aghaei-Zarch et al., 2023). These signals induce permeabilization of the outer membrane of mitochondria due to the activation of Bcl-2, a proapoptotic protein. The permeabilization enables the liberation of various proapoptotic factors, in particular, cytochrome c, from the intermembrane space of mitochondria into the cytoplasm of the cell, where they escalate the death of the cell (Wu & Bratton, 2013). The cytochrome c in the cytoplasm facilitates the development of the caspase-3 enzyme. When caspase-3 successfully initiates the destruction of cell causes apoptosis, caspase-9 is activated by apoptosome, a seven spoke ring shaped structure assembled by multiple proteins (Rosier et al., 2020). Antiapoptotic proteins such as Bcl-2, Bcl-XL, BCL-2-A1 try to reduce the activity of proapoptotic proteins. The Bcl-2 protein regulates the sensitivity and resistance to apoptosis. Dysregulation in the function of these proteins can consequently cause the formation of multiple tumors in humans, therefore, these proteins are considered as potential targets in drug discovery (Gupta et al., 2023).

Caspases (Cysteine-dependent aspartate specific proteases) are proteins that are able to specifically recognize and cleave the specific substrates. They are considered as the promoters of cell death via apoptosis. A nucleophilic cysteine is present in the active site of caspase which targets the aspartic acid residue of other protein and cleave that protein (Galluzzi et al., 2018). Caspases are categorized into three functional groups i.e., initiator caspases, executioner caspases and inflammatory caspases. These types of caspases are discussed in Table 2.

Billions of cells die in our body on daily basis, these cells must be immediately eliminated from our body to save ourselves from any undesirable immune response. Therefore, the cells have adapted apoptosis to kill and eliminate the undesired cells in a programmed manner (Boada-Romero et al., 2020). Apoptosis is a homeostatic process of maintaining the population of cells in tissues during development and aging. It is a critical homeostatic process due to its capability to regulate the number of cells either by direct deletion or via suicide. It also influences the homeostasis of the cell, tissue and organism due to its effect on other cells. Additionally, it is involved in the phagocytic removal of dead bodies of cells. However, the disruption in apoptotic process may induce various diseased conditions such as autoimmune disorders, neurodegenerative diseases and various types of cancer (Kabel et al., 2016). Excessive apoptosis due to any sort of mutation or DNA damage can contribute to cancer, Alzheimer's disease, Parkinson's disease as well as stroke (Paquet et al., 2018).

CROSSROADS OF OXIDATIVE STRESS, INFLAMMATION AND APOPTOSIS

Oxidative stress inflammation and apoptosis are interlinked with each other, where one process can trigger and regulate the other processes. OS is induced by the excessive amount of ROS, which can be produced in various parts of the cells. Out of these, mitochondria are the primary generator of ROS, as they generate approximately 90% of the cellular ROS produced under normal physiologic situations (Tirichen et al., 2021). As oxidative phosphorylation (a process in which molecular oxygen is reduced to water) occurs inside the mitochondria, so, it produces excessive ROS. The electron can be lost from the electron transport chain in mitochondria bringing about the reduction of oxygen to O-2 (Bardaweel et al., 2018). If the generation of ROS exceeds the capacity of the cell to restore redox homeostasis, it can have harmful effects on the structure and function of the cell, leading to OS. OS has been linked with multiple diseases, disorders and pathologies (Hoffmann & Griffiths, 2018).

OS has been reported to release pro-inflammatory cytokines through NF-κB and MAPK signaling pathways, which provides evidence of its link with inflammation. During OS, the degradation of IκB (Inhibitor of κB) occurs, thereby releasing NF-κB which then moves into the nucleus and

Table 2. Types of caspases and their role in apoptosis

Caspase Type	Function	References
Initiator caspases	Caspase-2, -9, -8 and -10 are initiator caspases. These regulate the link with proximal molecules that initiate apoptosis. They are zymogens and possess long pro-domains that facilitate their interaction with specific signaling complexes.	Sahoo et al., 2023
Executor caspases	These are activated by initiator caspases. They carry forward the apoptosis and cut various cellular components and proteins into peptides and amino acids. Caspase-3, -7 and -6 are executor caspases.	Kumari et al., 2023
Inflammatory caspases	They play a role in inflammation. Caspase-1, -5, -4, 13, -11, 12 and -14 are inflammatory caspases. These caspases are found to increase inflammation by producing proinflammatory cytokines.	Akhtar & Sah, 2020

controls the transcription of its target genes (Huang et al., 2010). Furthermore, OH, HOCl and O_2 reactive species have been reported to instigate nuclear translocation and NF-κB activation. In vivo and in vitro research has revealed that ROS activates NF-κB, which in turn stimulates proinflammatory cytokines, leading to pulmonary injury and fibrosis (Monteiller et al., 2007). Moreover, OS is also linked with apoptosis. It has been revealed in various studies that, ROS disrupt the permeability of mitochondrial membrane which results in the release of apoptotic markers i.e., Bax, caspase-3 and cytochrome c, in the cytoplasm. These apoptotic markers ultimately trigger the mitochondrial apoptotic pathway. Furthermore, this event also reduces the level of Bcl-2, degrades mitochondrial DNA and disturbs ATP formation process in an oxidative phosphorylation system (Bertero & Maack, 2018).

CONCLUSION

In conclusion, OS, inflammation and apoptosis are linked closely with each other. OS can trigger both inflammation and apoptosis which subsequently leads to various unwanted anomalies. Although inflammation and apoptosis are a part of the immune system, but their uncontrolled process can be harmful. Various studies have reported that if we can target these pathways, we can tackle many fatal diseases. However, it is important to note that there is a dire need of further studies to fully understand and develop the therapeutic strategies to target these molecular pathways.

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