PERSPECTIVE

Molecular mechanisms of oxidative stress in stroke and cancer

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ABSTRACT

Oxidative pressure is a quiet member in all ongoing moderate pathology and degenerative issues. Neurodegeneration and mental hindrance are brought about by expanded imbalanced oxidative pressure and down-controlled normal enemy of oxidant battle systems. Malignant growth is the final product of cell glitch and the enactment of cancer explicit qualities, which are controlled by explicit geneomolecular pathways. Intense stroke is the pathology of oxidative pressure and a diminishing in the body's fighting safeguard components. Oxidative pressure, which results from an unevenness among oxidative and antioxidative exercises in cells, has been connected to the etiology of various persistent degenerative infections, including malignant growth and stroke. The destructive impacts of ROS and their job in sore movement after disease and ischaemic stroke are obvious; nonetheless, the restorative handiness of enemies of oxidants in this situation stays questionable. In this audit, we have summed up the intense atomic systems which assume an imperative part through initiation of different pathways and related progressed designated therapeutics to battle disease and stroke like constant pathologies.

Key word: *Anti-oxidants; Autophagy; Cancer; Stroke; Oxidative stress*

INTRODUCTION

The current definition of Oxidative Stress (OS) has progressed from the basic concept of "oxidant-antioxidant imbalance" to "an imbalance between pro-oxidants and antioxidants with associated redox circuitry disturbance and macromolecular damage" [1]. This picture blends a hierarchical redox circuitry system with a systems biology idea based on redox nodes and potentials [1]. Reactive Oxygen Species (ROS), reactive nitrogen species (RNS), Reactive Lipid Species (RLS), and free radicals are all produced in pathological OS [2]. ROS and RNS are partially reduced oxygen and nitrogen metabolites with a high reactivity and oxidising capacity. Free radicals such as Superoxide Radicals (O2), Hydroxyl Radicals (OH), and nitric oxide radicals make up ROS and RNS (NO). Normal cells create modest levels of ROS, which allows for cellular signalling and long-term homoeostasis, whereas aberrant cells (such as cancer cells) produce higher levels of ROS, which has negative consequences. An increase in NO synthesis paired with an increase in ROS production causes nitro-oxidative stress [2]. ROS are produced by the NOX family, which includes xanthine oxidase/xanthine dehydrogenase (XO/XDH), Myeloperoxidase (MPO), cytochrome P450s, Nitric Oxide (NO) Synthases (NOSs), and phospholipase A2. Furthermore, ROS sources such as mitochondria, endoplasmic reticulum, and peroxisomes contribute to oxidative stress. The majority of ROS is produced in mitochondria by Oxidative Phosphorylation (OXPHOS) when reducing oxygen via the electron transport chain of the inner mitochondrial membrane [3].

Furthermore, particular plasma membrane oxidases produce ROS in response to growth factors and cytokines, which act as secondary messengers for specific signalling pathways as well as regulatory molecules for gene expression. Protein phosphorylation, transcription factor activation, apoptosis, and immunity are all affected by the amount of Reactive Oxygen Species (ROS) in the cell.

Antioxidant enzymes in cells act as a defence system, keeping ROS at physiologically appropriate levels. The malfunction of these enzymes, which convert free radicals into more stable, less damaging chemicals, can result in OS. ROS scavengers include endogenous antioxidant enzymes (Superoxide Dismutase (SOD), catalase, and Glutathione Peroxidase (GPX)) as well as exogenous non-enzymatic substances (vitamins, melatonin, and glutathione) (SOD converts O2 to H2O2, catalase oxidises H2O2 to produce H2O and O2, GPX decomposes H2O2 and Lipid Hydroperoxide (LOOH), and the thioredoxin reduction cycle reduces H2O2 to produce H2O, as well as exogenous

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detoxification by glutathione transferase [4]. ROS buildup oxidises sensitive biomolecules like cellular proteins, membrane lipids, and nucleic acids, resulting in cellular damage and impaired cell functionin. Increased ROS levels, such as those seen in inappropriate cellular compartments or during oxidative activities, can contribute to the development of a variety of chronic degenerative illnesses by damaging bio macromolecules.

The most active time for biomolecule oxidation is mitosis. Prolonged mitotic arrest increases the generation of Reactive Oxygen Species (ROS) and the frequency of oxidatively damaged proteins and nucleotides such as cysteine-sulfenic-acid-proteins and 8-oxoguanine. High levels of Reactive Oxygen Species (ROS) in both G2 and mitosis are connected to oxidative damage to proteins and nucleotides in mitotic cells, which inactivates Cdc14B phosphatase and activates Cyclin-Dependent Kinase 1 (Cdk1) to enhance mitotic entry and tumour growth. Cancer cells, on the other hand, rely on ROS absorbers more than non-cancer cells and are more sensitive to oxidatively damaged macromolecules. A minor rise in ROS levels appears to accelerate cancer cell development by activating growth signalling cascades via phosphatases and limiting growth predominantly through oxidation of catalytic cysteine residues, providing cancer cells with chemotherapy-resistant stress [5].

The primary drivers of tumour cell proliferation, growth, and survival are mitogenic signalling cascades. Negative feedback loop controllers, including as MAPK/ERK1/2, PI3K/AKT/mTOR, and PKD, are oxidised by ROS and influence long-term cell survival and proliferation through a variety of pathways. ROS also inhibit Foxo, Bim, Bad, Bax, p53, PTEN, and PTP1B, as well as the JNK pathway, which are downstream tumor-suppressive targets. Through ERK1/2 activation and the pro-survival PI3K/AKT signalling pathways, ROS and H2O2 have been associated to enhanced proliferation.

Toxic quantities of ROS promote inflammation by changing the Tumour Microenvironment Dramatically (TME). Inflammation promotes cancer start and progression by vascularization and TME remodelling, which is a masterstroke for tumour cell survival. DNA damage, as well as the activation of growth factors, cytokines, and cell survival genes, is promoted by ROS and RNS-rich inflammatory cells [6]. G-MDSCs are granulocytic myeloid cell-derived suppressor cells that suppress CD8+ T-cells and contribute to tumour growth and progression by creating Reactive Oxygen Species (ROS). Furthermore, stimulating oxidant-producing enzymes including NOX, XO, iNOS, and MPO, which enhance nitration, oxidation, and mutation, produces ROS/RNS in these cells.

The metabolisms of cancer cells have adapted to meet the increased energy needs imposed by their rapid growth and proliferation. OS causes I enhanced lipid metabolism, (ii) changed sulfur-containing amino acid metabolism, and (iii) reprogrammed sugar metabolisms, among other reprogrammed metabolisms in cancer [7]. As a result, cancer cells produce more ROS than normal cells in order to maintain normal subcellular activities like signal transmission and gene expression. Increased mitochondrial ROS levels cause cancer through mutation of mtDNA, disruption of the electron transport chain, and redox signalling.

Ischemia-induced neuro-apoptosis is triggered by aberrant pro- and anti-apoptotic signals. H2O2 or superoxides are key mediators of intrinsic and extrinsic apoptotic cell death in cerebral ischaemia and reperfusion. H2O2 can also activate nuclear transcription factors including NF-kB, AP-1, and p53, causing death proteins to be expressed or survival protein inhibitors to be produced. In animal models of cerebral ischaemia, there is accumulating evidence that p53 contributes to neuronal death. ROS have been linked to apoptosis by inducing single-strand DNA breaks, which activate DNA-dependent kinases and the ATM protein, resulting in the activation, stabilisation, and up-regulation of p53, implying a key involvement in neuronal loss in the penumbra [7,8].

Through phosphorylation, OS can moderately alter p53-dependent transcription, translocation, and pro-survival AKT signalling. TLR4-mediated apoptosis triggered by ischaemia-reperfusion damage also involves NOX4 isoforms. As a result, mitochondrial malfunction and OS could affect neuronal death and survival after stroke and neurodegeneration.

During ischemic insult, an autophagy regulator protein and microtubule-associated protein 1 Light Chain 3 (LC3) was shown to be increased. An ischemic rat model revealed significant increases in Beclin 1 levels in pneumbric neurons and astrocytes. OS and enhanced ROS generation have been proven to be important autophagy stimulants during bouts of nutritional deficiency, hypoxia, ischaemia/reperfusion, and cellular stress. During cellular famine and nutritional deprivation, the PI3K/beclin-1 dependent pathway increases mitochondrial-derived H2O2.

Furthermore, ROS damages organelles and cytosolic proteins during reperfusion, as well as lipid peroxidation in the mitochondria, all of which speed up autophagy. Oxidised Low-Density Lipoproteins (ox-LDL) may activate autophagy by boosting the production of beclin-1, LOX-1, and Proline Oxidase (POX). Autophagosomes, it turns out, target antioxidant enzymes like catalase and SOD, causing an increase in Reactive Oxygen Species (ROS) and a positive autophagic feedback loop that leads to cell death. AMPK activity reduces after reperfusion, resulting in an increase in autophagic death and beclin-1 overexpression. It's crucial to understand redox signalling pathogenesis through the balance of autophagy, stress management, and cell death [8,9].

Balanced ROS production and removal via conserved detoxification processes including antioxidants such as glutathione peroxidase, SOD, and catalase, as well as the transcription factor Nrf2, keep a normal cell's redox homoeostasis. In contrast to normal conditions, oxidative stress results of an increase in pro-oxidants over antioxidants, as well as an increase in ineffective scavengers. In terms of cancer progression, the dualistic character and varied action of ROS in stage-specific tumour cells has lately been highlighted. Moderate ROS levels in a precancerous cell produce oncogenesis, tumour proliferation, metastasis, and survival at an early stage. In a tumour cell, elevated ROS levels trigger an adaptation reaction that restores redox balance, whereas in malignant cells, elevated ROS levels above the lethal threshold cause cytotoxicity, apoptosis, and senescence [9,10].

CONCLUSION

In the scientific world, oxidative stress has gotten a lot of attention as a common mediator in the pathophysiology of many human illnesses. Oxidative stress causes an imbalance between free radicals and antioxidants. OS is responsible for cancer and stroke disease events by activating various signalling cascades and mediating key diseases. Although our understanding of the molecular mechanisms by which ROS and antioxidants interact directly with important signalling

molecules to activate signalling in a variety of cellular functions is far from complete, a closer examination of the molecular mechanisms by which ROS and antioxidants interact directly with important signalling molecules to activate signalling in a variety of cellular functions is necessary. More mechanistic investigations on the biology of ROS and antioxidants in diseases, as well as the creation of effective ROS-targeted disease treatment methods by antioxidants are being pursued by researchers. Finally, while the effectiveness of combining anti-oxidant protection with known anticancer medicines, thrombolytics, and novel neuroprotectants has yet to be proven, it has the potential to be a significant way to improve outcomes following these catastrophic and debilitating oncogenic and ischaemic events.

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