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Redox molecules in health and disease-then and now

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Abstract

Redox biology can be defined as the total sum of all oxidation and reduction reactions occurring in a healthy cell. Cellular homeostasis is maintained by a group of molecules viz. NADP: NADPH; GSH: GSSG; GSH dependent enzymes, hypoxia inducible factor; nuclear factorKB; MAP kinases and aryl hydrocarbon receptors. However, several stimuli/ factors like drugs, chemicals, pathogens, xenobiotics and diseases can disrupt the redox control over the cell leading to oxidative or nitrosative stress. Functions of redox molecules are governed through a redox code.

Integrated groups of GSTome, seleno-cysteine-proteome and redox couples constitute a redoxosome, and their functions are regulated by a couple of redox switches. These redox switches determine cellular homeostasis and are controlled by redox check points like GSH, TRx, caspase-9 and 3, MLKL, GSDMD, GPx and MOMP. It is assumed that the nature of stimulus, cell type and hierarchy of inter-organelle cross talk(s) might result into different modalities of cell death under the shared network of redox signaling pathways. Recently, a few redox responsive systems have been developed. These include a high concentration of ROS and glutathione that are characterstic of tumor microenvironment (TME). Redox responsive nanoparticles include GSH responsive disulfide, ROS responsive thioketal, arylboronic ester, bilirubin as well as GSH/ROS dual responsive diselenide and dicarbonyl thioethers. Redox switches offer answers to many biological paradigms.

Present review is an attempt to summarize the available information on molecular players of redox biology. Further, the role of redox system in human diseases viz. ageing, fibrosis, cancer, cardiovascular and neuro-degenerative diseases has also been discussed. Benchmark investigations made in redox biology may be translated into a new discipline of redox medicine in near future.

Key words: Free radicals, Human diseases, Oxidative stress, Peroxy redoxins, Redox couples, Thioredoxins

Introduction

Molecular fabric of a cell is woven by certain molecules. A phenotype selects these molecules through a continued process of evolution. These components function inter-dependently with other components to maintain cellular homeostasis employing biological oxidation-reduction reactions. These reactions constitute a system known as redox system, comprising a group of reactions that are interactive, cooperative, specific and kinetic (Yoshida and Hisabori, 2016). These components can be grouped as redox couples viz. NADP: NADPH., GSH: GSSG., antioxidant proteins i.e. GSH dependent enzymes, thioredoxins (TRX) and peroxiredoxins (PRDXs) and free radicals i.e. superoxide anion ($O_2^{\cdot-}$.), hydrogen peroxide (H_2O_2), nitric oxide (.NO) and hydroxyl (.OH) radicals (Forman *et al*., 2010). Additionally, the major endogenous sources of reactive oxygen species (ROS) for redox signalling include NADPH oxidases (NOXs), dual oxidases (DUOXs), nitric oxide synthetases and the mitochondrial electron transport chain (ETC). The downstream regulators of redox system include transcription factors viz. hypoxia inducible factor 1- alpha (HIF1α), aryl hydrocarbon receptor (Ahr) and nuclear factorkB (NFk-B), MAP kinases and GTPases (Hawkins *et al*., 2016).

Redox reactions contribute to fundamental processes of cellular homeostasis such as redox regulation, redox signalling and redox control. Intriguingly, when disturbed they can induce cell injury/death due to over-production of strong oxidants, and may also lead to diseases like cancer, AIDS, rheumatoid diseases, Parkinsonism, Alzheimers' disease, ischemia and reperfusion. Several drugs/ xenobiotics are also known to manifest their toxicity by generating ROS. They penetrate the

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mitochondria and interact with one or more electron transport chain complexes in the inner mitochondrial membrane thus blocking the normal electron flow and consequent increase in the production of ROS. Repeated oxidation and reduction of xenobiotics may result into diverse toxicological consequences (Rana, 2021). While maintenance of redox steady state in the cell is essential for health, its disruption can manifest into disease. Oxidative stress is an example of deviation from redox steady state (Sies, 2015).

Cellular metabolism is also governed by redox processes. Fine tuning of reaction cascades and/or direct involvement in signalling pathways involves molecular switches and redox active metabolites viz. H_2O_2, NO and H_2S. Enzymes and micronutrients too, play a major role in redox biology (Sies, 1993). Present review summarizes benchmark discoveries that have revolutionized our understanding on the role of redox molecules in health and disease. It addresses the significance of redox molecules/systems i.e. free radicals, oxidative stress, nitrosative stress, antioxidant enzymes, GSTome, redoxosome, selenocystome, NFkB, MAP kinases, hypoxia inducible factor and aryl hydrocarbon receptors in cell death with suitable examples. Emerging concepts of redox code and redox sensors in health and disease have also been discussed.

Molecular components of redox system: Different components of redox system can be broadly classified into following five categories. Small molecule redox couples (NADPH:NADP+, NADH:NAD+; GSH:GSSG); Antioxidant proteins such as peroxyredoxins (PRDXs), thioredoxins (TRXs), and GSH utilizing enzymes; small metabolites derived from oxygen such as superoxide (O_2^{-}.), hydrogen peroxide (H_2O_2) and nitric oxide (.NO); Hydrogen sulphide (H_2S) and cysteine are small molecule effectors that participate in redox processes but do not use oxygen (Auclair *et al*., 2013). Further, these redox players may have several integrated components that exhibit spatio-temporal diversity. The major endogenous sources of ROS for redox signalling include NADPH oxidases (NOXs), dual oxidases (DUOXs), nitric oxide synthetase and the mitochondrial electron transport chain and transcription factors such as nuclear factor erythroid 2-related factor (NRF2), hypoxia inducible factor –alpha (HIF1α), aryl hydrocarbon receptor and nuclear factor NF-kB, kinases such as MAP kinases (MAPKs) and GTPases (Hawkins *et al*., 2016).

The NAD and NADP systems along with GSH/GSSG systems are central to the redox code. The NAD system uses powerful dehydrogenases involved in the metabolism of biomolecules with covalent bonds of C, O, S, N and H. The ratio of free NADH and NAD is in equilibrium with the reduced and oxidized substrates of major cellular dehydrogenases (Brigelius-Flohe and Flohe, 2011). Redox chemistry of thiols involves both one electron and two electron transfer reactions of cysteine (cys/cystine (CYSs), GSH/GSSG, protein thiols and oxidized forms and protein bound cysteines / disulfides. Selenocysteine also play an important role in controlling the redox functions of proteins (Jacob *et al.,* 2003). In addition, hemoproteins, cuproproteins, iron-sulfur proteins, flavoproteins, pteroproteins, molybdoproteins also act as the components of an interacting redox system.

Redox code: Redox code, as defined by Jones and Sies (2015) is a set of principles that define the positioning of nicotinamide adenine nucleotide (NAD, NADP) and thiol/disulfide (GSH/GSSG) and other redox molecules as well as thiol redox proteome in space and time in a biological system. It might have evolved with the genetic code, histone code and epigenetic code in the molecular logic of life. It applies to the redox organization of cells and tissues of all organisms. Redox code might have evolved in muticellular organisms with the increase in atmospheric oxygen about 600 million years ago (Rytkonen and Storz, 2011). Four principles mainly govern the redox code.

The first principle involves the use of reversible electron accepting and donating properties of NAD and NADP. The second principle suggests that metabolism is linked to protein structure through kinetically controlled redox switches in the proteome, which determine tertiary structure, macromolecular interactions and trafficking. R The third principle suggests that activation/deactivation cycles of redox metabolism, especially involving H_2O_2 support spatio-temporal change in differentiation and life cycles of cells and organisms. The fourth principle suggests that redox networks do form an adaptive system to respond to the environmental conditions, from micro-compartments to sub-cellular systems and to the cells and tissue organization. This adaptive network is required to maintain cellular health in a changing environment and if functionally impaired, will contribute to disease and organism failure.

Redix signaling: Kamata and Hirata (1999) defined redox signalling as the deployment of ROS in cell signalling. ROS can oxidize cellular proteins to allosterically change their confirmation and function (Tan and Suda, 2017). H_2O_2 functions as a secondary messenger for intracellular signalling through cysteine based modifications while other ROS are more associated with cell injury (Rana, 2021). Redox sensors recognize ROS levels and trigger antioxidant responses, gene transcription, differentiation, cell growth, proliferation and apoptosis (Rana, 2007). Redox sensors include members of the fork head box O (FOXO), hypoxia inducible factors (HIFs), kelch-like ECH-associated protein 1 (KEAP 1) with nuclear factor erythoid 2 (NRF2) and the p53 tumor suppressor. The direct or indirect effects of ROS on these redox molecules have been precisely reviewed (Lee **et al**., 2019). Further, enzyme families of kinases and phosphatases do modulate redox systems (Fig.1).

A cross talk between different sources of ROS does facilitate redox signalling. In a cell, ROS are produced by different compartments. Interactions amongst their sources stimulate each other in a feedback mechanism that further complicates oxidative stress and redox signaling network. ROS released from one organelle triggers ROS production by another organelle

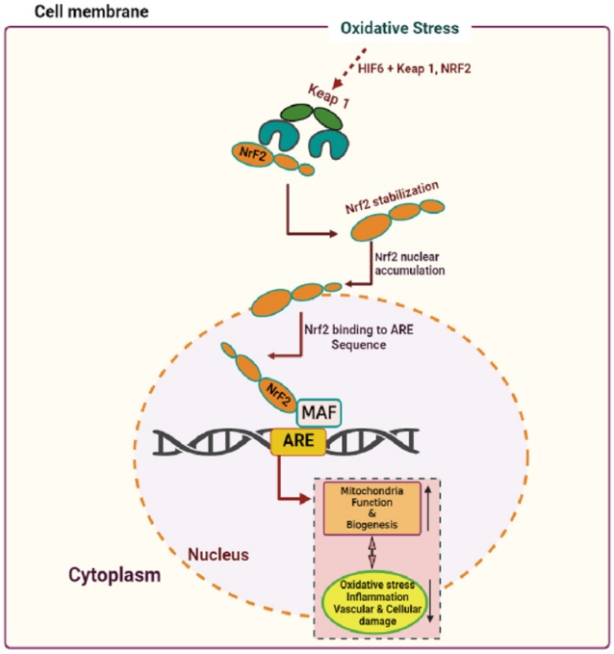

Fig. 1: The figure shows regulation of NrF2 under normal and stressed conditions. Ubiquitination maintains a low level of adaptive protein Keap1 under normal conditions. Stress releases Nrf2 from Keap 1 and translocates it to nucleus where it binds to ARE. Nrf2- ARE pathway triggers the transcription of multiple genes involved in the expression of antioxidants, phase-I and phase-II enzymes, glutathione and ATP synthesis.

(Schulz *et al.*, 2014). Two different mechanisms have been suggested form TROS enhancement. In both pathways, the opening of the mTATP-sensitive potassium channels (mitoKATP) seems to play an important role (Schulz *et al.,* 2014). Mitochondrial ROS released into the cytoplasm activates protein kinase C (PKC) leading to NOx ensemble. Inhibition of NOx enzymes and consequent prevention of mT dysfunction induced by angiotensin II, conforms this interaction (Dilkalov, 2011).

Free radicals-the major players of redox system: Only in the beginning of last century, Moses Gomberg, a chemistry professor at university of Michigan discovered an organic free radical known as tri phenyl methyl $(C_6H_5)_3C$ radical (Gomberg,1900). The scientific community recognized the importance of free radicals in 1929, when Friedrich Paneth and William Hofeditz produced a methyl free radical (CH_3) by pyrolysis of tetramethyl lead adopting the system used by Bonhoeffer in 1924. In 1933, Morris Kharasch and his student Frank Mayo discovered the "peroxidase effect". Today, free radicals are used in the synthesis of polymers that are used to produce paints, adhesives, films, carpeting and piping etc.

Role of free radicals in biological systems: ROS have been classified into two groups: free oxygen radicals and non- radical ROS. Free oxygen radicals include superoxide ($O_{2^{\cdot}}^{-}$), hydroxyl radical (.OH), nitric oxide (NO.), organic radicals(R*), peroxyl radicals (ROO*), alkoxy radicals (RO*), thiyl radicals (RS*), sulfonyl radicals (ROS*), thiylperoxy radicals (RSOO*), and disulfides (RSSR). Non radical ROS include hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), ozone (O_3), organic hydroperoxides (ROOH), hypochloride (HOCl), peroxynitrile ($ONO\_$), nitrosoperoxycarbonate anion ($O{=}NOOCO_2^-$), nitrocarbonate anion ($O_2NOCO_2\_$), dinitrogen dioxide (N_2O_2), nitronium (NO^+) and highly reactive lipid-orcarbohydrate derived carbonyl compounds). Amongst them, superoxide, hydrogen peroxide and hydroxyl radicals are best studied ROS in health and disease (Liou and Storz, 2010). Although radical mediated processes occur normally in cellular system (Pryor, 1976), their involvement in aetiology of several diseases and experimentally induced cell injury was also recognized (Recknagel *et al.*, 1989). Tappel (1978) defined Lipid peroxidation as deterioration of membranous polyunsaturated fatty acids found to be responsible for cell injury induced by chlorinated methanes). Many diseases have been attributed to lipid peroxidation (LPO) (Farber, 1982).

Superoxide anion: Superoxide anion is considered as primary oxygen species whose generation can lead to the formation of more reactive secondary species (Fee, 1982). The discovery of superoxide anion is linked with the discovery of superoxide dismutase (SOD) by McCord and Fridovich (1969) in bovine erythrocytes. SOD is reported as a scavenger of superoxide anion. These researches propounded the super oxide theory that suggested that oxygen toxicity was caused by superoxide radical). Superoxide exists naturally as a small anion which is more prone to donate its electrons rather than to accept a second electron from a biological molecule. Thus role of superoxide in cellular toxicity remained controversial for some time (Sawyer and Valentine, 1981).

Hydrogen peroxide: Hydrogen peroxide and hypochlorous acid (HOCl) are also known as powerful oxidizing agents that too participate in free radical mediated reactions. Mitochondrial (mT) production of H_2O_2 was reported by Jensen (1966) in bovine heart. Soon it was demonstrated for the first time that under aerobic conditions, H_2O_2 could be generated by the mitochondria of pigeon heart in the presence of succinate (Loschen *et al.*, 1971). H_2O_2 formation in later researches was linked with mono-oxygenation of xenobiotics since pretreatment of animals with phenobarbitol increased the formation of H_2O_2 (Hildebrandt and Roots, 1975). NADPH dependent chain of microsomes can also generate, H_2O_2 and superoxide radicals (Aust *et al.*, 1972). Peroxidases also contain oxidases that reduce oxygen to hydrogen peroxide at the expense of an enzyme catalase that reduces H_2O_2 to water (de Duve, 1965).

Reactive nitrogen species (RNS): Nitric oxide (NO) is considered as a primary RNS. The discovery of NO as a biological molecule is linked with vasodilation, cyclic guanosine monophosphate (GMP) and endothelial derived relaxing factor (EDRF). In 1990, an enzyme nitric oxide synthetase (NOS) responsible for NO synthesis was purified from rat cerebellum

(Bredt and Snyder, 1990). After the discovery of NO, it's reactions with O_2-. was also studied. Beckman *et al.* (1990) suggested that the reaction product of superoxide and nitric oxide was a peroxynitrite which decomposes when protonated to form hydroxyl radical and nitrogen dioxide.

$$O_2 + NO \longrightarrow ONOO\text{-}=$$

$$ONOO^- + H^+ \longrightarrow ONOOH \longrightarrow NO_2 + OH$$

Furthermore, peroxinitrite and its protonated form peroxynitrous acid (ONOOH) can cause oxidative modifications through one or two oxidation processes. Only a few chemical groups can directly react with peroxynitrite *viz.* thiols (Radi *et al.,* 1991) and iron sulphur centres (Castro *et al.,* 1994). Peroxinitrite decomposition produces highly reactive OH radicals as well as nitrogen dioxide which are strong oxidants with immense cytotoxic potential (Patel and Block, 1986). Reaction between carbon dioxide and peroxynitrite also produces nitrogen dioxide and a radical anion carbonate (CO_3.-).

$$ONOO^- + CO_2 \longrightarrow CO_3^{\cdot-} + NO_2$$

Carbonate radical is more selective than hydroxyl radical and can initiate many damaging reactions commonly attributed to hydroxyl radicals in biological systems (Goldstein and Merenyi, 2008).

NAD(H) and NADP(H) redox couples: $NADP^+$ and NADPH are involved in maintaining redox balance, synthesis of fatty acids and nucleic acids (Ying, 2008). These redox couples are thus essential for maintaining a large array of biological processes viz. energy metabolism, mitochondrial function, gene expression and signalling pathways (Yang, 2016). Fessel and Oldham (2018) defined this couple as redox currency of the cell. Intriguingly, the loss of redox homeostasis between these couples has been linked to a variety of diseases such as cardiovascular diseases, neurodegenerative diseases, cancer and ageing (Xiao *et al*., 2018).The intracellular distribution of NAD/NADH and NADP/NADPH redox couples is highly compartmentalized due to specific localization of biosynthetic enzymes and bioavailability of NAD precursors.

Oxidative stress: Mechanisms of oxygen toxicity have been widely debated. Despite being a free radical, O_2 does not exhibit high reactivity. However, singlet oxygen is much more reactive than the ground state oxygen (Taube, 1965). The univalent pathway of oxygen reduction requires that intermediates of oxygen reduction be generated which are reactive and can damage biological molecules (Halliwell and Gutteridege, 1985).

The term oxidative stress was first introduced by Paniker *et al.* (1970). Sies (1985) introduced and defined the term oxidative stress as the imbalance between pro-oxidants and antioxidants in favour of the former. This was the original definition of oxidative stress that was updated as "an imbalance between oxidant and antioxidants in favour of the oxidants leading to disruption of redox signalling and control and/or molecular damage (Sies, 2007)". He further identified oxidative stress to its subforms like nutritional oxidative stress, dietary oxidative stress, post prandial oxidative stress, physiological stress, photoxidative stress, radiation induced oxidative stress, nitrosative stress and reductive stress (Sies, 2007). Lushchak (2014) classified oxidative stress as basal oxidative stress, low intensity oxidative stress, intermediate intensity oxidative stress and high intensity oxidative stress. Role of oxidative stress in liver injury caused by environmental xenobiotics was reviewed by Rana (1997).

Nitrosative stress: Stress induced by reactive nitrogen species is defined as nitrostaive stress. Nitrosative and oxidative stress pathways overlap and reciprocate each other (Maes *et al*., 2011). The ONOO- can nitrate several biomolecules viz. proteins, lipids and DNA to generate 3-nitro -tyrosine (3-NT). Ohshima et al. (1990) detected 3-NT and 3-nitrophenyl acetic acid in human urine and proposed that 3-NT can be used as marker of endogenous protein nitration. In recent years, various studies have demonstrated that 3-NT is a specific biomarker of nitrosative stress (Zhang and Wei, 2013). Nitrostive stress has been closely associated with cardiovascular diseases. Fundamental mechanism of cell death caused by nitrosative stress has been recently discussed by Wang *et al*. (2021).

Glutathione system (GSTome): The GSH/GSSG couple plays acrucial role in two electron reduction of peroxides. GSH is a co-substate of GPxs for H_2O_2 removal. In this context two molecules of GSH donate two electrons to reduce H_2O_2 to water and are themselves oxidized to GSSG, which is recycled back to GSH by glutathione reductase (GR) using NADPH as electron donor. GSH is also involved in many other metabolic processes including ascorbate metabolism (Sohini and Rana, 2007). It maintains communication between cells through gap junctions (Barhoumi *et al.* 1993). It prevents the oxidation of protein SH groups and cross linking. GSH/GSSG is the major couple that controls redox status of the cell.GSH plays a major role as antioxidant. It can react with OH., HOCl, ONOO-, RO., RO_2., CO_3.-, NO_2., and carbon centred radicals. Rana *et al.* (2002) discussed its role in different pathological conditions and designated it as "*inevitable glutathione*".

Glutathione-S- transferase (GST) super family: Glutathione is involved in the metabolism of several xenobiotics. Many of them are metabolized by conjugation with GSH, catalyzed by glutathione-S-transferases.

$$RX + GSH \longrightarrow RSG + HX$$

Liver is especially rich in GST enzymes. GST family consists of three super families: the cytosolic, mitochondrial and microsomal-also known as membrane associated proteins in eicosanoid and glutathione metabolism (MAPEG) - proteins. GST super family is extremely diverse in amino acid sequence. Functions of many of them are still not known. Formerly, they were known as ligandins. GST activity in liver cytosol was first reported

by Eric Boyland *et al.* (1961) and Combes and Stakelum (1961). The pivotal role of GSTs in the protection of cells against carcinogens and electrophilic metabolites was elucidated by Boyland *et al.* (1969). The enzyme from rat liver was purified and characterized with overlapping substrate specificities in the laboratory of Mannerwick in 1975 (Askelof *et al.* (1975). Subsequently, GST from other major organs of rat was purified and it was found that "isoenzyme" distribution was different amongst tissues (Mannerwick *et al.,* 1983). Furthermore, isoenzymes in rat and mouse liver were found to be differently expressed in normal tissues and also responded differentially to inducers of drug and carcinogen metabolism (Guthenberg *et al.* 1980). Neoplastic transformations have shown major changes in GST expression, and also the role of enzyme in tumor- drug resistance has been suggested (Mannerwick *et al.* 1987).

Novel GSTs: The possibility of exon shuffling or other combination of gene sequences may contribute to the evolution of novel enzymes (Mannerwick, 1985). By the judicious choice of endonucleases, it was made possible to combine sequences derived from different GST sequences (Bjornestedt *et al.,* 1992). Several recombined GSTs were generated and found to be catalytically important. Thus it was demonstrated that different segments of primary structures can be joined to obtain multiple GST variants (Board and Mannerwick, 1991).

GSTs and ageing: Certain findings suggest that over expression of GSTs is associated with longevity. Transcriptome analysis of worm (*Caenorhabditis elegans*), fly (*Drosophila melanogaster*) and mice (*Mus musculus*) demonstrated that long lived strains of each species over expressed a limited number of genes of GSTome. The extended life time is explained by the fact that corresponding GSTs confer an elevated detoxication capacity towards toxic compounds produced by oxidative stress. Over expression of certain GSTs may have similar effects in humans. Lower levels of glutathione and GSTs in elderly individuals raise their susceptibility to degenerative diseases like Parkinson, Alzheimer disease, artherosclerosis, cataracts and diabetes (McElwee *et al.,* 2007). Role of GSTs in preventive medicine is more important than conjugation of xenobiotics.

Glutathione peroxidase: Glutathione peroxidase (GPx) is the general name given to an enzyme family with peroxidative activity whose main biological function is to protect the organism from oxidative damage. It was discovered in 1957 by Gordon C Mills. It was the first mammalian protein shown to incorporate selenium in the form of selenocysteine C into its catalytic site and was assumed to be associated with the antioxidant activity of selenium (Forstrom *et al.,* 1978). GPxs are well known for catalyzing the reduction of hydrogen peroxide and organic hydroperoxides, thus protecting the cells from oxidative damage. In humans, eight GPxs are known, five of which are seneocysteines and two contain cysteine instead of selecocysteine. GPx1 is the most abundant version, found in the cytoplasm of all mammalian tissues, whose preferred substrate is hydrogen peroxide. GPx4 has a strong preference for lipid hydroperoxides. It is expressed in all mammalian cells. GPx2 is an intestinal and extracellular enzyme, while GPx3 is abundant in plasma. Thus these isozymes differ in their tissue distribution and their substrate specificity for peroxide degradation (Brigelius-Flohe *et al.,* 2002).

Redox proteome: Redox proteome provides a distinct basis to link metabolism and structure through kinetically controlled redox switches. These molecular switches determine tertiary structure, molecular activity, macromolecular interactions and trafficking principally through alterations in thiol and disulfide structures (Kemp, 2008). Cellular Cys/CySS and GSH/GSSGare maintained at a substantially more reduced state than the extracellular counterparts. Like NAD and NADP systems, redox potential of a cell differs in subcellular compartments. Mitochondria are more negative (reducing) while endoplasmic reticulum is more positive (oxidizing) than cytosol. Human genome contains extensive number of Cys (>200,000) that contribute in redox organizational structure (Jones, 2008). It is assumed at present that evolution of cys proteome might have occurred along with the evolution of multicellular organisms, advanced O_2 sensing and H_2O_2 signalling systems (Miseta and Csutora, 2000).

Cysteine redoxome: Multiple properties of cysteines make them excellent and relatively specific redox sentinals due to their thiol side chain that can form seven stable oxidation states in vivo (Giles *et al.,* 2003). They are the rarest amino acids. Cysteine redoxome was defined by Thamsen and Jacob (2011) as the composite of all redox active cysteines that can integrate with many redox modules viz. ROS, redox couples, ROS producers and GSH linked enzymes (Kemp *et al.,* 2008). As cysteines are rare, buried and highly selected for specific functions in proteins, it is assumed that each cysteine could be considered as a unique sentinel tuned to a set of context specific factors forming one or more redox modules.

Selenoproteiome: Selenocysteine is the Se-analogue of cysteine having structure similar to cysteine, but with an atom of selenium that replaces the usual sulphur. Selenocysteine is present in several enzymes *viz.* glutathione peroxidases, thioredoxin reductases, formate dehydrogenases, glycine reductases, tetraiodothyronine 5'deiodinases, selenophosphate synthetase 2 andsome dehydrogenases. It occurs in all three domains of Life (Johansson *et al.,* 2005). As of 2021, 136 human proteins (in 37 families) are known to contain selenoproteins (Romagne *et al.,* 2014). Only a few of the 25 identified mammalian selenoproteins have so far been functionally characterized. Most of these selenoproteins exhibit enzymatic redox functions via SeC which confers them a catalytic or antioxidative activity. Cellular processes that require selenoproteins include biosynthesis of dNTPs for DNA, removal of damaging peroxides, reduction of oxidized proteins, membrane regulation of redox signalling, thyroid hormone metabolism, selenium transport and storage and protein folding. Selenoproteins can be divided in two groups. First group includes all thioredoxin reductases *viz.* Sel S, Sel R, Sel, O, and Sel I. The second group contains the remaining selenoproteins viz.

selenoprotein P, selenoprotein 15, selenoprotein N, selenoprotein W, selenoprotein R, selenoprotein M, selenophosphate synthetase 2, selenoprotein 5 and selenoprotein K. Thus, human diseases associated with selenium deficiency may be attributed to increased oxidative stress and alterations in redox signalling. Combined selenium and iodine deficiency leads to pathogenic condition named myxedematous cretinism (Kohrle *et al.,* 2005).

NFkB (Nuclear factor kappa-light chain enhancer of activated B cells): NF*k* B is a protein complex that controls transcription of DNA, cytokine production and cell survival. It is found in all animal cell types and is involved in cellular responses to free radicals, stress, heavy metals and ultraviolet radiation. Disturbed regulation of NF*k*B has been linked to cancer, inflammation and autoimmune diseases, ageing, atherosclerosis, pancreatitis and rheumatoid arthritis (Concetti and Wilson, 1981). It is the best responder to harmful cellular stimuli and oxidative stress. The NF*k*B protein is adimer of two subunits, named by their molecular mass, p50 and p65.The inactive form of NF*k*B is found in cytoplasm that is kept inactive by an inhibitor protein 1-*k*B. Uponstimulation 1-*k*B is phosphorylated, ubiquitinated and rapidly degraded. The free NF*k*B then rapidly translocates into the nucleus where it binds with DNA (Fig. 2).

Mitogen activated proteinkinases (MAPKs): These protein kinases phosphorylate their own dual serine and threonine residues (autophosphorylation), or those found on their substrates to activate or deactivate their target molecules. Thus they regulate important cellular processes such as proliferation, immune response, stress response and apoptosis. These kinases are ubiquitously expressed and evolutionary conserved in eukaryotes. The activation of MAPK cascade occurs in a module of consecutive phosphorylations, *i.e.,* after a previous stimulus, each MAPK is phosphorylated by anupstream MAPKs. A MAPK module comprises a MAP3K that activates a MAP2K which in turn activates MAPK (Peti and Page, 2013). Mammalian cells possess three MAPK pathways; the ERK1/2, the c-Jun N-terminal kinase 1, 2 and 3 and the p38MAPKα, β, γ, and δ pathways. JNK1/2/3 and p38 MAPK α, β, γ and δ are activated by cellular and environmental stresses in addition to pro-inflammatory stimuli (Kyriakis and Avruch, 2012). Reactive species can activate all three subfamilies of MAPK (Lee and Esselman, 2002). Addition of ONOO- to different cell types can activate all the three members of MAPK family (Klotz *et al.,* 2002). It has been hypothesized that under stress conditions, ERK activation leads cell survival whereas prolonged JNK activation leads to apoptosis/ cell death. A balance between ERK and JNK is essential for cell survival (Chu *et al.,* 2004).

Hypoxiainducible factor: Hypoxia inducible factor- 1 (HIF-1) was identified by Semenza in 1992. It activates transcription in response to hypoxia in all metazoan cells (Semenza, 2007).He established that absolute deficiency of HIF-1αcan lead to embryonic lethality with failure of circulatory system development. Partial deficiency can lead to impaired physiologic responses to hypoxia orischemia. HIF-1 binds to hypoxia response element (HSE) sequences essential for transcriptional activation of erythropoietin (EPO) gene in response to hypoxia (Semenza, 1991). It is established now that besides EPO, HIF-1 mediates transcriptional regulation of several hundred genes in response to hypoxia, which include genes coding for angiogenesis as well as those that control energy metabolism (Fig. 3). HIF- 1α genes have been found to be upregulated in majority of human cancers (Zhong *et al.,* 1999). HIF-1is also implicated in vascular morbidities associated with ageing, diabetes and pathogenesis of pulmonary hypertension (Semenza, 2005). Regulation of glucose/energy metabolism and redox homeostasis appears to be primordial function of HIF-1.

Thioredoxins (Trxs): Thioredoxins are ubiquitous proteins that play a vital role in several biological processes including redox signalling. In humans, thioredoxins are encoded by TXN and TXN2 genes. Mutation in these genes is lethal at four cell stage of the developing embryo. Thioredoxin is a 12-kD oxidoreductase protein. The primary function of TRx is a reduction of oxidized cysteine residues and the cleavage of disulfide bonds. Thioredoxins are maintained in a reduced state by the flavoenzyme thioredoxin reductase in a NADPH dependent reaction (Arner *et al.,* 2000). Thioredoxins act as electron donors to peroxidases and ribonucleotide reductase (Arner *et al.,* 1996). The related glutaredoxins share many functions of thioredoxins, but they are reduced by glutathione rather than specific reductase. TRx1 has been shown to downregulate cardiac hypertrophy by interacting with several different targets. Further different functions of Trx *viz.* redox sensitive signal transduction, transcriptional activation of stress response genes, DNA repair, post injury cell proliferation have been reported.

Peroxyredoxins (Prxs): Peroxiredoxins (PRX) are a family of ubiquitous antioxidant proteins that use specialized cysteine residues to breakdown hydroperoxides (Rhee *et al.,* 2005). Six types (I-VI) of PRx have been identified in mammals. Further, they can be categorized by their subcellular localization *i.e.* in mitochondria, endoplasmic reticulum and peroxisomes. Their deficiency or loss may lead to haematological disorders, cancer and increased susceptibility to diseases associated with oxidative stress (Li *et al.,* 2007). A few mechanisms have been suggested for PRxs involvement in redox signalling. According to a floodgate model proposed by Wood *et al.* (2003a), PRxs consume low levels of endogenous H_2O_2 in cell, but can be inactivated by high levels of H_2O_2. Another mechanism suggests that PRxscause structural changes following oxidation that could change protein-protein interactions generating a signal. Prx1 can facilitate oxidation of the apoptosis signaling cascade (ASK1) (Jarvis *et al.,* 2012). However, further research is needed to establish role of PRxs in apoptosis (Hampton and O'Connor, 2016).

Arylhydrocarbon receptor (AHR): Aryl hydrocarbon receptor (AHR) is present in different types of cells, however, epithelial cells possess it in high concentration. It is abundantly present in thymus, lung and placenta and to a lesser extent in liver, kidney, heart and spleen. It is found in the cytoplasm as a complex of two

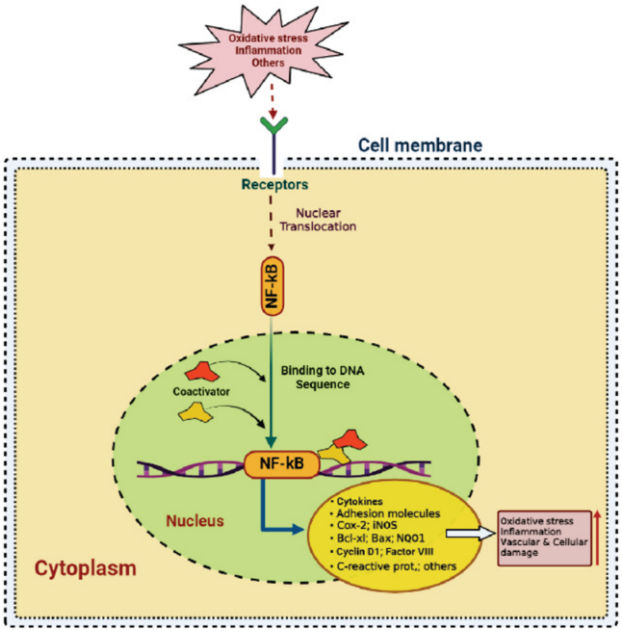

Fig. 2: NFkB signalling in cell injury. The inactive form of NF-KB is kept latent by IKBα. The active form of NF-KB is translocated to nucleus where it binds with DNA and induces oxidative stress and inflammation.

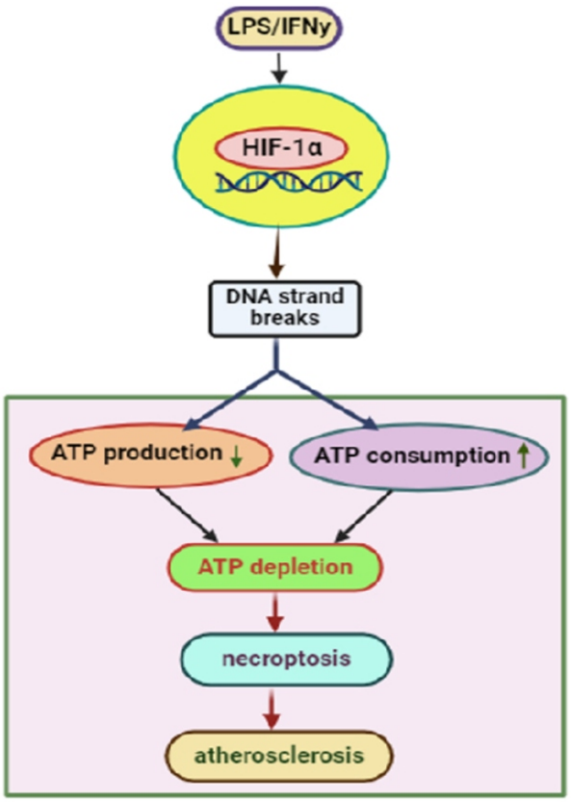

Fig. 3: Hypoxia inducible factor 1α promotes macrophage ATP depletion, necroptosis and atherosclerosis.

other proteins *viz.* hsp 90 and an immunophill in like ARA9/ AIPI/ XAP2. These proteins act as chaperones that allow ligand binding. After binding to a ligand AHR sheds off its chaperone and translocates into the nucleus. There it forms a heterodimer with anotherprotein of PAS family known as ARNT (AHR nuclear translocator). This heterodimer binds to xenobiotic response enhancers called XRE that are located close to promoter region of the genes viz. CYP 1A1, CYP1A2 and CYP1B1. Additionally, a few phase-II enzymes are also activated. AHR activation is regulated by an AHR repressor (AHRR). It competes with AHR for associating with ARNT and binding to XRE on DNA.

Redox switches: The importance of cross talk amongst different mechanisms of cell death has been discussed earlier by a few authors (Orrenius, 2019; Rana, 2021). The concept of molecular switches in cell survival and death has also been debated. However, thiol- redox switches and their role in apoptosis, necrosis and other types of cell death is a recently emerged issue. Regulated cell death (RCD) can be controlled by "redox check points". These check points are potent molecules *i.e.* GSH, TRx, caspase- 9 and caspase -3, MLKL, GSDMD, GPx4 and MOMP. They exercise multifunctional roles in oxidative stress, redox signalling and in cell survival/death (Fig.4). The existence of a multimeric- mitochondria-peroxisome- ER associated protein complex known as "redoxosome", has been hypothesized by a few authors (Yoboue et al. 2018; Siegenthaler and Sevier, 2019).

Redoxosome facilitates the interplay between various sources of ROS. This cross talk occurs through membrane contact sites (MCS) of different organelle in eukaryotic cells. However, the molecules that mediate the cross talk are not known at present. A complex role of calcium in this interplay has been suggested (Booth *et al.,* 2016). Calcium released from ER can be taken up by mitochondria leading to the stimulation of mitochondrial electron transport chain (ETC). Mitochondrial calcium uptake leads to the compression of mitochondrial cristae that are forced to release peroxides from mitochondria to ER. Thus redox events connecting ER and mitochondria can culminate into apoptosis. The redoxosome allows the cell to maintain a balance in the production and elimination of ROS within the ER, mitochondria and

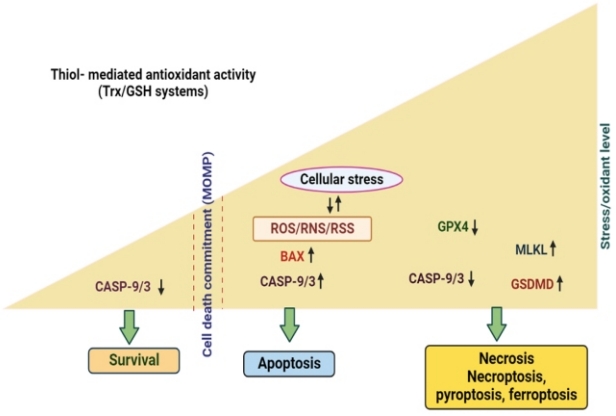

Fig. 4: Role of redox checkpoints in regulated cell death.

peroxisome triangle and to adjust in stress conditions. Interaction amongst these redox partners is facilitated by shuttling of beta oxidation intermediates between peroxisomes and mitochondria.

Role of redox molecules in human diseases: Experimental evidence gathered in recent years suggest that ROS could function as second messengers that regulate numerous cellular processes *viz.* cell cycle, ageing, cancer, fibrosis, cardiovascular diseases, neurodegenerative diseases and diabetes.

Aging: Aging has been defined as anondescript colloquialism that can mean any change over time, whether during development, young adult life or senescence. Theories of aging can be classified as "error and program theories". The free radical theory of aging was originally proposed by Harman (1956) as an example of error theory of aging. According to program theory, aging is controlled by pre-existing external and internal programs. The program theory includes both the "Haylick limit" and telomere shortening phenomenon. The role of catalase and MnSOD in aging has also been reported (Schriner *et al.* 2005). Further, cellular senescence is believed to be caused by telomere shortening. Telomeres are repetitive DNA sequences (TTAGGG) in vertebrates present at the ends of chromosomes and are essential for maintaining chromosomal integrity. Telomeres shorten with each cell cycle thus producing a phenotype known as senescence (Smith and Pereira-Smith, 1996).

Cancer: Cancer risk is linked with ROS production or decrease in ROS removal or both (Liou and Storz, 2010). Carcinogenesis can be divided into three distinct stages: initiation, promotion and progression. Initiation can occur due to mutations in one or more genes that result in gain or loss of function. Promotion is the functional enhancement or alteration of the pathway induced by initiation. Progression is the continuous change of the unstable karyotype often leading to aberrant proliferation. Aberrant proliferation could be due to loss of redox control of cell cycle. Oberley and Beuttner (1979) were the first to report that cancer cells exhibit lower levels of antioxidant enzymes compared with respective normal cells. It has been widely accepted now that oxidative stress could significantly contribute to cancer progression possibly by disturbing the redox control of cell cycle (Haliwell, 2007). Redox potential can significantly affect the function of a tumor suppressor gene (Hoffman *et al.,* 2008). Metabolic redox signalling pathways can also initiate and promote carcinogenesis (Gius and Spitz, 2006).

Fibrosis: Fibrosis can be defined as the formation of fibrous tissue as reaction or repair process attributed to disease or exposure to chemicals. It involves the excess synthesis of collagen and commonly observed in lungs, liver, heart and peritoneum. Different cells of the liver *viz.* parenchymal cells, Kupffer cells, stellate cells and endothelial cells are sensitive to oxidative stress (Rana, 1997). The cellular redox environment of hepatocytes and Kupffer cells may be regulated by ROS, followed by univalent reduction of oxygen to superoxide anion (DeMinisis and Brenner, 2007). Further, ROS signalling could be influenced by the activities of various antioxidant enzymes whose expression is regulated by redox active transcription factors viz. NFkB and NRF1. Redox sensitive activation of NFkB could regulate the expression of NFkB targeted genes providing an appropriate cellular redox threshold to quiescent cells to enter proliferation. Thus cellular redox environment regulate increased collagen synthesis in hepatic stellate cells that results in fibrosis (Maurizio and Novo, 2005).

Cardiovascular diseases: Redox signalling has been implicated in the pathogenesis of all major diseases of cardiovascular system. ROS may function as secondary messengers and signalling molecules that regulate redoxsensitive processes during vascular smooth muscle cell (VSMC) and cardiac myocyte cell cycle progression. This hypothesis has been supported by a number of reports. Hydrogenperoxide was found to increase c-myc and c-fos mRNA levels that affected cell cycle progression (Rao and Berk, 1992). Protective effects of NO against ischemia and reperfusion have been attributed to scavenging of superoxide (Burdon *et al.,* 1989). Catalase can inhibit VSMC proliferation indicating a link between ROS signalling and cell proliferation (Sundaresana *et al.,* 1995). It has also been suggested that application of antioxidants could be a viable redox based therapy for preserving the redox control of cell cycle in VSMCs and cardiomyocytes.

Diabetes: Although etiology of diabetes is not completely understood, there is a general agreement that cellular redox environment could significantly contribute to the development of diabetes mellitus. A recent report suggests that increased ROS activate insulin resistance in TNFα and glucocorticoid dexamethasone treated adipocytes. This resistance can be suppressed by prior treatment with N-acety cysteine (NAC) (Houstis *et al.,* 2006). These authors suggested that 3T3-L1 adipocytes over expressing CuZnSOD, MnSOD and catalase were able to prevent insulin resistance in this experimental model of diabetes. Other studies showed that the increase in ROS precedes hyperglycemia and insulin resistance suggesting a causal role of ROS in the disease process (Blair *et al.,* 1999). A possible link between insulin/IGF-1 and ROS/RNS signalling pathways has been suggested by (Papaconstantinou, 2009). β-cell dysfunction in the pancreas is one of the earliest mechanisms known for the progression of type-II diabetes (Valko *et al.,* 2007). β- Cells possess low levels of antioxidant enzymes, and thus are sensitive to ROS and eventual damage to macromolecules enzymes (Grankvist *et al.,* 1981). Some of these cell cycle proteins, *i.e.* p27, CDK4 myclin D1 and D2 are also linked to diabetes (Uchida *et al.,* 2005). Thus perturbations in the control of cell cycle proteins could significantly affect β cell proliferation and the development of diabetes.

Neurodegenerative diseases: Neurodegeneration is a pathological condition affecting the nerves of brain and spinal cord. Neuronal death occurs over a course of time or due to the effects of xenobiotics. Alzheimers' disease is the commonest form of dementia (Evans *et al.,* 1989). The hallmark pathology is the accumulation of β–amyloid and neuro fibrilatory tangles which are tau protein aggregates. β- amyloid after binding with copper

and iron has been considered as the major source of Alzheimers' disease (Behl, 1994). Parkinsonism is characterized by rigidity, resting tremers and bradykinesia (Coyle and Puttfarcken, 1993). The disease is caused by selective degeneration of neuromelanin containing neurons that cause a decrease in dopamine in substantia niagra. Affect cells contain Lewy bodies and cytoplasmic inclusions of synuclein protein. Another progressive neurodegenerative disease is amyotrophic lateral sclerosis (ALS) that has been associated with ROS. Mutations in Cu/ZnSOD account for -20% of all ALS cases (Saeed *et al.,* 2009). More than 100 mutations are known to exist in Cu/ZnSOD. The key players in neuronal cell death are superoxide anion and hydrogen peroxide. Intriguingly, low levels of ROS could be mitogenic (Nguyen *et al.,* 2003). It has been suggested that absence of appropriate redox control in neurones could activate cell death pathways resulting into neurodegenerative diseases.

The review presents an update on history and recent discoveries on all those molecules involved in cellular redox homeostasis. It summarizes the concepts of redox code; redox signaling and redox proteome. It discusses the role of redox molecules in human diseases. Finally, the role of redox switches in biology and medicine has been discussed.

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