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Oxidative Stress in Human Health and Disease

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1. Introduction

Oxidative stress arises when the antioxidant capacity of cells to scavenge the excess production of reactive oxygen species(ROS) falls short. It may also be due to changes in the redox status of the cell. In health, pro-oxidants engage in useful signaling pathways that are important for growth and cellular health. Overstimulation of signaling pathways leads to sustained pro-oxidant production in the form of ROS that disrupt cellular structures and impair function leading to disease. Normally, antioxidants counteract the activity of pro-oxidants to retain cellular homeostasis and therefore a state of health.

In this review the cellular sources of reactive oxygen species (ROS) will be discussed in addition to its effect on macromolecular structures, cellular function and health. The ROS referred to in the text are:superoxide, hydrogen peroxide, hydroxyl radicals; reactive nitrogen species (RNS) nitric oxide and peroxynitrite.

The primary source of ROS is molecular oxygen (O_2). In aerobic cells during electron transport about 10% of reducing equivalents from NADH leaks to produce superoxide ($O_2^- \cdot$) and hydrogen peroxide (H_2O_2). These diffuse out of mitochondria and form the starting materials for subsequent generation of ROS through a serial one electron acceptor process. RNS (NO) also fuel ROS generation through a similar interaction with cytochrome *c* oxidase to give rise to $O_2^- \cdot / H_2O_2$ or react with $O_2^- \cdot$ to generate peroxynitrite (ONOO-).

The oxidative stress effect on health is discussed from the point of view of infectious/communicable diseases, non-infectious/non communicable diseases, genetic diseases and oxidant stress factors (mutation/hemolysis).

The respective infectious/communicable and non communicable diseases that are discussed are malaria, HIV/AIDS, and diabetes, obesity, sickle cell disease and ageing. Except for ageing, the biology of the diseases is briefly outlined and host immunological responses to the disease state that augments ROS generation and its effects are discussed.

The review ends with a brief on oxidative stress and ageing and a summary of how oxidative stress is at the core of the physiological processes that maintain a healthy body and longevity.

2. ROS activity in normal cell function

The designation 'reactive oxygen species' refers to the unpaired electrons on an oxygen atom, molecule or ion that confers reactivity to the species (1, 2). By this definition oxygen molecule is the weakest radical as the ground state has two unpaired electrons (1) although it is unreactive. Multicellular organisms maintain a network of signals to ensure growth, defense and repair. These signals begin outside of the cell, with ligand receptor interaction, followed by conformational changes in the receptor that enables it to be activated through phosphorylation by kinases and inhibition of phosphatases (3, 4). The signal is then carried by second messengers for transduction into the cell nucleus (5, 6). Transcription factors constitute the terminal signal receivers to initiate gene expression critical for normal cell function. ROS act as second messengers in signal transduction in normal housekeeping cell functions (7, 8). ROS signaling can also be through regulation of ion channels, in particular potassium and calcium ion channels to modulate nerve conduction and apoptosis (9).

In normal cell function ROS is generated constitutively by non-phagocytic cells and in response to injury, trauma or infection by phagocytic cells (10, 11). A common functional attribute of the two sources of ROS is that moderate amounts is largely associated with signaling activity while increasing amounts is important in cellular defense and or repair (12). Moderate amounts of ROS are generated through electron transport, vascular smooth muscle cell (VSMC) and endothelial cell (EC) activities (13). Other cellular sources of ROS that may be limited by the changes in cellular metabolic activity include lipoxygenases, cyclooxygenase, cytochrome P450 enzyme activities and lipid peroxidation (7).

2.1 ROS generation in non phagocytic conditions

Non phagocytic generation of superoxide occurs constitutively and intracellularly in fibrobrast , smooth muscle cells (14), renal mesanglial cells (15), hematopoietic stem cells, neurons, hepatocytes, vascular endothelium and for the cellular organelles mitochondria, peroxisomes and the cytochrome P450 system. When generated, ROS participate in the maintenance of baseline signal transduction needed for normal cell function in the absence of activation (16-18). The non phagocytic oxidases (NOX) are transmembrane proteins that transport electrons across cell membranes to reduce oxygen to superoxide. To date six human isoforms have been isolated (Nox 1, 3, 4, 5, and Duox 1 and 2) (19, 20). They utilize a system that is dependent on NADPH, although, NADH can also be used as substrate (21). As a result they are referred to as NAD(P)H oxidases (12, 22). A large component of the non-phagocytic ROS is from mitochondria during electron transport under normal physiological conditions (23). The primary ROS is superoxide generated from reduction of oxygen. It has a short half-life and so its availability is limited, making it a poor signaling molecule (24). In low pH environments as in phagosomes however, the reactivity of superoxide is enhanced by conversion to hydrogen peroxide (25). Unlike superoxide, hydrogen peroxide which is generated from superoxide dismutation (26), is stable and can selectively diffuse through membrane pores to stimulate distant targets, including downstream kinases (27, 28). It also activates the antioxidant function of p53 which potentiates the activity of glutathione peroxidase to convert it to water (29). A summary of ROS generation in the mitochondria in normal physiology and some effects attributed to ROS is presented in Figure 1.
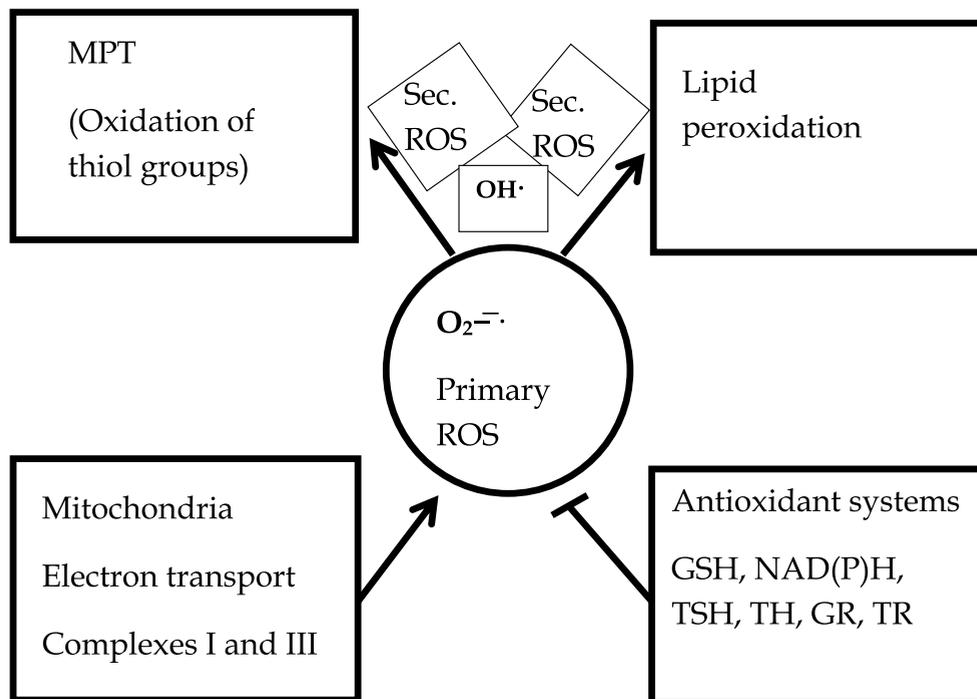
Fig. 1. Mitochondrial ROS generation sites by partial reduction of oxygen through a series of one electron acceptance and a role in oxidative stress effects.

2.2 ROS generation in the electron transport chain

At the end of the electron transport chain, molecular oxygen receives 4 electrons and is reduced to water providing energy for ATP synthesis. When oxygen is incompletely oxidized through the sequential acceptance of one electron, it gives rise to oxygen radicals that are more reactive than the molecule. These are in order of one electron acceptance, $O_2^-\cdot$, H_2O_2 and $OH\cdot$ (30, 31). Acquisition of an electron by molecular oxygen generates $O_2^-\cdot$ as the primary ROS. The sites in the electron transport chain known to significantly contribute to ROS are complex I and III. Complex I ROS production is mediated by NADH coenzyme Q reductase while in complex III ROS production is through the binding of NO to ubiquinol cytochrome c oxidase to produce $O_2^-\cdot$ and H_2O_2 (31-33). Mitochondrial nitric oxide synthase produces NO, the primary RNS which reacts with $O_2^-\cdot$ to give peroxynitrite. Therefore NO production is central to the generation of $O_2^-\cdot$ and H_2O_2 in the electron transport chain (34, 35). Mitochondria also functions as an oxygen sensor under hypoxia to produce hydrogen peroxide which stabilizes hypoxia inducible factor (HIF) to modulate its effect on hypoxia (36-38). HIF is degraded by the hydroxylation of prolyl residues and requires iron as an obligatory cofactor, so when ROS oxidizes iron, it is unavailable for hydroxylation thereby retaining cellular response to hypoxia (38). In normal cellular metabolism, low to moderate ROS/RNS are generated as part of the signaling pathways, cellular response to growth and in innate and adaptive immune response against danger signals (39).

2.3 ROS generation in VSMC and EC

ROS generation in non-phagocytic cells other than mitochondria, is through the activity of non-phagocytic NAD(P)H oxidase (Nox) following ligand binding to the cognate receptor (cytokines, growth factor and G-protein coupled receptor agonists, e.g. angiotensin II) (40, 41). Of particular note is the binding of vascular endothelial growth factor (VEGF), platelet derived growth factor and epidermal growth factor (EGF) to their cognate receptors that lead to receptor dimerization, auto-phosphorylation and signaling to activate redox sensitive transcription factors (eg. NF-κB) responsible for the expression of target genes (40).

2.4 Functional significance of ROS/RNS generation

ROS generated by non-phagocytic cells channel signals to induce cell migration, proliferation and vessel wall formation (42). This activity is particularly important for angiogenesis and in ischemia/reperfusion response (27). In order to sustain signal transduction, ROS generated from ligand receptor interactions can oxidize cysteine residues in phosphatases to inhibit their function and sustain signal transduction to the nucleus (43, 44). Within the endothelial cell (EC), hydrogen peroxide or angiotensin II (Ang II) stimulation of ROS production activates eNOS to produce NO which facilitates cell migration and proliferation (2, 45, 46).

2.5 ROS and danger sensing

The cells of the innate immune system sense danger by recognizing highly conserved pathogen associated molecular patterns (PAMP) present on all the major pathogens; bacteria, parasites, viruses and yeast, or danger associated molecular patterns (DAMP) through germ line encoded pattern recognition receptors (PRR) (47-50). While PAMP enables ROS generation in response to an infection, DAMP enables cellular response to danger (damage, stress) in the absence of an infection (51-53). These molecules that signal cell damage or stress include ATP, nucleotides and uric acid (54). Through ligand receptor interactions and phagocytosis, ROS signaling molecules (hydrogen peroxide and superoxide) are generated intracellularly to promote signaling cascades on one hand and/or activate inflammasome (55). The inflammasome is a descriptive term for cytosolic pattern recognition receptors belonging to members of the caspase-1 activating platform, nucleotide oligomerization domain (NOD) like receptor family (NLR) or AIM2 DNA binding proteins (56, 57). The proteins activate the expression of pro-inflammatory cytokines (IL-1β and IL-18) necessary to amplify ROS generation against pathogen elimination or containment through pyroptosis (57, 58). ROS can be generated extracellularly when a ligand binds to a receptor. This source of phagocytic ROS is through NADPH oxidase, largely in neutrophils engaged in phagocytosis, when activated by PAMP. Activated neutrophils undergo a burst of ROS production to eliminate the offending organism (59).

3. ROS in oxidative stress

Oxidative stress arises when the activity of oxidant species (ROS) overwhelms the cells capacity to counteract with antioxidants (60-65). In oxidative stress, excess ROS (O_2^-; H_2O_2, $OH \cdot$) are involved in three main activities:

a. Causing damage to cellular macromolecules (DNA, proteins and membrane lipids) due to their chemical reactivity,

b. Causing changes in membrane potential, which in the inner mitochondrial membrane directly causes mitochondrial permeability transition (MTP) and

c.   Acting as a sink for cellular antioxidants.

Whereas superoxide and hydrogen peroxide target Fe-S clusters and cysteine residues respectively, hydroxyl radical appears to be indiscriminate on targets, including oxidation of thiol groups in membrane proteins, making it the most damaging oxygen species (66-68).

a. ROS effect on macromolecules

DNA damage

The type of DNA damage attributed to ROS species may fall into several forms: single and double strand breaks; (69), sister chromatid exchange, DNA-DNA and DNA protein cross links and base modifications (71). Single strand breaks may be due to oxidation of phosphodiester bonds by direct abstraction of hydrogen by OH· from the deoxyribose-phosphodiester backbone giving rise to abnormal 3' and 5' ends which are not recognized by DNA polymerases (72). The bases may undergo hydroxylation or part of the ring may open up particularly for pyrimidine bases (73). Hydroxyl radicals also interact with DNA bases to form adducts. For instance reaction with guanine generates 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) adducts (74). Peroxynitrites generated from the reaction between NO and superoxide also react with guanine to form adducts (8-nitodG) (66, 71, 75, 76). The formation of DNA adducts can lead to loss of the bases giving rise to apurinic or apyrimidinic (AP) sites (77, 78). These adducts also contribute to accelerated telomere shortening, which regulates senescence. They can also lead to G→T transversion and microsatellite instability, a recipe for cell transformation (79). ROS attacks DNA to form hydroperoxides and peroxides (80-82). Lipid peroxidation by ROS is mediated through the Fenton reaction ($Fe^{2+} + H_2O_2 = Fe^{3+} + OH·$) to produce lipid hydroperoxides (LOOH) and 4-hydroxynonenal (4-HNE) (1, 67, 83). These reactive metabolites impair membrane function and lead to changes in Ca^{2+} flux (84). They also serve as signaling molecules for activating or inhibiting apoptosis through the activity of serine/threonine kinase Akt in the PI3K/Akt pathway (85). Lipid peroxides are the major end products for stress induced oxidative damage that mediate apoptosis (86).

Protein damage

Oxidative ROS damage of proteins can lead to disruption of several vital cellular activities such as replication, transcription, and protein synthesis (78, 87, 88). The breakdown of amino acids occurs largely through the reactivity of hydroxyl radicals. Hydroxyl radical is generated by Fenton Chemistry through superoxide in the Haber-Weiss reaction ($O_2^- + H_2O_2 \rightarrow O_2 + ·OH + OH^-$) (88). It attacks amino acids abstracting hydrogen atom from the alpha carbon to generate the alkyl radical as the primary radical (89). This then undergoes a series of reactions to generate alkyl peroxide and alkoxyl radicals. These radicals not only disrupt the protein backbone but also engage in peptide bond cleavages to disrupt protein function (90). ROS can also oxidize almost all amino acid side chains, in particular sulphur containing amino acids, cysteine and methionine (1, 91). Other well-known targets are glutamyl and prolyl side chains to induce peptide bond cleavage. RNS also contribute to amino acid oxidation (nitration of tyrosine residues, nitrosation of cysteine sulfhydryl

groups and oxidation of methionine) through the activity of peroxynitrite generated from a reaction between NO and superoxide (87). Oxidized amino acids have a higher tendency to cross link which affects folding and function. A major physiological impact of protein oxidation is accelerated ageing (92-94). This is attributed to increased degradation of oxidized proteins, limiting function (83, 87, 91, 95).

b.   ROS and changes in mitochondrial membrane potential

Oxidation of mitochondrial membrane sulfhydryl groups is associated with membrane permeability transitional states (65). Mitochondrial membrane permeability transition (MPT) occurs when the inner membrane becomes non selectively permeable leading to accumulation of Ca^{2+}, loss of matrix components, impairment in mitochondrial function, excessive fluid accumulation and outer membrane burst (64, 96, 97). This leads to loss of cytochrome *c* and a drive towards apoptosis (96, 97). Currently, it has been shown that changes in mitochondrial redox status due to oxidation of NAD(P)H by ROS serves as the starting point for MPT (64, 98). NAD(P)H is critical for maintaining mitochondrial redox status through reduction of oxidized glutathione (GSSH) and thioredoxin (TSSH) necessary for reducing thiol groups in the inner membrane (27, 99, 100). Oxidized thiol groups in membrane proteins, cross link and aggregate to form the non selective permeability pores that disrupt mitochondrial function (101).

4. ROS in infectious diseases

4.1 Oxidative stress in malaria

Malaria is caused by parasites belonging to the genus *Plasmodium*. In humans four major species are responsible for the disease: *P. falciparum*, *P. vivax, P. ovale,* and *P. malariae* (102). Recently, *P. knowlesi* has been shown to be a major cause of malaria in parts of South East Asia (Borneo) (103, 104).The parasites are obligate and belong to the Phylum Apicomplexa (105). *P. falciparum* accounts for most severe malaria globally (106). The major vector for parasite transmission is the female anopheline mosquito (107). During a blood meal, sporozoites are inoculated under the skin and travel through the blood stream, liver sinusoids to settle in a hepatocyte after traversing several (108-111). This journey usually takes approximately 1 hour (112). Each sporozoite in a parasitophorous vacuole in the liver divides to generate between 10,000 to 30,000 merozoites (110). In *P. ovale*, *P. malariae*, and *P. vivax* some sporozoites turn to hypnozoites which can remain dormant for months or several years and then get reactivated (113, 114). Merozoite maturation occurs within two weeks in a process called tissue shizogony. The merozoites invade RBCs and develop into ring forms, trophozoites and blood schizonts which repeat the cycle of RBC invasion leading to significant hemolysis. The cycle repeats every 48 hours for *P. falciparum, P. ovale,* and *P vivax* called tertian malaria and every 72 hours for *P. malariae* called quartan malaria. Each RBC can harbor up to 20 trophozoites. Following a cycle of blood schizogony some merozoites develop into gametocytes which are the sexual forms. These are taken up in a next meal to undergo sexual reproduction and eventually generate sporozoites ready for inoculation(115) .

4.2 Generation of ROS in plasmodium infection

When Plasmodium species infects an individual, the clinical presentation may be described as uncomplicated (asymptomatic or mild) or complicated (severe). In uncomplicated

malaria host exposure to the parasite is significant enough to generate protective immunity such that the parasite burden is limited (116). This is usually seen in endemic areas (116, 117). In contrast, in low endemicity and low parasite exposure, because of lack or low host immune response, infection can lead to severe disease. It has been shown that whether an infection is uncomplicated or severe, there is a higher generation of ROS that is host and parasite derived (118). Host derived ROS generation arises from interaction of parasite ligands with host receptors during sporozoite invasion leading to phagocytosis and activation of NADPH dependent oxidases for ROS release (119). In addition polymorphonuclear neutrophil attraction to the site of infection and activation is associated with significant release of ROS as a defense mechanism for parasite clearance (120-122). This mechanism also occurs during blood schizogony to inhibit merozoite invasion of RBCs. During the period of blood schizogony, significant quantities of heme are released into circulation that overwhelms the scavenging activity of hemopexin, so that free heme is available to induce further neutrophil migration and catalyze its activation (123). Free heme also binds to and oxidizes lipoproteins in membranes increasing RBC breakdown (124, 125). Malaria parasites release a large quantity of ROS in the infected RBC in the process of converting heme to hemozoin for heme detoxification (126). It has been shown that hemozoin (Pf, Hz) mediates peroxidation of unsaturated fatty acids and contributes to the production of 4-hydroxynonenal (HNE) which reacts with proteins to form adducts disrupting their function (127). The impact of disrupted protein function is down regulation of receptors required for gene expression and cell division. This is suggested to be a factor in decreased erythropoiesis and malaria induced anemia. An additional source of ROS recently identified is from infected rbc membrane microparticles which enable activation of macrophages and increase ROS generation.

4.3 Oxidative stress in HIV infection

The classical pathway of HIV infection is through binding of the envelope glycoprotein to CD4+ cells mediated by the coreceptors CXCR4 and CCR5 chemokine receptors (128) .HIV-1 isolates that replicate primarily in activated CD4 T-lymphocytes in vitro are said to be T-tropic whereas isolates replicating in primary macrophages are M-tropic (129). Dual tropism is shown by isolates with the ability to infect both cells efficiently. CXCR4 and CCR5 act as coreceptors for T-tropic and M-tropic isolates respectively (129-131). CCR5 target cells appear to be important in the early phase of transmission switching to CXCR4 as the disease progresses (129, 132). For the most part however both receptors are expressed on known target cells (CD4+ T cells, monocyte/macrophages, dendritic cells, Langerhans cells and rectal and vagina mucosa) (133). Recently it has been shown that HIV-1 can be transmitted into cells directly by a tunneling mechanism independent of receptor functions (134). HIV-1 has been divided into nine subtypes called clade A-D, F-H, J and K based on variation in the viral envelope. Clade B is predominant in Europe, the Americas and Australia, while the rest are found in Africa and Asia (135).

A common comorbidity in HIV infection is dementia, which is a combination of behavioral, cognitive, and motor dysfunction following HIV infection (134, 136). It is estimated that in adults below the age of 40, HIV accounts for the most cause of dementia (137, 138). Data accumulated to date shows that oxidative stress is an underlying cause of HIV associated dementia (HAD) (139). Brain polyunsaturated fatty acids readily undergo peroxidation by free radicals to generate the 4-HNE which breaks bonds in cysteine, histidine and lysine

residues to disrupt protein function (140). 4-HNE also disrupts mitochondrial function to generate ROS aggravating oxidative stress in the process (141). Lipid peroxidation and protein oxidation also contribute to the generation of carbonyl groups, which characterize HIV dementia (142, 143). Some of the proteins that are affected due to lipid peroxidation include ATPases and glucose transporters. HIV regulatory protein Tat and structural protein gp120 are known to exert neurotoxicity by increasing ROS generation and lipid peroxidation (140). HIV gp41 is documented to induce iNOS expression and NO generation to react with superoxide forming peroxynitrite. Peroxynitrites cause nitration of tyrosine residues to disrupt protein function while its decomposition gives rise to hydroxyl radicals, a highly potent lipid peroxidizing agent (138). Over production of NO has been suggested to also increase HIV-1 replication. HIV-1 infection not only causes an increase in ROS generation but also leads to depletion of protective antioxidants in particular, glutathione (138, 144). Thus HIV disease is characterized by chronic oxidative stress which drives disease pathogenesis.

5. ROS in non communicable diseases

5.1 ROS in type 2 diabetes

Diabetes is a metabolic disease caused by derangement in carbohydrate and lipid metabolism due to defects in insulin secretion, action or both (145). Two major forms are defined, type 1 and 2. Type 1 is due to an absolute deficiency in insulin secretion attributed to autoimmune destruction of the β cells of the Islet and genetic factors (145, 146). Type 2 is a combination of insulin resistance and inadequate compensatory insulin secretory response. It is now confirmed that diabetes is an inflammatory disease with elevated plasma concentrations of IL-6, CRP, orosomucoid and sialic acid (146-148).

5.2 ROS in pancreatic β cell damage

In type 1 diabetes β cell damage partly initiates from cellular response to the danger signal, dsRNA which leads to overexpression of Toll like receptors (TLR3, 4). The TLR then activates redox sensitive transcriptions factors including NF-kB (149).The major source of ROS in pancreatic β cells is from mitochondria and activity of non phagocytic NADPH oxidase (98, 150, 151). When ROS generation is high, the β cell which is known to have lower levels of antioxidants (catalase, glutathione peroxidase and superoxide dismutase) compared to other cell types is damaged leading to decreased insulin secretion. It is also reported that autoimmune activities fuel an inflammatory phenotype to damage β cells. In insulin sensitive tissues glucose is transported intracellularly by specific membrane transporters (GLUT). Once inside the cell glucose is phosphorylated by glucokinase and goes through the glycolytic pathway (152, 153). Increased glycolytic activity feeds into higher ATP production, closure of K+ channels and increased intracellular Ca^{2+} which can stimulate ROS generation by mitochondria (153). The increased Ca^{2+} flux can also promote NADPH oxidase activity to produce more ROS (154). As previously noted, low levels of ROS generated by glucose metabolism, is important for glucose stimulated insulin secretion while higher levels damage β cells of the Islets and induce insulin resistance through activation of redox sensitive intracellular signaling pathways (6). Changes in glucose and lipid metabolism contribute to ROS generation through the formation of diacylglycerol (DAG), advanced glycation end products (AGE), increased polyol formation and increased

hexosamine pathway flux (155, 156). The polyol pathway involves the conversion of glucose to sorbitol when hyperglycemia persists. Metabolism of sorbitol generates fructose in a dehydrogenation reaction so that the NADH/NAD+ ratio increase favoring DAG synthesis. DAG potently stimulates protein kinase C, for activating non phagocytic NADPH oxidases (157). In addition increase in mitochondrial NADH/NAD ratio increases the proton gradient and probability of electron donation to molecular oxygen to generate superoxide (156). The β cell is insulin independent for glucose uptake so under elevated plasma glucose, the cells fail to down regulate glucose entry by insulin resistance. Free available reducing sugars (eg.glucose), can react with free amino groups to form a Schiffs base which rearranges into an Amadori glycation product (158-160). When accumulated in proteins, these AGEs modify protein function and or contribute to generation of ROS thereby damaging the cell (151). Another mechanism is the hexosamine pathway flux which functions under normal metabolism but is increased under hyperglycemia. In this process glucose metabolism in glycolysis is channeled into glucosamine phosphate from fructose 6-phosphate. The end product of the pathway is UDP-N-acetylglucosamine, which acts as a substrate for glycosylation of intracellular proteins, including transcription factors (161). Therefore, the expression of several genes including insulin is affected.

5.3 ROS and insulin resistance

In general insulin resistance leads to a sustained inflammatory state (162). Overt insulin resistance occurs from an initial impairment in insulin mediated glucose up take (IGT) (146, 163, 164). If this state is sustained, the impaired insulin response becomes blunted to constitute resistance (146, 164-166). In the end the blunted response leads to overt type 2 diabetes as glucose uptake is severely compromised leading to derangement in lipid metabolism (167, 168). Target tissues (muscle and adipose tissues) may fail to respond to insulin because of the diminished secretion or decreased sensitivity. Hyperglycemia, raised serum free fatty acids (FFA) and increased inflammatory phenotype indicated by high TNFα, CRP, IL-6 and IL-1β ((165, 167, 169) predominate in insulin resistance. High FFAs repress translocation of GLUT4 transporters to the plasma membrane and resistance to insulin mediated glucose uptake in muscle and adipose tissues, particularly (167). High FFA gives rise to elevated fatty acid metabolites; DAG, ceramides and fatty acyl CoA which activate protein kinase C resulting in activation of serine/threonine cascades (170). In skeletal muscle and adipose tissue the insulin receptor is phosphorylated at tyrosine sites upon binding by insulin (171, 172). The receptor in turn causes phosphorylation of substrates: insulin receptor substrate 1 and 2 (IRS1 and IRS2), which activates PI3-kinase, Akt/protein kinase B to recruit GLUT4 to the plasma membrane for glucose uptake ((167, 173). Elevated lipid metabolites scuttle this mechanism, and instead cause phosphorylation of serine sites on insulin receptor substrates, which inhibit their activation of phosphatidyl-inositol 3-kinase (PI3-kinase) and induce failure of transport of GLUT4 to the cell membrane (150, 171, 174). Also these metabolites decrease downstream signaling activities whereby insulin receptor substrates are activated for insulin secretion and response. ROS can also mediate these responses by inhibiting insulin receptor substrates 1 and 2 (IRS-1, and IRS-2) tyrosine auto-phosphorylation, while increasing phosphorylation of serine sites (173-175). Inhibition of tyrosine phosphorylation limits gene expression, cell growth and differentiation of the Islets.

5.4 ROS in obesity

Obesity is defined as a body mass index greater than or equal to 30 kg/m² (176). It is established to be a state of chronic low grade inflammatory disease (meta-inflammation) grouped together with insulin resistance, type 2 diabetes, cardiovascular disease and fatty liver disease as the metabolic syndrome (167). Excess calories stored in adipose tissue, causes it to expand, accompanied by infiltration of macrophages (176-179). The macrophages drive production of pro-inflammatory cytokines (TNFα, IL-6. iNOS, TGF-β, MCP-1) through toll like receptor 4 (TLR4) and so present the inflammatory phenotype (176, 180). In addition, increasing adiposity is associated with changes in the expression of adipokines (leptin, adiponectin, IL-6, resistin and TNF-α) which regulate energy intake and insulin sensitivity (176). With the exception of adiponectin, the expression of all the adipokines is increased with increasing fat mass (166, 178, 181). Adiponectin promotes insulin sensitivity by reducing fat and glucose storage. In Obese individuals, insulin resistance is characterized by upregulation of TNF-α by resident macrophages, a mechanism that is similar to that seen in type 2 diabetes (177). The location of the increased fat mass is known to affect the degree of inflammation. While visceral adipocity exacerbates, lower body fat mass has limited effect (177, 182). Enhanced DAG synthesis also affects downstream signaling pathways required to synthesize protein for Islet cell differentiation. As result islet cell differentiation is limited; this in turn affects insulin secretion and regulation of metabolic pathways (173).

5.5 ROS in sickle cell disease

Sickle cell disease arises from a mutation in the beta globin gene with substitution of glutamate for lysine at the 6th codon of β-globin to give hemoglobin S (HbS) variant (183-185). A homozygous HbSS is referred to as sickle cell anemia, while a heterozygous globin mutant with HbS constitutes sickle cell disease (186). The abnormal Hb has defining characteristics: it undergoes polymerization under low oxygen tension, precipitates when polymerized leading to generation of ROS which oxidizes the rbc membrane and makes it fragile and brittle (187). In sickle cell disease, the vascular endothelium becomes dysfunctional and shows increased inflammatory state, adhesiveness, and activation, concomitant with decreased NO bioavailability (188, 189). The disease makes subjects amenable to ischemic stroke, ischemia reperfusion injury, chronic renal disease, pulmonary hypertension, priapism, fetal wastage and growth retardation (190).

The propensity towards sickling is greatly enhanced if the transit time of rbc in the capillaries is increased. In the inflammatory state such delays become common place leading to severer hemolytic episodes and 'crisis'. Sickle cell anemia has high hemolytic episodes. The average life span of a normal rbc of 120 reduces to 14 days in sickle cell disease (190). The enhanced hemolysis contributes significantly to instigate a proinflammatory phenotype as free heme and hemoglobin are strong oxidants (191). Heme can donate electrons or Fe to membrane lipids through the fenton reaction to generate ROS that contributes to membrane damage and sustained hemolysis(188). Under sustained hemolytic conditions, the cellular mechanisms for scavenging hemoglobin and heme are overwhelmed (haptoglobin and hemopexin respectively) so that free heme and Hb are present intravascularly to initiate inflammation (192, 193). Extravascular hemolysis arising from ineffective scavenging of rbcs worn out or damaged, and ineffective erythropoiesis also contribute to heme and Hb leak

into circulation. So in essence, sickle cell anemia is a typical systemic proinflammatory disease with sustained ROS production. Typical sources of ROS include activated NADPH oxidases from activated monocytes and endothelium, increased Xanthine oxidase expression and diminished NO availability (194, 195, 196). Activated endothelium increase expression of adhesion molecules for binding leukocytes and rbcs which contribute to hemostasis, rbc lysis and increased inflammatory phenotype (194).

5.6 ROS and endothelial dysfunction

The endothelium is the organ situated at the interface between the wall of the blood vessel and blood stream, functioning as a sensor for modulating vasomotor function, hemostasis and inflammation (197). Endothelial dysfunction refers to impairment of these functions associated with vascular remodeling and vascular growth, but more commonly to impairment of endothelium dependent vasodilation due to depletion of NO in the vessel wall (198). The factors released by the endothelium may lead to vasodilation or constriction. Some of these factors are NO, prostacycling, C-type natriuretic peptide, and endothelium derived hyper polarizing factors which act as vasodilators. ROS along with Ang II, endothelin 1 (ET-1) and thromboxane A_2, act as vasoconstrictors and up regulate adhesion molecules, intercellular adhesion molecule (ICAM-I), vascular cell adhesion molecule (VCAM-I) and E-selectin (197). The major sources of ROS in the endothelium are mitochondria, lipoxygenases, cyclooxygenases, cytoP450s, xanthine oxidases and NADPH oxidases (2, 14, 198, 199).

5.7 NO depletion and endothelium

In endothelial dysfunction NO synthesis is reduced. This affects vasodilation, inflammation and hemostasis. NO synthesis is by eNOS using L-arginine as substrate in the endothelium. Suggested mechanism for reduced NO synthesis is substrate unavailability, reduced eNOS synthase activity and quenching of NO when synthesized (200-204). ROS constitutes a major quencher of NO bioavailability. Reaction of NO with superoxide generates peroxynitrite which in turn reacts with proteins, lipids, and eNOS cofactor tetrahydrobiopterin (BH_4). By oxidizing BH_4 to generate BH_2, eNOS synthase activity is uncoupled, so that instead of producing NO, more ROS is generated from increased reductase activity of eNOS (199, 205). ROS up regulates the expression of adhesion molecules, ICAM-1, VCAM-1 and chemoattractant molecules (MCP-1) for neutrophil and macrophage attraction and activation (206, 207). eNOS synthase may also be competitively inhibited by asymmetric dimethylarginine (ADMA). It has been shown that increased ADMA concentration correlates with high blood pressure (BP) as renal plasma flow is impaired while flow resistance is increased leading to high BP (208, 209). As protein degradation increases in the cell, ADMA concentration also rises and is excreted in the kidneys or degraded to citrulline by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) (208, 210, 211). As DDAH concentration increases in the cell, ADMA levels correspondingly decrease, associated with increased eNOS activation and reduced BP (211). Recently, the degree of endothelial dysfunction has been shown to inversely correlate with amount of endothelial progenitor cells in circulation. Endothelial progenitor cells have the capacity to develop into endothelial cells and are used to repair endothelial lesions (212, 213).

5.8 ROS in ageing

The free radical theory of ageing postulates that accumulated cellular damage by ROS over a period of time is associated with shortened life span (214). This includes effect on telomere shortening, dementia, accumulation of glycation end products and changes in signaling pathways that affect cellular function. A rise in the intracellular ROS generation as outlined previously damages cells, macromolecules and affects signaling pathways (1, 39, 214). These cumulatively drive cellular ageing.

6. Summary

Cumulative evidence shows that ROS is like a 'double edged sword' that on one side enables normal physiological cellular functions to be sustained and provides defense against invading organisms. However when in excess shown as oxidative stress, it plays a destructive role leading to cellular damage, senescence or death. These life attributes make ROS an essential investigative target in the biochemistry and physiology of health and pathological mechanisms of disease.

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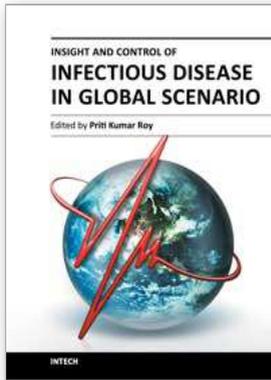
Insight and Control of Infectious Disease in Global Scenario

Edited by Dr. Roy Priti

This book is projected as a preliminary manuscript in Infectious Disease. It is undertaken to cover the foremost basic features of the articles. Infectious Disease and analogous phenomenon have been one of the main imperative postwar accomplishments in the world. The book expects to provide its reader, who does not make believe to be a proficient mathematician, an extensive preamble to the field of infectious disease. It may immeasurably assist the Scientists and Research Scholars for continuing their investigate workings on this discipline. Numerous productive and precise illustrated descriptions with a number of analyses have been included. The book offers a smooth and continuing evolution from the principally disease oriented lessons to a logical advance, providing the researchers with a compact groundwork for upcoming studies in this subject.

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