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REVIEW

AGENTS AND MECHANISMS OF OXIDATIVE STRESS IN HUMAN PATHOLOGY

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ABSTRACT

Reactive Oxygen Species and Reactive Nitrogen Species are well recognised for playing a dual role as both deleterious and beneficial species. Overproduction of Reactive Oxygen Species and Reactive Nitrogen Species results in oxidative/nitrosative stress, a deleterious process that can be an important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA. In contrast, beneficial effects of Reactive Oxygen Species and Reactive Nitrogen Species occur at low concentrations and play physiological roles in cellular responses, as for example in modulation of a number of cellular signalling pathways. This mini-review analyses the roles of Reactive Oxygen Species and Reactive Nitrogen Species in pathophysiological implications of altered redox regulation. Attention is focussed on inflammation and the pathogenesis of chronic kidney disease, hyperglycaemia and diabetes, ischemia/reperfusion injury, cardiovascular and neurodegenerative diseases. The question is also addressed, whether excess formation of free radicals is anyway a primary cause, or rather occasionally a downstream consequence of tissue injury.

Keywords: Reactive oxygen species; reactive nitrogen species; human physiopathology.

INTRODUCTION

The term "oxidative stress" established during the latest decades into the daily biomedical jargon describes the array of alterations produced in tissues, in cells and biological macromolecules exposed to an excess of prooxidant agents: both endogenous ones (e.g., those released by inflammatory cells), as well as exogenous ones (including a number of environmental pollutants). A controlled balance between prooxidant and antioxidant substances (the so-called "redox equilibrium") is essential for a whole series of physiological functions, since several proteins involved in the intracellular signal transduction (receptors, kinases and phosphatases, transcription factors) are sensitive even to slight alterations of such equilibrium. Minor changes usually produce physiological effects, i.e. modulatory ones, while major dysequilibria are likely to cause dysfunctions, cell injury, apoptosis or necrosis. Usually oxidative stress is the consequence of the action of chemical agents, free radicals in the first place. Importantly, however, prooxidant actions are also exerted by non-radical agents (e.g., hydrogen peroxide), as well as by ionizing radiations. When cellular antioxidant defenses are not sufficient to buffer prooxidant effects, cells might then suffer from damage at several levels: 1) on membrane phospholipids, eventually leading to membrane destruction with loss of compartmentation and selective transport; 2) on nucleic acids, with onset of mutations and altered gene expression; and 3) on proteins, where oxidation of cysteine residues and other amino acid side chains will cause alterations in structure and loss of functions: enzymatic, receptor, transport, etc. A detailed description of biochemical and molecular changes produced by oxidative stress is well beyond the scope of the present article. Processes involved are numerous, with participation of a large number of molecular species and modulatory factors and constant intersections of pathways; several exhaustive reviews present in the literature can give all required details [*Sies H., 1991; Pompella A., 1997; Dalle-Donne I. et al., 2003; Halli-*

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well B., 2007; Valco M. et al., 2007]. The overall cartoon depicted in Figure 1 offers a synopsis of biochemical species and molecular targets involved, highlighting the complex interactions connecting individual phenomena with each other. The great variety of mechanisms set into motion by a redox dysequilibrium accounts for the fact that oxidative stress reactions – with aspects different from time to time – are involved in a long series of human pathologies. In particular, in recent years the implication of these reactions has been increasingly acknowledged in inflammatory disease conditions, chronic kidney failure, diabetes, ischemia, cardiovascular diseases and selected neurodegenerative diseases. The present review will in fact analyze the main aspects of such "dangerous liaisons".

Oxidative stress: pathological significance

The list of human pathologies, in which an involvement of oxidative stress processes can be demonstrated is rather long, and its length is increasing in time **(**Table**)**. In a clinical perspective, apart from biochemical and molecular processes, other aspects of stress are probably more relevant in pathogenesis. In fact, when considering the real significance of oxidative reactions becoming apparent in the course of a pathological process, it is often difficult to judge to what extent they are acting as causative factors of the disease phenomena, whether they participate in pathogenetic mechanisms of the damage occurring in tissues, or whether they rather take place as a late effect of the disease process (Figure 2). Yet a precise understanding of the precise role would immediately impact on therapeutic strategies to be implemented: in the first and the second instance, oxidative reactions should be counteracted, e.g., by supplying antioxidants and carefully choosing their nature, dosage and route of administration. Instead, in the third instance – oxidative stress as a mere effect of pathology – it will gain importance, as far as clinical diagnosis and therapeutic monitoring are concerned. Clinical researchers are constantly working to elucidate these aspects, which may vary in different pathologies or even in subsequent stages of a single condition.

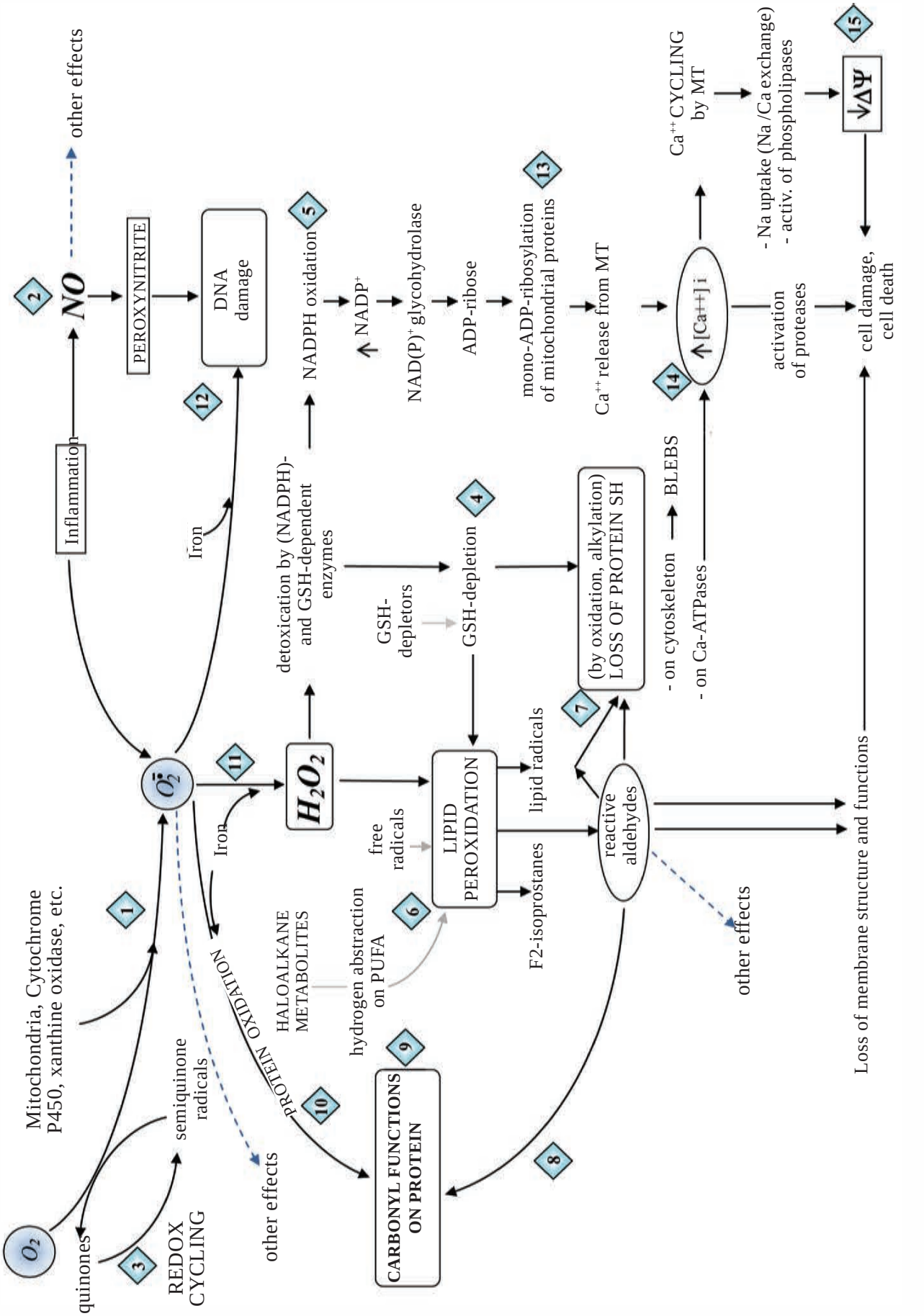
Oxidative stress in human diseases

Inflammation: Prooxidants are primary agents released in tissues by macrophages and granulocytes during inflammation, and play a central role in what is usually defined as "natural immunity" (toxic action on pathogens, modulation of microcirculation, coordination of earlier immune reactions). The action of several enzyme activities

Table.

Main human pathologies with recognized involvement of oxidative stress reactions

Inflammatory processes	- Glomerulonephritis - Autoimmune diseases - Rheumatoid arthritis
Respiratory diseases	- Effects of cigarette smoke - Emphysema - Hyperoxic damage - Cystic fibrosis - Toxicity of ozone, NO_2, SO_2 - ARDS - Asbestosis - Lung fibrosis
Ischemia-reperfusion	- Myocardial infarction - Stroke - Transplants
Cardiovascular diseases	- Alcoholic myocardiopathy - Atherosclerosis - Hypertension - Doxorubicin cardiotoxicity
Skin diseases	- Porphyria - Radiation injury
Neurological diseases	-Alzheimer's disease -Parkinson's disease - Multiple sclerosis - Muscular dystrophies - Aluminium toxicity - Allergic encephalopathy - Brain hemorrhage
Blood diseases	- Sickle cells anemia - Favism - Fanconi's anemia - Malaria - Drug toxicity
Kidney diseases	-Chronic effects of dialysis - Heavy metals toxicity
Eye diseases	- Cataract - Retinal degenerations
Other pathologies	- Diabetes -Alcoholism -Toxic liver injury - Acute pancreatitis
Ageing	



OXIDATIVE STRESS >>> (other factors) >>> **disease**	**CAUSATIVE ROLE:** indication for prevention
(other factors) >>> **OXIDATIVE STRESS** >>> **disease**	**PATHOGENIC ROLE:** indication for therapy
(other factors) >>> **disease** >>> **OXIDATIVE STRESS**	**BIOMARKER ROLE:** indication for diagnosis, monitoring and prognosis

Figure 2. *Three distinct roles for oxidative stress in pathology.*

leads to production of molecular species provided with high reactivity: Reactive Oxygen Species (ROS), as well as Reactive Nitrogen Species (RNS). Interactions occur between the two families of compounds, leading, e.g., to formation of highly reactive peroxynitrite and causing the pathophysiologically relevant phenomenon of protein nitrosation (Figure 3). However, at variance with this – physiological – defensive function, prooxidant species produce in the inflamed tissue a variety of noxious effects, whose intensity concurs to originate pathological phenomena. In the case, e.g., of pulmonary inflammation, excess activation of neutrophils can cause the necrosis of epithelial, as well as vascular structures with degradation of connectival matrix, leading to major disease conditions, such as the acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD) and lung fibrosis [*MacNee W., 2001; Rahman I., Adcock I., 2006*]. Tissue damage occurs as a result of the effects exerted by ROS and RNS at molecular level to proteins, lipids and nucleic acids. Moreover, the prooxidant/activating effects on transcription factors, such as nuclear factor kappa-B (NFkB) and activator protein-1 (AP-1) – capable of activating in turn the expression of chemotactic interleukines such as IL-8 – represent a mechanism to further perpetuate the inflammatory process **(**Figure 4**)**.

Rheumatoid arthritis, a severe autoimmune disease causing chronic inflammation of joints and periarticular tissues with infiltration of macrophages and T-lymphocytes, is another example of the pathogenic role potentially played by free radicals and prooxidant agents. Increased levels of F_2-isoprostanes, prostaglandin-like products of lipid peroxidation [*Basu S. et al., 2001*], can be detected in the synovial fluid of these patients. In T-lymphocytes isolated from diseased joints the levels of reduced glutathione (GSH) are decreased, and the resulting condition of oxidative stress appears to be responsible for abnormal cellular activation, e.g., due to alterations in phosphorylation status of the adaptor protein linker for activation of T-cell (LAT), as well as to expression of selected adhesion molecules [*Griffiths H., 2005*].

Chronic kidney failure. Oxidative reactions contribute to progression of kidney failure, since elevated levels of ROS are produced in patients undergoing dialytic treatments due to activation of

◄ **Figure 1.** *Relationships among the biochemical processes taking place in cells exposed to oxidant stress conditions.* Reactive oxygen and nitrogen species are normally produced by physiological reactions [1, 2]. Superoxide anion can also result from the redox cycling [3] of a number of drugs and xenobiotics, as well as of several endogenous compounds. Dismutation of superoxide (either spontaneous or catalyzed by superoxide dismutase) will lead to production of hydrogen peroxide. The metabolism of hydrogen peroxide by glutathione peroxidase can lead to glutathione (GSH) depletion [4]; the activity of NADPH-dependent GSH reductase in re-reducing oxidized glutathione will in turn result in a depletion of NADPH [5]. GSH depletion makes the cell susceptible to lipid peroxidation [6], a process also directly triggered by toxins such as haloalkanes. Reactive aldehydic products of lipid peroxidation can bind to protein, thus causing a loss of reduced sulfhydryl groups [7]; the latter can also occur as a consequence of GSH oxidation and depletion. Lipid-derived unsaturated aldehydes (4-hydroxynonenal in the first place) can bind to protein sulfhydryls still preserving their carbonyl functions [8]; protein will exhibit then an increased carbonyl content [9]. The appearance of carbonyls on cellular protein can also be the result of a direct oxidation of amino acid side chains – a process catalyzed by metal ions (iron in the first place: "metal-catalyzed protein oxidation") [10]. Iron ions are also involved in the promotion of lipid peroxidation in the presence of hydrogen peroxide [11], as well as in the oxidative DNA damage induced by reactive oxygen [12]. The increase in cellular oxidized NADP+ can trigger the ADP-ribosylation of mitochondrial proteins [13], a process leading to release of mitochondrial calcium in the cytoplasm [14]. A sustained increase of cytosolic Ca++ ions is also an effect of the loss of critical sulfhydryls on plasma membrane Ca-ATPases; the final consequence of it can be a severe impairment of the mitochondrial membrane potential [15].

neutrophils following contact with poorly biocompatible materials present in dialytic apparatuses. Ongoing oxidative processes lead to consumption and chronic deficiency of major plasmatic antioxidants resulting in a vicious circle. The latter is further aggravated by the fact that one such major antioxidant in plasma is uric acid, i.e. one of the catabolites that dialysis will remove from plasma [*Gerardi G. et al., 2002*]. Oxidative stress is detectable by an increased oxidation of plasmatic proteins, with the appearance of carbonyl functions in their structure and loss of sulfhydryl (SH) groups. Oxidation of albumin, being itself an important antioxidant factor in plasma, further decreases the antioxidant potential in plasma. Chronic uremia is often associated with muscle weakness, and the observation of oxidative damage in lipids and proteins of skeletal muscle suggests the existence of a real "hemodialytic myopathy". The repeated occurrence of oxidative alterations is also responsible for the accumulation of irreversible macromolecular aggregates ("hemodialytic amyloidosis" in tissues [*Morena M. et al., 2005*], as well as for a precocious onset of atherosclerosis, likely favoured by the oxidation of low-density lipoproteins.

HYPERGLYCEMIA AND DIABETES

A common feature of both type-1 and type-2 diabetes is an absolute or relative impairment of insulin secreting beta-cells of pancreas. Different effector mechanisms can produce this deficiency: immune stimuli in type-1 diabetes, as well as metabolic/inflammatory factors in type-2 diabetes converge on common signal transduction pathways leading to functional derangement and cellular injury, and it is believed that oxidative stress plays a critical role in beta-cellular loss [*Kaneto H. et al., 2005*]. In type-1 diabetes beta-cells are the subject of an autoimmune attack by mononuclear cells ("insulitis"). Death of beta-cells during insulitis is likely caused by direct contact with activated macrophages and T-lymphocytes, and/or by the exposure to soluble mediators secreted by these cells, such as cytokines, ROS, RNS. In type-2 diabetes hyperglycemia, often associated with hyperlipidemia, induces an increased production of superoxide radical by mitochondria, resulting in increased exposure of cells to ROS [*Lowell B., Shulman G., 2005*]. Besides, the excess production of ROS promotes the induction of inducible nitric oxide synthase (iNOS) and thus an increased production of nitric oxide (NO): the simultaneous presence of increased levels of superoxide and NO favours in turn the formation of cytotoxic peroxynitrite anion. It should be also considered that beta-cells are particularly vulnerable to oxidative stress, as their

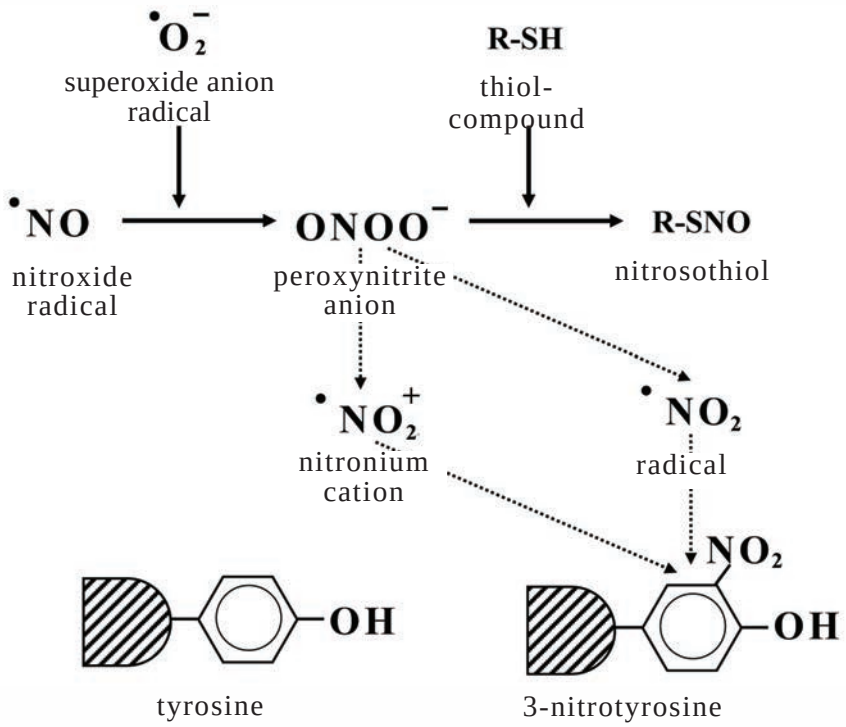


FIGURE 3. *Interactions between reactive oxygen and nitrogen species can produce regulatory effects on cellular injury and protein nitrosation process, e.g., on tyrosine residues, with pathophysiological relevance.*

own antioxidant defenses are significantly lower than in other cell types **[***Kaneto H. et al., 2006*].

Conditions of increased oxidative stress also concur to determine many of the clinical complications of diabetes. The presence of a general oxidative stress in the diabetic patient can be inferred from generally decreased levels of antioxidants, such as vitamins E and C. Studies performed with the use of inhibitors of oxidative phosphorylation have recently highlighted that redox dysequilibrium likely originates in mitochondria, where the exposure to elevated glucose concentrations causes an increase in production of ROS **[***Nishikawa T. et al., 2000***]**. Hyperglycemia can anyway stimulate ROS formation through a series of additional mechanisms, involving direct action by glucose and activation of several enzyme activities, such as nicotinamide adenine dinucleotide phosphate

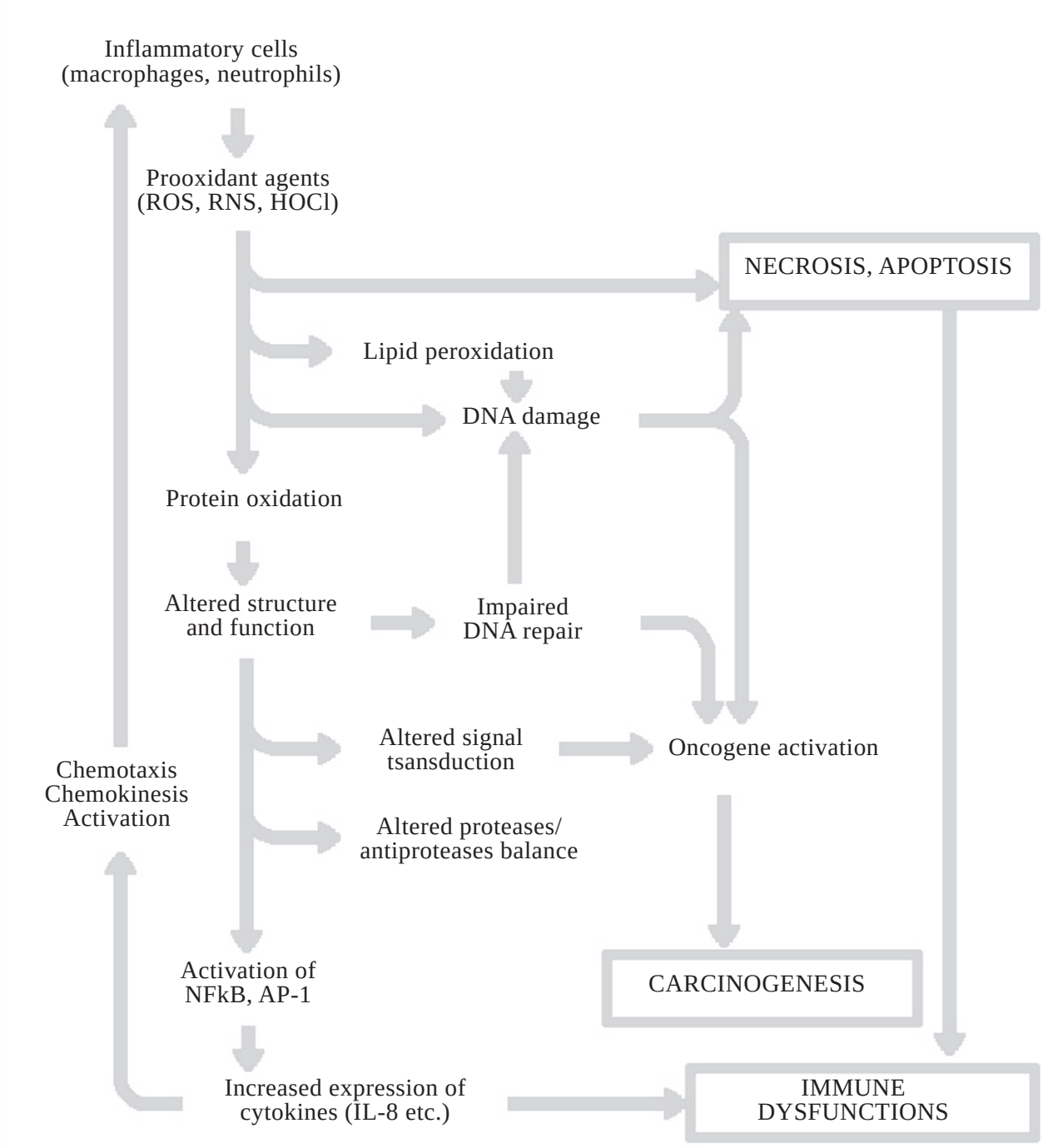


Figure 4. *Involvement of oxidative stress in inflammatory processes: mechanisms and molecular targets of ROS and RNS produced by activated phagocytic cells.*

(NADPH) oxidase (Nox), xantine oxidase, lipoxygenases, cytochromes P450, and nitric oxide synthases (NOS)**[***Maiese K. et al., 2007***]**. Glucose can directly react with amino groups of amino acids, peptides and proteins leading first to formation of Schiff bases and then to the appearance of carbonyls in these structures ("protein glycation", Maillard's reactions). Modified molecules (advanced glycation end-products) can easily form aggregates. It is believed that the phenomenon participates – besides alterations typical of diabetes in various body organs/systems – also in the general process of ageing, in diabetics, as well as in healthy subjects. Hyperglycemia seems to upregulate the expression and activity of NOS in the vascular system, with increased production of NO; the occurrence of a real "nitrosative stress" in diabetics has been suggested [*Stevens M., 2005*]. A primary role in oxidative processes is played by the NADPH oxidase enzymatic complex, whose activation has been documented in various cell types (macrophages and neutrophils, but also fibroblasts, myocardiocytes, endothelium and smooth muscle cells). Protein kinase C and angiotensin II are involved in the activation of NADPH oxidase **[***Wei Y. et al., 2006***]**, which suggests a connection with pathogenesis of hypertension.

ISCHEMIA/REPERFUSION INJURY

Restoration of blood perfusion in a tissue after a period of ischemia, e.g., following the occlusion of a coronary vessel and its subsequent recanalization, is accompanied by conditions of oxidative stress capable of causing considerable damage in tissue. The problem is of particular relevance in chronic and diffuse pathologies, such as ischemic cardiopathy and encephalopathy, and concurs to determine the damage occurring in various body districts (e.g., kidney) in patients affected by severe and prolonged shock. Transplant medicine is also a primary field of investigation, since – by definition – transplantable organs suffer from ischemia, when they are removed from donors, and from reperfusion, when are reconnected to vessels in the receiving patient. During ischemic period already a moderate elevation of ROS levels can be detected, likely originating from derangement of mitochondrial respiration. On the other hand, the massive production of ROS at reperfusion has different sources, and essentially originates by two mechanisms: 1) the activation of xantine oxidase following the accumulation in tissue of purine catabolites of ATP consumed during hypoxia causes a massive production of superoxide anion and hydrogen peroxide intracellularly; 2) incoming neutrophils adhere to endothelium damaged by hypoxia and become activated producing – extracellularly in this case – high levels of prooxidants **[***Jordan J. et al., 1999*].

CARDIOVASCULAR DISEASES

Many of the phenomena and processes described in previous paragraphs are associated with cardiovascular pathologies, first of all those involving atherosclerosis and ischemia but also hypertension, myocardial hypertrophy, cardiomyopathies and congestive heart failure. Noxious effects of the oxidative attack occur through various mechanisms, converging in the first place on alterations of ionic calcium subcellular compartmentation. In myocardial cells, lipoperoxidation of the sarcoplasmic membrane causes the inhibition of Ca^{++}-ATPase and release of calcium in the cytoplasm; the same is produced when superoxide anion and/or hydrogen peroxide directly oxidize SH groups of the enzyme **[***Dhalla N. et al., 1999***]**. On the other hand, both ROS and lipoperoxidation products provoke the uncoupling of mitochondrial oxidative phosphorylation, thus altering Ca^{++} transport at that site as well. Then, the increased cytoplasmic levels of Ca^{++} appear to promote several distinct pathological processes in cardiovascular tissues, such as endothelial hyperplasia of initial atherosclerosis, vasoconstriction related to hypertension, myocardial injury during ischemia-reperfusion and hypertrophy preluding to heart failure.

Pathological effects may also ensue from alteration of reciprocal levels of ROS and RNS, and of their temporal/spatial distribution. ROS contribute to myocardial damage both by oxidizing cellular components critical for the excitation-contraction coupling and by hampering biological effects of nitric oxide. NO levels regulate several processes both in myocardium and in the vessel wall, e.g., contraction, endothelial functions, vascular tone and oxygen supply to tissues. ROS can attenuate NO effects by directly reacting with it **(**Figure 3**)** or by oxidizing selected sites on proteins, thus making them unavailable to nitrosation. In physiological conditions, NO concentrations tend to be higher

than those of superoxide anion, and thus protein nitrosation is favoured. On the other hand, the unbalance between superoxide and NO levels can favour oxidative reactions and formation of nitrosating agents that preferentially react with SH groups, thus altering the usual pathways of protein nitrosation.

Interactions of this kind likely play a role in pathogenesis of hypertension as well. Increased levels of superoxide anion can react with nitric oxide and produce peroxynitrite. Apart from harmful effects of this compound, the process results in a net decrease of available NO, with a reduction of its vasorelaxant and hypotensive function. As mentioned above, the formation of ROS by smooth muscle cells in the vessel wall can be stimulated by angiotensin II, which further contributes to explain the involvement of this protein in pathogenesis of hypertension.

It is well assessed that low-density lipoproteins (LDLs) are involved in atherosclerosis. LDLs accumulate – in oxidized forms – in the intimal space, and this establishes an activation signal for several cell types capable of producing prooxidants, in the first place, macrophages. Several studies have shown that atherosclerotic plaques contain sufficient levels of iron as to sustain the so-called Fenton reaction, thus catalysing the formation of highly reactive and harmful hydroxyl radicals (•OH):

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-.$$

Oxidative stress processes in atherosclerotic plaques can promote progression and instabilization of lesions with various mechanisms, e.g., by exerting a chemotactic action on inflammatory cells, by altering the protease/antiprotease balance in connectival matrix or by stimulating the proliferation of fibroblasts, smooth muscle cells, and fibromyocytes **[***Stocker R., Keaney J., 2004***]**. Recent research has documented that a contribution to alter redox equilibria in the diseased vessel wall might be given by gamma-glutamyltransferase (GGT). Several epidemiological reports have confirmed the correlation of slightly increased levels of GGT in serum with an unfavourable cardiovascular prognosis. The experimental studies carried out in our own laboratory during the last decade have ascertained that atherosclerotic lesions contain high amounts of enzymatically active GGT **[***Paolicchi A. et al., 1999; 2008; Emdin M. et al., 2005***]**, in the form of macromolecular complexes originating from the blood stream **[***Franzini M. et al., 2009*].

Oxidative processes are also responsible for stimulation of apoptosis of myocardial cells, e.g., in conditions of heart failure. It is known that one of the signals leading to ignition of apoptosis is given by leakage of cytochrome ***c*** from mitochondria, and that this protein is associated with the phospholipid cardiolipin within the inner mitochondrial membrane. Lipid peroxidation can destabilize such molecular association, and at the same time the oxidation by ROS of SH groups in proteins of the membrane pore structures can directly produce the mitochondrial permeability transition required for release of cytochrome ***c*** in the cytoplasm **[***Petrosillo G. et al., 2003***]**.

Neurodegenerative diseases

Central nervous system is particularly vulnerable to oxidatve processes due to the high amounts of oxygen required by neuronal metabolism, to the high content in unstaurated fatty acids prone to undergo lipid peroxidation in phospholipids of cellular and myelinic membranes, and to the presence – especially in selected brain regions – of significant deposits of redox-active metals (iron, copper). In Alzheimer's disease, the accumulation of beta-amyloid in tissue is accompanied by significant oxidative damage. It has been recently reported that oligomeric (rather that fibrillar) forms of beta-amyloid are capable of stimulating the formation of hydrogen peroxide and promoting lipid erosidation **[***Tamagno E. et al., 2006*]. The phenomenon appears to be determined by the ability of beta-amyloid to bind and reduce transition metal ions: iron, copper and even zinc. The processes started in this way ("redox cycling" reactions) can in fact lead to the formation of ROS, including hydroxyl radical, i.e. a compound especially active in initiation of lipoperoxidation. In diseased brains several biomarkers of oxidative stress can be therefore detected: increased levels of malondialdehyde, 4-hydroxy-nonenal, oxidized proteins, oxidized DNA; decreased levels of unsaturated fatty acids; formation of peroxynitrite and presence of nitrosated proteins in microglial cells surrounding the fibrous plaques.

Akin redox cycling reactions appear to participate in pathogenesis of the injury occurring – in

Parkinson's disease – in dopaminergic neurons of *substantia nigra* in mesencephalon, a region in fact peculiarly rich in iron. On the other hand, complex and not yet elucidated interactions also involve in the process glutathione, NO and dopamine, the latter itself capable of catalyzing redox cycling reactions of iron and copper **[***Halliwell B., 2006***]**.

A separate discussion should be dedicated to Amyotrophic Lateral Sclerosis. The observation that, in familiar forms of the disease, mutations are inherited in genes coding for copper/zinc superoxide dismutase (now defined as SOD-1) led researchers to hypothesize that a loss of antioxidant function of this enzyme was essential in pathogenesis (SOD in fact participates in detoxication of superoxide anion). However, subsequent studies have shown that mutated protein actually forms cytotoxic aggregates, and that loss of enzyme function may not be involved. Nevertheless, the disease holds mysterious aspects still awaiting for elucidation **[***Shaw B., Valentine J., 2007***]**.

CONCLUSIONS: oxidative stress, cause or effect?

In the present overview, the role potentially played by oxidative stress in other important pathologies – e.g., cancer – has been purposively overlooked: genetic and molecular aspects involved would in fact require a separate argumentation, and the reader is therefore addressed to more specific publications [*Klaunig J., Kamendulis L., 2004; Toyokuni S., 2006; Nair U. et al., 2007*]. Anyway, basing on the elements concisely reported above it should be obvious that, generally speaking, free radicals and prooxidants – besides the physiological functions they perform at various levels in cellular life – can elicit significant damage to biological macromolecules when they are produced in excess with respect to antioxidant defenses. On the other hand, the vexed question whether an uncontrolled production of ROS or RNS is always the cause of pathological processes, or rather the latter can themselves originate the formation of prooxidant species, cannot receive an unambiguous answer valid in all instances. Free radicals undoubtedly play a causative role in producing alterations on DNA, e.g. during chronic inflammation. However, other conditions present with less defined features. As far as, e.g., ischemia-reperfusion damage, it is well established that this is directly related to increased levels of cytosolic calcium. Calcium induces the activation of proteolytic enzymes, which are directly responsible for injury to macromolecules. Nevertheless, with still poorly defined mechanisms, increased calcium levels are also responsible for a further increase in ROS production; thus, in this case the latter represent a mere biomarker of the ongoing pathological process. Moreover: in case of Parkinson's disease, it is unlikely that oxidative stress is the primary, initial event in the degenerative process leading to depletion of mesencephalic dopaminergic neurons. However, the occurrence of oxidative phenomena in the course of the disease is well established, substantially participating in progression of neuronal damage. It can be thus misleading to think of oxidative stress as the origin of all processes, in which it can be detected. Rather it is certainly wiser to consider it as one step – often an important one – in a chain of events of varying length. The monitoring of oxidative stress levels, even in cases, in which it is not the initial cause of the disease process, can anyway enable to interrupt the chain and limit progression of damage.

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