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Role of the Neutrophil NADPH Oxidase and S100A8/A9 in the Pathophysiology of Chronic Inflammation

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1. Introduction

Reactive oxygen species (ROS) are low-molecular-weight inorganic and highly reactive compounds that are produced during normal aerobic cell metabolism. At low level, ROS have a transient mode of action and important physiological roles in maintaining intracellular cell redox status, physical-chemical properties of membranes, protein kinase and transcriptional factor activities. They participate in the regulation of many aspects of fundamental cellular function, including growth-specific and migration-related signalling pathways, gene expression, GTPase-dependent cytoskeletal rearrangements, cell proliferation and apoptosis. Multiple endogenous macromolecules, participating in cellular signalling networks, bear redox-active moieties (e.g., methionine, cysteine, guanine) at functional regions that render them sensitive to ROS. Consequently, ROS emerge, not only as second messengers, but also as diffusible modulators able to produce stable secondary signalling molecules.

A major source of ROS are phagocytic cells such as polymorphonuclear neutrophils that are found activated and adherent to the endothelium or migrating through the extravascular tissue matrix. ROS produced by neutrophils are designed to kill the invading pathogens and have an important role in priming the immune system. The phagocyte NADPH oxidase, also referred as NOX2, is composed of several membrane-bound and cytosolic subunits that assemble rapidly in the phagosomal or plasma membrane (Fig. 1). This allows the concentrated release of ROS at sites of inflammation where the pathogen is located (Ohno et al., 1982) and diffusion over short distances, enabling these second messengers to act on adjacent neighbouring targets. Since many years, it is known that ROS interactions with lipids contribute to disturbances in cell structure (Thaw et al., 1983) and alterations of functional activities (Bellomo et al., 1982; Poot et al., 1988) enhancing the ability of the phagocytes to kill invading microorganisms (Quinn et al., 1995).

Under physiological conditions, ROS are eliminated by several defence mechanisms (e.g., antioxidant enzymes) to maintain a normal intracellular redox environment and control the signalling cascades.

However, when these protective mechanisms are overwhelmed by excessive amounts of ROS, due to inappropriate activation of phagocytes or alterations of the antioxidant defence system, a situation of oxidative stress can occur resulting in abnormal physiological

responses. During a prolonged period, focal regions of the endothelium can be exposed to aberrant levels of ROS, which in turn cause the destruction of healthy tissue. Indeed, at high concentrations and continued exposure, ROS can damage all types of biomolecules including DNA, lipids, carbohydrates and proteins.

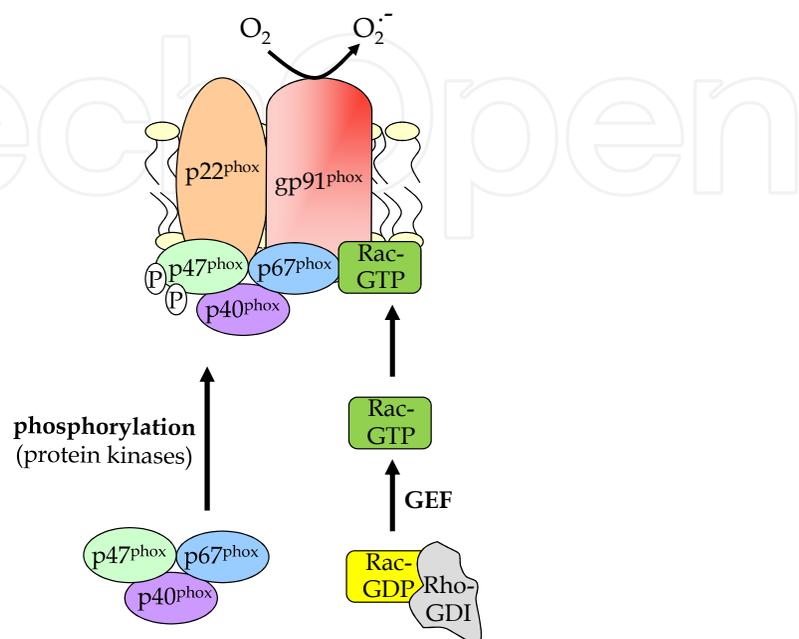


Fig. 1. Assembly and activation of the phagocyte NADPH oxidase, NOX2 (for reviews, see Babior et al., 2002; Sheppard et al., 2005). NOX2 activation is mediated by the assembly of cytosolic subunits (p40^{phox}, p47^{phox}, and p67^{phox}) with the membrane subunits (p22^{phox} and gp91^{phox} constituting the flavocytochrome b₅₅₈). Phosphorylation of p47^{phox}, by protein kinases, is notably required for translocation of p47^{phox} to the membrane and binding to p22^{phox}. The guanine nucleotide exchange factor (GEF) triggers GTP binding to Rac promoting the membrane translocation and the binding to p67^{phox} necessary to the assembly of active NOX2 and superoxide anion production.

2. Toxicity of neutrophil NADPH oxidase (NOX2)-mediated release of ROS: Pathophysiological roles

2.1 Molecular damage caused by ROS

Irreversible oxidative modification of macromolecules including proteins, lipids, DNA and carbohydrates are typically viewed as the primary cellular targets of ROS and contribute to cell injury. Consequently, oxidized biomolecules are linked to the pathophysiology of multiple chronic human diseases and are the most commonly used biomarkers of oxidative damage isolated from tissues and biological fluids (for review, see Dalle-Donne et al., 2006).

2.1.1 Lipid peroxidation

Lipid peroxidation is a complex process in which oxidants, generated by NADPH oxidase of activated neutrophils, react the most abundantly with polyunsaturated fatty acids (e.g., linoleic acid and arachidonic acid) to form a variety of products including aldehydes, lipid radicals and hydrocarbons. Peroxidation of lipids can disrupt the organization of the

membrane modifying its physical properties and causing changes in fluidity and permeability, inhibition of metabolic processes, and alterations of ion transport (Nigam & Schewe, 2000).

Polyunsaturated fatty acid residues of phospholipids nearby membrane were found to be extremely sensitive to oxidation by the highly reactive hydroxyl radical (Siems et al., 1995). The initial reaction of hydroxyl radical with polyunsaturated fatty acids produces an alkyl radical, which in turn reacts with molecular oxygen to form a peroxy radical in a perpetuating chain reaction. Once formed, peroxy radicals can undergo subsequent cyclization to generate endoperoxides, which leads to the final production of malondialdehyde (Mao et al., 1999; Marnett, 2002). Malondialdehyde reacts with DNA, predominantly with deoxyguanosine, to form exocyclic adducts most of which are mutagenic in mammalian cells.

The major aldehyde product of lipid peroxidation other than malondialdehyde is 4-hydroxy-2-nonenal (4-HNE) that is a weakly mutagenic metabolite but with a high cytotoxicity. The cytotoxic effects are thought to be due to the ability of 4-HNE to react readily with sulfhydryl groups by a Michael addition mechanism to form stable thioether derivatives (Esterbauer et al., 1975; Esterbauer et al., 1991). 4-HNE is a potent inhibitor of sulfhydryl enzymes, such as the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) via modification of the cysteine residue (Cys-149) at the catalytic site (Uchida & Stadtman, 1993). Later, it was suggested that 4-HNE inactivation of GAPDH is not due to the modification of the catalytic center but to the sequential and selective modification of amino acids (His-164, Cys-281, Cys-244, His-327 and Lys-331) primarily located in the surface of the GAPDH molecule (Ishii et al., 2003).

4-HNE reacts also with selective histidine residues of proteins including insulin (which lacks cysteine) contributing to the cytotoxic action of 4-HNE (Uchida & Stadtman, 1992). In certain proteins, lysine ϵ -amino groups, but not histidine, is the major target amino acid of 4-HNE. Lysine modification in glucose-6-phosphate dehydrogenase via Schiff-base formation is associated with a loss of enzyme activity (Sweda et al., 1993) and 4-HNE modification on low density lipoproteins have been implicated in the pathophysiology of atherosclerosis (Jessup et al., 1986; Vindis et al., 2007).

2.1.2 Protein oxidation

Many different types of oxidative modification of proteins can be induced by ROS. Cysteine and methionine residues of proteins are highly susceptible to oxidation by various forms of ROS. Oxidation of cysteine residues can lead to the formation of a mixed disulphide between protein thiol groups and low molecular weight thiol compounds (reversible S-glutathiolation). Carbonyl groups are major products of ROS-mediated oxidation proteins and the concentration of these derivatives is an adapted marker of protein oxidation (Berlett et al., 1997; Chevion et al., 2000). Protein modifications elicited by oxidative attack on lysine, arginine, proline or threonine, or by secondary reaction of cysteine, histidine or lysine residues with carbonyl compounds can result in the formation of protein derivatives possessing highly reactive carbonyl groups such as aldehydes and ketones (Berlett et al., 1997). Oxidation of some critical methionine residues causes a complete inhibition of actin polymerization and destabilization of the structure of actin filaments (Dalle-Donne et al., 2002).

Oxidative modification of proteins by ROS is implicated in the etiology and/or progression of a broad variety of age-related degenerative pathologies, atherosclerosis, muscular dystrophy, rheumatoid arthritis (Chevion et al., 2000; Moreira et al., 2010; Stadtman &

Berlett, 1997). Various human diseases have been associated with carbonylated proteins (Table 1): acute respiratory distress syndrome, Alzheimer's disease, rheumatoid arthritis, chronic lung disease, and diabetes (for review, see Dalle-Donne et al., 2003).

2.1.3 Nucleic acid oxidation

Permanent genetic material damage due to oxidative stress can represent the first step to mutagenesis, carcinogenesis, and ageing. ROS are known to react with all components of the DNA molecule and impair DNA repair mechanisms. DNA modification can affect both the purine and pyrimidine bases and also the deoxyribose backbone (Aruoma et al., 1989). DNA modification has been reported to accumulate over the life span of the cell participating to ageing (von Zglinicki et al., 1995). Telomere DNA is deficient in the repair of single-strand breaks produced by hydroxyl radicals affecting telomere length and hence active cell division (Oikawa et al., 2001; Petersen et al., 1998; Saretzki et al., 1999). The most extensively studied DNA lesion is the formation of 8-oxo-7-hydrodeoxyguanosine (8-OH-guanine) generated by the reaction of hydroxyl radicals with guanine repeats. 8-OH-guanine is particularly mutagenic and cytotoxic. It is elevated in leukocytes and sera of patients with rheumatoid arthritis (Table 1) and probably participates in joint inflammation by activating immune cells, which in turn produce excessive pro-inflammatory cytokines (Hajizadeh et al., 2003).

2.1.4 Carbohydrate oxidation

Glycosaminoglycans (GAGs) are major components of extracellular matrix and their increased synthesis and degradation are hallmarks of chronic inflammation and tissue fibrosis. GAGs determine the structure, viscosity and permeability of the ground substance in connective tissue and play a critical role in ion transport, nutrient diffusion, water homeostasis, intercellular signalling and collagen synthesis. GAG oxidation is known to have important biological consequences in particular on endothelial cell adhesion and proliferation (Underwood et al., 1998; Vissers et al., 1991) that are involved in atherogenesis. Chondroitin sulphates and hyaluronic acid, which contain glucosamine and glucuronic acid, are critical GAGs present in synovial joints that have been shown to be fragmented by ROS (Rees et al., 2004). The hypochlorite-mediated depolymerization of GAGs has been shown to produce polymer-derived chloramide, the major species formed due to the reaction of hypochlorite with glucosamine or galactosamine residues (Hawkins & Davis, 1998; Rees et al., 2003). Lower molecular weight hyaluronic acid fragments accumulate during inflammation and may have a role in the activation of phagocytes through the stimulation of interleukin-1 β and TNF- α expression (Noble et al., 1993) resulting in an exacerbation of the inflammatory process and tissue damage.

2.2 NOX2-derived ROS and inflammatory diseases

Chronic inflammation was hypothesized as the loss of balance between apoptosis and wound healing leading to disruption of protective mechanisms of immune system (Khatami, 2005, 2008, 2009). Unresolved inflammation-induced excessive expression of pro- and anti-inflammatory mediators causes erosion of tissue integrity initiating the development of chronic inflammatory diseases or cancer (Khatami, 2011).

Molecular alterations, induced by exaggerated ROS generation during oxidative stress, represent an important cause of injury in many inflammatory diseases (Table 1). ROS

production is a prominent feature in various cardiovascular-related diseases such as hypertension, atherosclerosis, and ischemic heart diseases. Moreover, it was suggested that ROS play a role in a variety of age-related diseases such as some neurological diseases like Alzheimer's disease, type 2 diabetes or even reproductive disorders (for reviews, see Kukreja & Hess, 1992; Reddy et al., 2009; Valko et al., 2007). Among this pleiad of diseases, ROS derived from the neutrophil NADPH oxidase complex (NOX2) have notably been implicated in the pathophysiology of rheumatoid arthritis, atherosclerosis, chronic obstructive inflammatory disease and inflammation-associated cancer.

2.2.1 Chronic inflammatory diseases

Rheumatoid arthritis is the most common type of rheumatological disorder with a prevalence of 0.4% to 0.7% worldwide (Alamanos et al., 2006; Englund et al., 2010). Rheumatoid arthritis is a chronic, destructive, autoimmune joint disease resulting in enormous pathologic sequelae including pain, stiffness, deformity, swelling, as well as systemic effects associated with inflammation limiting activities of daily living. Rheumatoid arthritis principally affects peripheral synovial joints but additionally extra-articular complications, including atherosclerotic vascular disease and premature mortality, can be associated to the disease (Carroll et al., 2006). Indeed, cardiovascular complications are the leading cause of death (42%) among patients with rheumatoid arthritis (Callahan et al., 1995). The pathogenesis of rheumatoid arthritis is a complex process with several distinguishing features involving macrophage-like synoviocytes and fibroblast-like synoviocytes proliferation, pannus formation, cartilage and bone erosion.

The presence of abundant numbers of neutrophils in the synovial fluid of patients with rheumatoid arthritis participate to joint damage via the release of potent effectors of cartilage destruction such as proteases and NOX2-mediated ROS production. The pathogenesis of rheumatoid arthritis is predominantly linked to the formation of ROS to the site of inflammation and tissue lesions caused by elevated ROS concentration participate to the perpetuation of inflammation. These oxidative derivatives may depolymerize hyaluronic acid and inactivate endogenous inhibitors of proteases (Chatham et al., 1993; Edwards & Hallett, 1997; Larbre et al., 1994; Robinson et al., 1992). Rheumatoid arthritis fluids can also contain large quantities of immune complexes and their deposition has been considered to be a major determinant of neutrophil-mediated destructive joint process which is characteristic of rheumatoid arthritis. Indeed, neutrophils primed and isolated from the synovial fluid of patients with rheumatoid arthritis can secrete substantial quantities of ROS in response to immune complexes (Ottonello et al., 2002).

Neutrophils have also been found at sites of atherosclerotic plaque rupture where they appear to be functionally active to generate ROS. Infiltrated neutrophils into atherosclerotic plaque underline the fact that these pro-inflammatory cells contribute to plaque vulnerability and erosion (Hosokawa et al., 2011).

The inflammatory processes in the lung are characterized by an influx of neutrophils into the airways. Increased levels of NOX2-derived ROS produced by inflammatory cells of the airways in the lung have been recognized to contribute importantly in the pathogenesis of asthma and chronic obstructive pulmonary disease (Rahman, 2002). The enhanced expression of surface adhesion molecule Mac-1, which favours the recruitment of neutrophils to the inflammatory site, is coupled with an increase of NOX2 activity. It augments the potential of ROS to induce lung injury, contributing to the development of chronic obstructive pulmonary disease (Noguera et al., 2001). Oxidative stress can reduce

the histone deacetylase activity allowing the access of transcription factors as NF- κ B, AP-1 and Nrf2 to the DNA and leading to enhanced pro-inflammatory or reduced antioxidant gene expression in various lung cells (Ito et al., 2001; Kersul et al., 2001; Mercado et al., 2011). Moreover, ROS may play a role in enhancing the mucus secretion through the modulation of enzymatic activities such as src homology 2-containing protein tyrosine phosphatase, p38 MAPK or receptor tyrosine kinases (epidermal growth factor receptor) (Jang et al., 2010; Kohri et al., 2002; Meng et al., 2002).

2.2.2 Cancer-associated inflammation

Persistent chronic inflammation contributes to increase the risk of cancer and promote cancer development and progression. The inflammatory response triggered by infection is involved in the pathogenesis of approximately 20% of human tumors (e.g., *Helicobacter pylori* infection is associated with gastric cancer). Cancer-related inflammation is characterized by the presence of infiltrating immune and inflammatory cells (notably T-lymphocytes, tumor-associated macrophages and neutrophils) in the microenvironment of the tumor increasing generation of ROS and angiogenic factors, matrix-degrading enzyme and growth factor activities, and altering cytokine and chemokine expression. Accumulating evidence shows that chronic inflammation can promote an environment that is favourable to all the stages of human tumors. Six hallmarks have been proposed by Hanahan & Weinberg (Hanahan & Weinberg, 2011) to characterize the multistep of the carcinogenesis including sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. It has been proposed that the genome instability leading to cancer-related inflammation represents the seventh hallmark of tumorigenesis (Allavena et al., 2008; Mantovani, 2010).

The link between chronic inflammation and cancer has been suggested by the enhanced colorectal cancer susceptibility of persons with inflammatory bowel disease (e.g., ulcerative colitis and Crohn's disease). Repeated injury and repair triggered by chronic inflammation may increase cell turnover and permanent changes in the genome leading ultimately to tumorigenesis. It is generally accepted that cancer initiation may be a pathological consequence of ROS-induced DNA lesions that in turn result in mutations activating oncogenes or inactivating tumor-suppressor genes (Klaunig & Kamendulis, 2004). Chronic exposure to ROS may also alter normal cellular and molecular signalling pathways. ROS have been shown to activate transcription factors such NF- κ B, AP-1 and STATs. NF- κ B is known to be constitutively activated in a variety of malignancies (Brar et al., 2003) contributing to abnormal malignant cell division through enhanced expression of anti-apoptotic factors (Bcl-2), and proliferative factors, such as cyclin D1 (Brar et al., 2003). The interest in the role of neutrophils in the inflammatory origin of cancer (Table 1) is recent and has considerably increased over the last years. In addition of its function in host defence, a critical role for NOX2-mediated ROS production has been pointed in the induction and development of malignant cells. Human neutrophils can directly damage DNA and can induce malignant transformation, which suggest that phagocytic cells are carcinogenic (Brar et al., 2003; Knaapen et al., 1999). The leukotriene LTB-4 and cytokine IL-8 are recognized to play a crucial role in neutrophil recruitment into airways during lung cancer in particular when progressing to the next stage of cancer (Carpagnano et al., 2011).

Source	Targets/alterations	
ROS	Nucleic acid oxidation Hyaluronic acid depolymerization Protease inhibitor inactivation	Rheumatoid arthritis
ROS	Lipid peroxidation Atherosclerotic plaque erosion	Atherosclerosis
ROS	Histone deacetylase activity reduction p38 MAPK, EGFR, SHP2 modulation	Chronic obstructive pulmonary disease
ROS	DNA lesions Transcription factor activation	Lung cancer
ROS	Carbonylated proteins	Diabetes, Alzheimer's disease
S100A8/A9	NF-κB, p38 MAPK activation	Rheumatoid arthritis
S100A8/A9	Myeloid-derived suppressor cell accumulation p38 MAPK, p44/42 kinase activation	Cancer

Table 1. Some human inflammatory diseases associated with ROS and S100A8/A9

3. Description of the signal transduction pathways regulating NOX2 with emphasis on the role of Ca²⁺ mobilization

Ca²⁺ is a ubiquitous second messenger that functions over a wide and defined spatio-temporal range. Normal cytosolic free Ca²⁺ concentration ([Ca²⁺]_c) in resting mammalian cells is maintained to low levels, in a range of 50-150 nM, compared to an endoplasmic reticulum and extracellular Ca²⁺ concentration of ~500 μM and ~2000 μM, respectively. When Ca²⁺ channels are opened in the plasma membrane, Ca²⁺ can rapidly flows into the cytosol and reach a concentration of 1 μM in a few seconds. Alternatively, Ca²⁺ influx can be delivered to low sustained Ca²⁺ levels to control appropriate cellular activities. A broad class of Ca²⁺ channels, differing for regulatory mechanisms and intracellular distribution, can be activated allowing the control by adapted Ca²⁺-signalling systems of many divergent cellular processes (exocytosis, muscle contraction, gene transcription, fertilization, meiosis, immune response, muscle contraction) with the right frequency and intensity. Fluctuations in [Ca²⁺]_c are initiated at a localized site and diffuse inside the cell in the form of intracellular Ca²⁺ waves. In this view, neutrophils show irregular [Ca²⁺]_c spikes during phagocytosis and after stimulation by the bacterial chemopeptide fMLF (Dewitt et al., 2006; Jaconi et al., 1988).

3.1 Store-operated Ca²⁺ entry mechanism

The receptor-mediated Ca²⁺ influx required for NOX2 activation in neutrophils is predominantly the result of the activation of the so-called store-operated Ca²⁺ entry (SOCE), which is initiated by a fall in intracellular Ca²⁺ store content. The store depletion is coupled to the opening of store-operated Ca²⁺ channels (SOCs) localized in the plasma membrane,

giving rise to a substantial Ca^{2+} influx. The SOCE mechanism involves G-protein-coupled receptors (e.g., N-formylpeptide receptor, FPR) that are associated to phospholipase C activation. This enzyme generates inositol 1,4,5 trisphosphate, which in turn mediates the depletion of Ca^{2+} from endoplasmic reticulum (Fig. 2). The fall of Ca^{2+} within the stores is sensed by the stromal interaction molecule protein 1 (STIM1) that translocates through the endoplasmic reticulum membrane to aggregate with SOCs (for review, see Putney, 2007). Activation of SOCs results in a Ca^{2+} influx into the cell and subsequent $[\text{Ca}^{2+}]_c$ elevation.

Direct evidence in support of SOCE has been provided by the electrophysiological demonstration of Ca^{2+} currents evoked by depleting intracellular Ca^{2+} stores (Hoth & Penner, 1992). This current was termed Ca^{2+} release-activated Ca^{2+} current (I_{crac}). I_{crac} is a non-voltage activated, an inwardly rectifying and a highly selective current for Ca^{2+} with a very positive reversal potential level (greater than + 60 mV) (Parekh & Penner, 1997). I_{crac} is not the only store-operated Ca^{2+} current, and it is now apparent that SOCE encompasses a family of Ca^{2+} -permeable channels as judged by their diverse biophysical properties in different cell types. This disparity indicates that SOCs are likely to possess different molecular structures (for review, see Salido et al., 2011). Recent advances in the understanding of the potential molecular composition of SOCs has been the discovery of two families of transmembrane proteins, STIM and Orai (Peinelt et al., 2006; Prakriya et al., 2006; Soboloff et al., 2006). The selective I_{crac} channel pore is formed by a tetrameric arrangement of Orai1 dimers, which is induced by the interaction with the C-terminus of STIM (Penna et al., 2009). STIM1 acts as a Ca^{2+} sensor/activator of Orai1 and Orai1 constitutes the pore-forming component of I_{crac} channels (Mercer et al., 2006). However, SOC currents that display distinct properties from I_{crac} may involve channels composed of transient receptor potential canonical (TRPC) subunits. In this sense, novel insights into the molecular components and the regulation of SOCs have been provided. TRPC1 and Orai1 could constitute distinct Ca^{2+} and I_{crac} channels, respectively, both of which are gated by STIM1 in response to store depletion and contribute to SOCE (Cheng et al., 2011).

3.2 Non-store-operated Ca^{2+} entry mechanism

SOCE is not the only pathway for Ca^{2+} influx in non-excitabile cells; it can be supplied by alternative pathways dependent on the generation of second messengers but unrelated to store depletion. Constitutive STIM1 in the plasma membrane could regulate the activity of the arachidonic-acid-regulated Ca^{2+} -selective channels (ARC channels) (Mignen et al., 2007), whose activation is entirely independent of store depletion. The molecular structure of functional ARC channels is formed by a pentameric assembly of Orai1 and Orai3 subunits; these latter subunits determine the selectivity of ARC channels for arachidonic acid (Mignen et al., 2009). Beside ARC channels, other Ca^{2+} channels are activated by a variety of second messengers. Accumulating evidence show that members of TRPC could be activated by diacylglycerol (Brécharde et al., 2008; Hofmann et al., 1999). In addition, cyclic adenosine diphosphoribose, via its hydrolysis product (adenosine diphosphoribose), could support Ca^{2+} entry through the activation of TRPM2, a member of transient receptor potential family (Heiner et al., 2006; Howard et al., 1993; Lange et al., 2008).

3.3 Ca^{2+} dependence of NOX2 activation

It is well-known that, among complex transductional networks, Ca^{2+} mobilization acts a primordial role in receptor-mediated activation of NOX2 by neutrophils (Brécharde et al.,

2008; Foyouzi-Youssefi et al., 1997). Knock-down of putative constituents of SOCE mechanism (Orai1, STIM1) by specific siRNA or decrease of SOC activity by pharmacological inhibitors (MRS1845, SK&F96365 or 2-APB) led to a diminished NOX2 activity in the plasma membrane (Brécharde et al., 2008, 2009; Lee et al., 2005) underlining the preponderant function of SOCE in the regulation of NOX2. Activation of Ca^{2+} signal is reported as an on-switch for NOX2 activity not directly correlated with spiking activity in cytosolic Ca^{2+} (Brasen et al., 2011).

Extracellular Ca^{2+} entry is also required for intraphagosomal oxidative activation and has been temporally correlated with NOX2 activity (Dewitt et al., 2002). Ca^{2+} influx appears to be necessary for an optimal intraphagosomal oxidative activity but not sufficient to initiate oxidative activation (Dewitt et al., 2002). Orai1 and STIM1 contribute to the regulation of phagosomal NOX2 activity through the activation of store depletion-regulated Ca^{2+} influx (Braun et al., 2009; Steinckwich et al., 2011).

On the other hand, Itagaki et al. (Itagaki et al., 2005) suggest that Ca^{2+} influx occurring through a mechanism other than SOCE could be a relevant event to activate NOX2. In addition, the TRP channel, TRPC3, appears to be involved in non-SOCE-dependent regulation of NOX2 (Brécharde et al., 2008).

Taken together, these results provide strong evidence for the involvement of two separate Ca^{2+} signalling pathways in NOX2 regulation but no direct correlation between non-SOCE or SOCE and NOX2 has been yet formally established.

3.4 Ca^{2+} targets for the regulation of NOX2 activity

3.4.1 Protein kinase C (PKC)

Activation of protein kinase C (PKCs), a phospholipid-dependent family of serine-threonine protein kinases, is one of the earliest events in multiple signal transduction pathways that control a variety of cellular responses (secretion, gene expression, proliferation and muscle contraction) including NOX2 activity. The PKC family is categorized into three classes on the basis of structure and activation requirements. At least eleven different PKC isoforms have been characterized so far and these isoforms can be grouped into the following three subgroups based on Ca^{2+} dependency, activators and molecular structure. Conventional (classical) PKCs (α , β I, β II, and γ) are Ca^{2+} -dependent via their C2 domains while novel (δ , ϵ , μ , θ and η) and atypical (ζ and τ/λ) PKCs are Ca^{2+} -independent. Both conventional and novel PKCs are directly activated by phosphatidylserine, diacylglycerol and phorbol esters (such as PMA) through their cysteine-rich C1 domains while atypical isoforms are insensitive to phorbol esters (Hug et al., 1993; Newton 1995; Sargeant & McPhail, 1997). Atypical PKCs, unlike classical and novel PKCs, feature a C1-like domain which does not bind to either diacylglycerol or phorbol esters.

In addition of Ca^{2+} -independent PKCs, conventional PKCs (α and β isoforms) have been found to regulate NOX2 activity (Fig. 2) as shown by studies using antisense strategy or pharmacological inhibitors. Down-regulation of PKC β and PKC α activity affect superoxide anion production in neutrophil-like HL-60 cells underlying the importance of these two enzymes for a full activation of NOX2 (Korchak et al., 2007).

Since it is known that NOX2 activation is critically dependent on p47^{phox} phosphorylation, a lot of effort has been put into identifying PKCs responsible of this downstream event. The role of PKC α , PKC β , and PKC β II in the direct phosphorylation and subsequent membrane translocation of p47^{phox} has been pointed by several studies (Fontayne et al., 2002).

Consistent with these assumptions, Brasen et al. (Brasen et al., 2011) postulated that Ca^{2+} -dependent phosphorylation of NOX2 by PKCs may be in accordance with a slower intermediary step between $[\text{Ca}^{2+}]_c$ elevation and increases in NOX2 activity.

3.4.2 Monomeric G protein Rac

Rac is a member of the Rho subfamily of small GTPases that is essential in NOX2 regulation (for review, see Bockoch & Diebold, 2002). Three isoforms of Rac are known but only Rac1 and Rac2 are found in neutrophils. In the cytosol, Rac is maintained in an inactive GDP-bound form in a complex with RhoGDI, which regulates Rac targeting to the plasma membrane. RhoGDI must dissociate to allow Rac to translocate to the membrane and interact with its downstream effectors. The guanine nucleotide exchange factors (GEF) induce activation by exchanging GDP for GTP, whereas GTPase activating proteins enhance the intrinsic rate of hydrolysis of bound GTP to GDP, resulting in Rac inactivation. Rac translocation is correlated with its activation (Fleming et al., 1996), but both events are probably regulated independently.

Because Ras-GRF exchange factors harbor a Ca^{2+} -calmodulin binding site (Farnsworth et al., 1995) and Tiam1 exchange factor is phosphorylated by Ca^{2+} -calmodulin-dependent protein kinase II (Fleming et al., 1999), changes in $[\text{Ca}^{2+}]_c$ has been proposed to regulate GDP/GTP exchange on Rac1. PKC α and Ca^{2+} /calmodulin-dependent protein kinase II phosphorylate the Rac1-specific exchange factor Tiam1 but only Ca^{2+} /calmodulin-dependent protein kinase II regulates the activity of this exchange factor toward Rac1 (Fleming et al., 1999). Later, it was reported that PKC α , activated by thrombin, can phosphorylate RhoGDI and regulates the dissociation of Rac/RhoGDI complex catalyzing the release of bound GTPases, and subsequent Rac translocation to the plasma membrane (Mehta et al., 2001). Consistent with these findings, Valentin et al. (Valentin et al., 2001) determined that Ca^{2+} influx plays a primordial role in the plasma membrane translocation of Rac1 in neutrophil-like HL-60 cells (Fig. 2). Price et al. (Price et al., 2001) proposed a mechanism whereby $[\text{Ca}^{2+}]_c$ elevation triggers conventional PKC dependent Rho-GDI phosphorylation. This event leads to Rac dissociation from the Rac-RhoGDI complex followed by the membrane translocation of Rac and its activation by guanine exchange factors.

3.4.3 Cytosolic PLA₂ (cPLA₂)

cPLA₂ causes the release of arachidonic acid from membrane phospholipids via the hydrolysis of fatty acids at the sn-2 position (Marshall et al., 2000). Several studies put forward that cPLA₂ is recruited at the plasma membrane in a Ca^{2+} -dependent pathway and PKC α is required for cPLA₂ activity (Li et al., 1999; Schievella et al., 1995; Shmelzer et al., 2003). Although underlying mechanisms need to be investigated further, cPLA₂ has been associated with the regulation of NOX2. cPLA₂ is not required for the membrane translocation of cytosolic NOX2 subunits but appears to have a critical role in NOX2 activation after its assembly (Dana et al., 1998). Indeed, arachidonic acid has been described as a cofactor enhancing the affinity of the assembled NOX2 for NADPH (Shmelzer et al., 2003).

3.4.4 Ca^{2+} -binding protein S100A8 and S100A9

In recent years, members of the large S100 family of proteins containing two EF-hand Ca^{2+} -binding motifs have been involved in the regulation of NOX2. S100A8/A9 have been described as the molecular switch between the receptor-activated, Ca^{2+} -dependent signalling cascade and NOX2 activation.

4. Intracellular functions of S100A8 and S100A9 with particular attention to their role in NOX2 activation

The phagocyte-specific Ca^{2+} -binding proteins S100A8 and S100A9 are largely expressed in the cytoplasm of phagocytes where they exert an intracellular function. The formation of S100A8/A9 heterocomplexes is probably a pre-requisite for their biological activities (Leukert et al., 2006). S100A8 and S100A9 are known to interact with NOX2 subunits (Berthier et al., 2003) and have been proposed as regulators of NOX2 activity. The relevant role for S100A8/A9 complex in oxidative response is probably mediated via their Ca^{2+} - and phosphorylation-dependent translocation upon complex formation at the plasma membrane (Lominadze et al., 2005; Roth et al., 1993; Schenten et al., 2010, 2011) where NOX2 is activated.

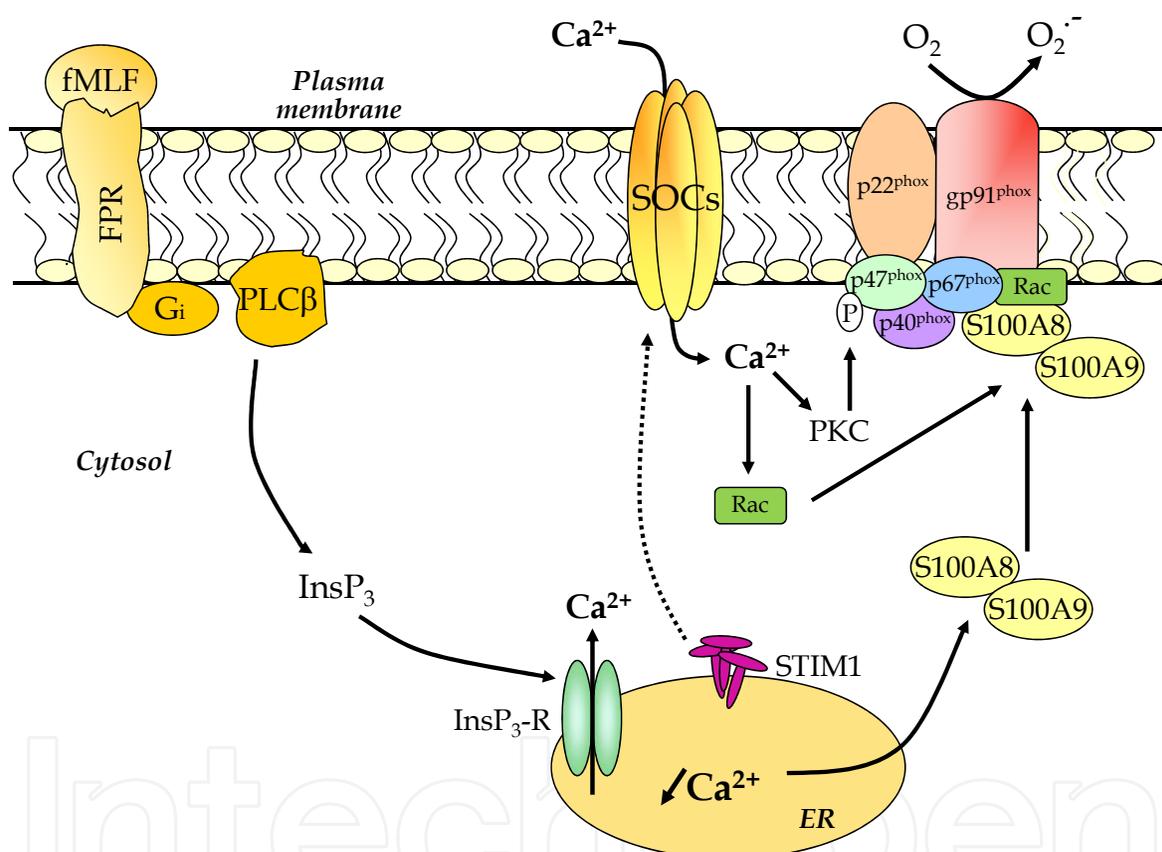


Fig. 2. Model depicting the Ca^{2+} -dependent regulation of NOX2 activity in neutrophils. Binding of the bacterial chemopeptide fMLF to its G-protein-coupled receptor (FPR) leads to the production of inositol 1,4,5-trisphosphate (InsP_3) via phospholipase C (PLC) activation. InsP_3 interacts with its specific receptor-channel ($\text{InsP}_3\text{-R}$) on the surface of the endoplasmic reticulum (ER) triggering intracellular Ca^{2+} store depletion and subsequent elevation of $[\text{Ca}^{2+}]_c$. The fall of Ca^{2+} within the ER is sensed by the stromal interaction molecule protein 1 (STIM1) resulting in the activation of store-operated Ca^{2+} channels (SOCs) at the plasma membrane and extracellular Ca^{2+} entry. Intracellular Ca^{2+} store depletion participates to the membrane translocation of S100A8/A9 and subsequent NOX2 activation. Elevation of $[\text{Ca}^{2+}]_c$ induced by extracellular Ca^{2+} entry mediates the membrane translocation of Rac and stimulates PKC activity involved in the phosphorylation of cytosolic phox proteins.

4.1 Translocation of S100A8/A9 complex to the plasma membrane

An elevation of $[Ca^{2+}]_c$ is necessary for S100A8/A9 relocalization to the plasma membrane. Intracellular Ca^{2+} store depletion appears to be partly responsible for this phenomenon (Schenten et al., 2010) (Fig. 2) but, a supplementary signal for S100A8/A9 translocation is probably required. In this view, it was established that recruitment of S100A8/A9 to the plasma membrane is dependent on S100A9 phosphorylation and subsequently intervene in the regulation of NOX2 activity. This phosphorylation is mediated by p38 MAPK (Vogl et al., 2004) on threonine 113. It has been shown to be regulated by sphingosine kinase activation, which depends on the depletion of intracellular Ca^{2+} stores (Schenten et al., 2011). Furthermore, it has been hypothesized that PKCs plays a role in the regulation of S100A8/A9 by phosphorylating sphingosine kinases. On the other hand, PKCs could modulate S100A8/A9 translocation within cellular compartments by phosphorylating S100A8 (Guignard et al., 1996).

4.2 Interactions between S100A8/A9 and NOX2

To clarify NOX2 regulation processes a method, to isolate the reconstituted assembled NOX2 complex, has been developed, through the purification of neutrophil cytochrome b_{558} . (Berthier et al., 2003; Doussi re et al., 2002). The isolated NOX2 complex was able to produce constitutively superoxide anion in absence of any stimulus. NOX2 turnover was only dependent on the source of cytosol (Palet et al., 2007). The addition of Ca^{2+} -loaded S100A8/A9 to NOX2 complex prepared with neutrophil cytochrome b_{558} and B lymphocyte cytosol, increased the constitutive activity of cytochrome b_{558} to reach a maximum NOX2 turnover $\sim 120\text{ s}^{-1}$. Moreover, cytochrome b_{558} bound to the heparin-agarose matrix, was also activated by using recombinant S100A8/S100A9, instead of cytosolic factors and without any stimulus.

During the activation process of NOX2, it was shown that S100A8/A9 proteins enhance or induce a transition from an inactive to an active state of cytochrome b_{558} . This change of structural conformation was illustrated by atomic force microscopy (Berthier et al., 2003). The data suggest a specific interaction between S100A8/A9 and cytochrome b_{558} . Moreover, S100A8/A9 complex, which enhances the affinity of $p67^{\text{phox}}$ for cytochrome b_{558} , was introduced as a positive allosteric effector of NOX2 activity. Upon translocation, Ca^{2+} -loaded S100A8/S100A9 complex appears to interact preferentially with $p67^{\text{phox}}$ that might favour the organization of a scaffold oxidase complex at the membrane level. However, preincubation of S100A8/S100A9 in the absence of Ca^{2+} led to an interaction of this complex with cytochrome b_{558} but not to its conformational change resulting in ROS production. It supports the fact that the role of S100A8/A9 in NOX2 activation is dependent on Ca^{2+} (Berthier et al., 2009).

5. Pro-inflammatory roles of secreted S100A8/A9: Involvement in pathophysiology

Beside their intracellular functions, S100A8 and S100A9 have been introduced as important pro-inflammatory factors of innate immunity secreted by phagocytes and are considered as damage-associated molecular pattern molecules (Foell & Roth, 2004; Loser, et al., 2010). S100A and S100A9 are known to have antimicrobial effects, transport arachidonic acid to endothelial cells and activate expression of endothelial cell adhesion molecules. Furthermore, the role of S100A8/S100A9 on degranulation (Simard et al., 2010) and on

neutrophil migration (Vandal et al., 2003) has been suggested. S100A8 was recently identified as an endogenous ligand of Toll-like receptor 4 (TLR4), amplifying phagocyte activation during inflammation upstream of TNF- α -dependent effects.

A new inflammatory syndrome characterized by an extraordinary high expression of S100A8/A9 proteins has been described by Sampson et al. (Sampson et al., 2002), which underlines the particular relevance of these two proteins for inflammatory pathologies. This disease is hallmarked by recurrent infections, systemic inflammation, hepatosplenomegaly, hyperzincaemia and hypercalprotectinaemia.

The S100A8/S100A9 complex is found in high concentrations at local sites of inflammation or in the serum of patients with inflammatory diseases. Since S100A8/S100A9 are dramatically up-regulated in rheumatoid arthritis synovial fluid (Baillet et al., 2010; Berntzen et al., 1991; Frosch et al., 2000); they are considered as inflammation biomarkers providing more important and sensitive information about the extent of local inflammation in the affected joints than conventional parameters (such as C-reactive protein) of systemic inflammation (Foell, & Roth, 2004). S100A8/A9 may amplify pro-inflammatory cytokine responses through activation of NF- κ B and p38 MAPK pathways in rheumatoid arthritis (Sunahori et al., 2006). Indeed, the receptor for advanced glycation end products (RAGE), able to bind S100 proteins (Hofmann et al., 1999), has been implicated in the pathogenesis of rheumatoid arthritis and atherosclerosis through its ability to amplify inflammatory pathways via the recruitment of p38 MAPK and downstream activation of NF- κ B (Ehlermann et al., 2006). S100A8 and S100A9 proteins are likely involved in chronic recurrent disorders by modulating activity of matrix metalloproteinases and inducing the pseudotumoral transformation of the synoviocytes (Hiratsuka et al., 2006; Yong et al., 2007). High expression of S100A8/A9 was described in various other chronic inflammatory diseases, such as cystic fibrosis, inflammatory bowel disease Crohn's disease, giant cell arteritis, cystic fibrosis, Sjogren's syndrome, systemic lupus erythematosus, and progressive systemic sclerosis (for reviews, see Foell et Roth., 2004; Gebhardt et al., 2006). In addition, overexpression of these proteins has also been seen in many tumor-infiltrating cells (Gebhardt et al., 2006; McKiernan et al.; 2011; Su et al., 2010) underlining the fact S100A8/A9 levels may serve as a potential marker for metastatic progression in certain type of cancers. Human chromosome 1q21, where S100A8 and S100A9 are clustered, is frequently rearranged in human epithelial tumors and tumors of soft tissues, suggesting a link between S100 proteins and tumor formation and metastasis (for reviews, see Gebhardt et al., 2006; Heizmann et al., 2007). The strong up-regulation of S100A8/A9 both in inflammation and in cancer suggests these proteins may play an important role in cancer-associated inflammation by enhancing inflammatory responses. S100A8 and S100A9 promote tumorigenesis by inducing the accumulation of myeloid-derived suppressor cells in the tumor microenvironment and thereby repress host-mediated tumor immunity (Sinha et al., 2008). S100A8/A9 can also promote tumorigenesis by activating pro-tumorigenic signalling pathways. S100A8/A9 have been shown to promote cell growth via p38 MAPK and p44/42 kinase activation in tumor cells in a RAGE-dependent manner (Ghavami et al., 2008).

Taken together with the pro-inflammatory properties described above, the role of S100A8/S100A9 as protective mechanisms in inflammation should also be considered. They are more sensitive to oxidation than low-density lipoproteins and S100A8 is a key target of oxidation by peroxide, hypochlorite and nitric oxide. Thus, post-translational modifications of S100A8/S100A9 proteins induced by ROS may switch their biological properties from a pro-inflammatory towards an anti-inflammatory pattern preventing exaggerated tissue damage by scavenging oxidants (McCormick et al., 2005).

6. Conclusion

Despite many decades of intensive research, the etiology of most chronic inflammatory diseases remains elusive. Current anti-inflammatory therapy focuses on the management of the symptom rather on the maintenance of the function. Substantial increases in the cost of chronic inflammatory diseases are expected in the coming years due to the ageing of the population. For these reasons, there is growing interest in identifying biomarkers and attractive targets for novel anti-inflammatory therapies. Neutrophil NADPH oxidase and S100A8/A9 proteins have pro-inflammatory functions and play a fundamental role in host defence but also have the potential for pathological outcomes. Although physiological responses of neutrophils have been solidly documented, perturbations in S100A8/A9 signalling pathways and regulation of the NADPH oxidase activity have not yet been adequately explored. Given their importance in the pathophysiology of various chronic diseases, global understanding of NADPH oxidase and S100A8/A9 roles is likely to become of major importance over the coming years. It bears the potential to valid novel therapies and diagnostic markers for disease development and risk assessment.

7. References

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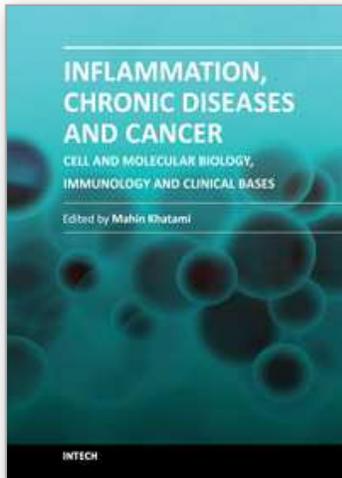
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Inflammation, Chronic Diseases and Cancer - Cell and Molecular Biology, Immunology and Clinical Bases

Edited by Dr Mahin Khatami

ISBN 978-953-51-0102-4

Hard cover, 430 pages

Publisher InTech

Published online 09, March, 2012

Published in print edition March, 2012

This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sabrina Bréchar, Véronique Schenten and Eric J. Tschirhart (2012). Role of the Neutrophil NADPH Oxidase and S100A8/A9 in the Pathophysiology of Chronic Inflammation, *Inflammation, Chronic Diseases and Cancer - Cell and Molecular Biology, Immunology and Clinical Bases*, Dr Mahin Khatami (Ed.), ISBN: 978-953-51-0102-4, InTech, Available from: <http://www.intechopen.com/books/inflammation-chronic-diseases-and-cancer-cell-and-molecular-biology-immunology-and-clinical-bases/role-of-the-neutrophil-nadph-oxidase-and-s100a8-a9-in-the-pathophysiology-of-chronic-inflammation>

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