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TOPIC HIGHLIGHT

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Inflammation and reactive oxygen species in cardiovascular disease

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Abstract

Reactive oxygen species (ROS) have long been proposed to be mediators of experimental cardiovascular pathology. There is also a wealth of data indicating that ROS are involved in clinical cardiovascular pathology. However, multiple clinical studies have shown little benefit from anti-oxidant treatments, whereas nearly all experimental studies have shown a marked effect of anti-oxidant therapy. One reason for this discrepancy is that ROS are produced through multiple different mechanisms of which some are clinically beneficial; thus, in a defined experimental system where predominately pathological ROS are generated does not mimic a clinical setting where there are likely to be multiple ROS generating systems producing beneficial and pathological ROS. Simple inhibition of ROS would not be expected to have the same result in these two situations; ergo, it is important to understand the molecular mechanism underlying the production of ROS so that clinical treatments can be tailored to target the pathological production of ROS. One such example of this in cardiovascular biology is tissue specific inflammation-mediated ROS generation. This and the following series of articles discuss the current understanding of the role of ROS in cardiovascular disease, specifically focusing on the molecular mechanisms of ROS generation and the actions of ROS within the cardiovascular system. Although there are still many areas with regard to the effects of ROS in the cardiovascular system that are not completely understood, there is a wealth of data suggesting that blocking pathological ROS production is likely to have beneficial clinical effects compared to traditional anti-oxidants.

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Key words: Anti-oxidants; Inflammation; Oxidants; Pathology; Reactive oxygen species

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The World Health Organization in 2004 estimated that 17.1 million people died due to a cardiovascular event. This represents 29% of all deaths and is the greatest single cause of death worldwide. Reactive oxygen species (ROS) play a critical role in the pathogenesis of cardiovascular disease[1,2] and clinically related disorders such as obesity[3]

and metabolic syndrome[4]. ROS inhibition has thus been proposed as a potential therapy for cardiovascular disease. Animal models confirm that inhibition of ROS generation, specifically from NAD(P)H oxidase, ameliorates and even prevents cardiovascular disease[5]; however, clinical studies indicate that antioxidants have, at best, a marginal effect in reducing cardiovascular disease[6,7]. One postulate for this disconnect is that clinically viable antioxidants merely scavenge all ROS indiscriminately, which will block pathological ROS production along with physiologically important ROS[8]. For example, hydrogen peroxide (H_2O_2) is a vasodilator and, in the proper concentration, is beneficial[9,10]. Since H_2O_2 is produced by superoxide dismutase, the proper concentration and location of superoxide (O_2^-), the most studied ROS, also has beneficial cardiovascular effects; thus, complete scavenging of O_2^- eliminates these benefits. Rather, the mediators of pathological ROS generation should be identified and targeted for the treatment of cardiovascular disease.

Recently, inflammation has been linked, both experimentally and clinically, to cardiovascular disease[11]. A key hallmark of inflammation is the generation of ROS, which can be due to immune cells [dendritic cells (DCs), lymphocytes, and macrophages] or interleukins and other inflammatory cytokines, such as tumor necrosis factor (TNF)-α[12,13]. Inflammatory cytokines activate vascular production of ROS, specifically O_2^-, primarily through activation of NAD(P)H oxidase. Vascular NAD(P)H oxidase is a multimeric protein complex consisting of five primary subunits: a Nox isoform, $p22^{phox}$, $p40^{phox}$, $p47^{phox}$ or its homologue NoxO1, and $p67^{phox}$ or its homologue NoxA1. Additionally, the Rho family small G protein Rac1 in its active (GTP-bound) state is required for activation of the complex[14]. There are a number of Nox isoforms (Nox 1-5, DUOX1 and 2) all of which share some homology with the first identified Nox subunit, $gp91^{phox}$/Nox2[15]. The Nox isoforms and $p22^{phox}$ are membrane bound and although the catalytic core is comprised within the Nox subunit, it requires $p22^{phox}$ to be active; similarly, the rest of the subunits are cytosolic and are involved in the regulation of the Nox subunit. The various components of NAD(P)H oxidase are differentially expressed and regulated, but all of the NAD(P)H oxidases generate O_2^-, which is known to participate in growth, apoptosis, and migration of vascular smooth muscle cells, as well as in the modulation of endothelial function, including endothelium-dependent relaxation and expression of the proinflammatory phenotype and in the modification of the extracellular matrix[16]. Additionally, O_2^- is also linked to hypertension, pathological states associated with uncontrolled growth, and inflammation leading to coronary artery disease[16,17]. However, the various Nox isoforms do not generate ROS equally, and moreover, they occur at specific locations within a cell and are activated *via* unique mechanisms[18]. Interestingly, recent data indicates that some Nox isoforms are localized within the endoplasmic reticulum (ER)[19-21], providing a molecular link to ER stress and cell death seen in atherosclerosis[22] and diabetes[23]. Although NAD(P)H oxidases have been identified as major players in redox signaling in several cardiovascular disorders, there are still many questions that remain regarding cell specific NAD(P)H oxidase localization and function. Recent and ongoing research tends to highlight the regulation[24], localization[25], and structure-function[26] of this enzyme complex, but further studies are required to completely understand the mechanisms of action of the multiple potential NAD(P)H oxidase complexes in normal physiology and disease.

The following articles in this editorial address several topical aspects of the roles of inflammation and ROS in cardiovascular disease. The overview articles by Zhang *et al*[27] and Zuidema *et al*[28] consider the effects of inflammatory cytokines and general mechanisms including the roles of DCs, immune cells and the relevance of ROS signaling, which summarize our current understanding of inflammatory and immune mechanisms in ischemic heart disease. This editorial is followed by articles from Capobianco *et al*[29], Gao *et al*[30], Lee *et al*[31] and Zhang *et al*[32] addressing recently identified novel mechanisms for cardiovascular dysfunction in ischemic heart disease regarding the roles of stem cells, endothelium-derived hyperpolarizing factor, exercise training and adipokines as mediators in cardiovascular disease. Picchi *et al*[33] evaluate the roles of hyperglycemia, oxidative stress, polyol pathway, protein kinase C, advanced glycation end products, insulin resistance, peroxisome proliferator-activated receptor γ, inflammation, and diabetic cardiomyopathy as a "stem cell disease". They also discuss the potential pathogenic importance of superoxide production by nitric oxide synthase (NOS), the enzyme that normally generates nitric oxide (NO) but can switch to ROS production when the NOS co-factor tetrahydrobiopterin is deficient-for example, in diabetic vasculopathy. Fay[34] reviews the linkage between inflammation and thrombosis by focusing on the role of C-reactive protein (CRP); the identification of elevated inflammatory marker CRP as a transient independent risk factor for endothelial dysfunction may provide an important clue to link a systemic marker of inflammation to progression of atherosclerotic disease. The review by Pung *et al*[35] discusses aspects of redox signaling in the growth of coronary collateral circulation. Finally, DeMarco *et al*[36] discuss the contribution of oxidative stress to pulmonary arterial hypertension (PAH), and suggest that statins may be an attractive option for treatment of PAH and cor pulmonale because they may simultaneously prevent further tissue damage by decreasing oxidative stress and enhancing repair to injured sites in both the pulmonary vasculature and right ventricle. Our aim in this mini-symposium is to provide an up-to-date overview of inflammation, oxidative stress and redox signaling as they relate to clinical cardiovascular disease.

Inflammation and ROS have increasingly been recognized to play an important role in cardiovascular disease and related pathologies manifested by obesity and diabetes. Available evidence suggests that low-grade inflammation is accompanied by a decreased bioavailability of endogenous NO, and, as summarized in the accompanying reviews, inflammation plays a larger, more complex, role in cardiovascular disease. Thus, randomized longitudinal studies are now needed to investigate whether or not vari-

ous anti-inflammatory treatment strategies (such as anti-TNF-α treatment) improve cardiovascular function and decrease the unacceptably high cardiovascular mortality rate. However, many of the mechanisms being scrutinized here need further elucidation. Our understanding of inflammation and ROS, especially with respect to structure–function and signal transduction relationships as well as their pathophysiological role in cardiovascular dysfunction, is still in its infancy. A potentially important and relatively new direction is the concept that inflammatory cells contribute to ischemic heart disease. Future studies are needed to understand the interaction of inflammation, immune cells and ROS with cardiovascular disease and how this might be interrupted to provide therapeutic benefit. We believe that further investigations in this exciting field will facilitate the development and/or delivery of selective anti-inflammatory agents (antioxidants) to specifically inhibit the pathological generation of O_2^-. These compounds and delivery systems are expected to provide for better management of cardiovascular diseases.

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