

Oxidative stress and atherosclerosis

In recent years, it has become established both that atherosclerosis represents an inflammatory process in its own right, and that conventional risk factors for coronary artery disease exert their deleterious effects via inflammatory mechanisms linked to increased oxidative stress. Vascular oxidative stress and increased production of reactive oxygen species are important causes of vascular dysfunction (mainly through endothelial dysfunction).^{1,2} This article briefly discusses the pathogenic basis of atherogenesis associated with endothelial dysfunction and oxidative stress.

Endothelial dysfunction, risk factors, and oxidative stress

Under physiological circumstances, the endothelium plays a key role in the modulation of vascular function and has a protective effect against atherosclerosis. Endothelium-derived nitric oxide (NO) produced by endothelial NO synthase (eNOS) is largely responsible for these effects of the endothelium, as it induces vasodilatation, inhibits platelet aggregation and adhesion, prevents oxidation of LDL cholesterol, controls vascular smooth-muscle-cell proliferation, and decreases the expression of proinflammatory genes that promote atherogenesis.² An essential element contributing to endothelial dysfunction is the reduced bioavailability of NO, with the consequent loss of the beneficial vascular actions of this compound. A large body of evidence exists at present indicating that endothelial function is impaired in the presence of cardiac risk factors such as hypertension, obesity, dyslipidemia, smoking, and diabetes mellitus.

Oxidative stress, which can be defined as an imbalance between the production of endogenous reactive oxygen species (ROS) and the presence of antioxidant molecules, is one of the most important mechanisms contributing to endothelial dysfunction.² Indeed, NO is rapidly inactivated by the oxidative action of the ROS superoxide anion. In addition, the production of NO is affected by persisting oxidative stress, as ROS induce molecular changes that result in a dysfunctional eNOS that produces superoxide instead of NO, further contributing to vascular dysfunction.

Even in the early stages of atherosclerosis, endothelial dysfunction is present, as assessed by tests of vasodilator function, and studies have shown that a reduced endothelial dependent vasodilatation is associated with impaired prognosis. Moreover, endothelial dysfunction, in its different forms of presentation, is known to represent a major mechanism in atherogenesis. Thus endothelial dysfunction can be considered both a marker of atherosclerosis and disease progression, and a pathogenic mechanism.²⁻⁴

Oxidative stress and atherogenesis

In recent years it has become apparent that atherosclerosis results from a chronic inflammatory process in the arterial wall. As recently reviewed in a scholarly article by Förstermann,² a number of proinflammatory genes responsible for the production of inflammatory molecules that participate in the atherosclerotic process are expressed in response to ROS production. These inflammatory molecules include, among others, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-

1), E-selectin, and monocyte chemoattractant protein 1 (MCP-1). As reviewed by Förstermann,² "the increased expression of these inflammatory molecules is mediated through redox-sensitive transcription factors such as nuclear factor kappa B (NFκB), activator protein 1 (AP-1), early growth response protein 1 (Egr-1), and hypoxia inducible factor 1 β (HIF-1 β). These factors are also important for proliferative signals involved in vascular smooth-muscle-cell growth, vascular remodelling, and atherogenesis." ROS can also activate mitogen-activated protein (MAP) kinases, and both receptor and nonreceptor tyrosine kinases, which mediate the proatherosclerotic effects of oxidative stress.⁵⁻⁷

Summary and clinical implications

Oxidative stress results in the reduced bioactivity of NO through the rapid oxidation of this compound and a reduced production of NO via uncoupling of eNOS. These result in endothelial dysfunction, with the loss of the beneficial and protective effects of NO, and the activation of inflammatory and proatherogenic mechanisms.

From a clinical perspective, understanding the mechanisms of atherogenesis that are regulated by ROS production will allow the design of translational studies that may hopefully result in the identification of effective therapeutic strategies.

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References:

1. Förstermann U, Münzel T. *Circulation*. 2006;113:1708-1714.
2. Förstermann U. *Nat Clin Pract Cardiovasc Med*. 2008;5:338-349.
3. Schächinger V et al. *Circulation*. 2000;101:1899-1906.
4. Heitzer T et al. *Circulation*. 2001;104:2673-2678.
5. Stocker R, Keaney JF Jr. *J Thromb Haemost*. 2005;3:1825-1834.
6. Kunsch C, Medford RM. *Circ Res*. 1999;85:753-766.
7. Viedt C et al. *Arterioscler Thromb Vasc Biol*. 2000; 20:940-948.