How Could a Genetic Variant of the p22\textsuperscript{phox} Component of NAD(P)H Oxidases Contribute to the Progression of Coronary Atherosclerosis?

Michael S. Wolin

Reactive O\textsubscript{2} species (ROS) are thought to contribute to the progression of atherosclerotic coronary artery disease (CAD).\textsuperscript{1,2} In this issue of Circulation Research, Cahilly and colleagues\textsuperscript{3} provide data supporting an association between a histidine\textsuperscript{72} to tyrosine mutation at the potential site for heme binding of the p22\textsuperscript{phox} subunit of NAD(P)H oxidases and increased severity and progression of CAD in patients from the Lipoprotein and Coronary Atherosclerosis Study (LCAS). Although it was previously shown that the p22\textsuperscript{phox} subunit of NAD(P)H oxidases is increased in atherosclerotic human coronary arteries,\textsuperscript{4} its precise role, if any, in disease pathogenesis and the impact of this mutation on the function of NAD(P)H oxidases remain to be elucidated. Given that the p22\textsuperscript{phox} subunit is a component of both the phagocytic cell oxidase and NAD(P)H oxidases in other cell types in the vessel wall, the mutation could affect the production of ROS and multiple signaling systems that influence the progression of CAD.

The best understood oxidase containing p22\textsuperscript{phox} is the NADPH oxidase of phagocytic cells (eg, neutrophils and macrophages), which are known to contribute to the development and progression of atherosclerotic vascular disease. Activation of these phagocytic cells causes the cytotoxic p47\textsuperscript{phox}, p67\textsuperscript{phox}, and p40\textsuperscript{phox} subunits and the G-protein rac-2 to bind with the membrane-bound flavohemoprotein gp91\textsuperscript{phox} and p22\textsuperscript{phox} subunits, producing the superoxide anion (O\textsubscript{2}"\textsuperscript{−})–generating form of the NADPH oxidase.\textsuperscript{5} The high capacity for O\textsubscript{2}"\textsuperscript{−} production, together with the ability of phagocytes to generate ROS and nitric oxide–derived reactive species, including hypochlorous acid, chloramines, peroxynitrite, and nitrogen dioxide, provides a mechanism to destroy phagocytized materials. These same factors also promote oxidant stress in the phagocytes and adjacent cells in the vessel wall. Although the consequences of phagocyte cell–derived oxidant stress on adjacent cells are not well understood, it is reasonable to hypothesize a contribution to the progression of atherosclerosis through processes involving cell signaling and injury.

Cell types normally present in the vessel wall such as endothelium, vascular smooth muscle (VSM), and fibroblasts also possess p22\textsuperscript{phox}–containing NAD(P)H oxidases, which could contribute to the progression of CAD.\textsuperscript{6} In contrast to phagocytes, the NAD(P)H oxidases present in these cell types have significant activity in the absence of cellular activation. For example, VSM contains an oxidase whose activity appears regulated by the redox status of cytosolic NAD(H). The O\textsubscript{2} requirements permit this oxidase to function as a physiological P\textsubscript{O}\textsubscript{2} sensor.\textsuperscript{7} Growth factors for VSM promote vascular proliferation by stimulating NAD(P)H oxidase activity and by increasing the expression of both the p22\textsuperscript{phox} subunit and a p65\textsuperscript{phox} subunit, which resembles the gp91\textsuperscript{phox} subunit of the phagocytic oxidase.\textsuperscript{6,8} Interestingly, the highest levels of p21\textsuperscript{phox} in human atherosclerotic coronary VSM occur in cells with an undifferentiated phenotype.\textsuperscript{4} In view of the fact that many genes are regulated by P\textsubscript{O}\textsubscript{2} and ROS signaling mechanisms, factors such as the enhancement of P\textsubscript{O}\textsubscript{2} gradients as the vessel wall thickens and oxidant stress in CAD could influence the progression of atherosclerosis. In addition, the apparently crucial role of NAD(P)H oxidase–derived ROS in cell growth and responses to stress\textsuperscript{6,11} could be a major contributor to changes that occur in the vessel wall in CAD.

There is currently a lack of essential information regarding the functional consequences of the histidine\textsuperscript{72} to tyrosine mutation. First, although it has been suggested that the histidine\textsuperscript{72} has a role in the binding of heme, the actual function of this residue is not known. Because the mutation is not associated with chronic granulomatous disease, which is seen in patients with defects in other components of the phagocytic NADPH oxidase,\textsuperscript{12–14} it is likely that the mutation has relatively subtle effects on the function of the oxidase that remain to be elucidated. Potential consequences of this mutation include an increase or decrease in O\textsubscript{2} production by the activated oxidase or disruption of O\textsubscript{2} sensing and processes regulated through alteration of heme binding. Alterations at the heme site of the oxidase could also alter its P\textsubscript{O}\textsubscript{2} dependence and change the way it would function in O\textsubscript{2} sensing regulated processes. Although there is a very high level of homology between the p22\textsuperscript{phox} subunits of the phagocytic cell NADPH oxidase and the NAD(P)H oxidase present in VSM, it is currently not known if the mutation is present in the vascular form of the oxidase. Thus, it is not yet possible to predict whether the histidine\textsuperscript{72} to tyrosine mutation directly affects the functions of p22\textsuperscript{phox}–containing NAD(P)H oxidases in the atherosclerotic vessel wall.

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The balance between the production and metabolism of ROS and nitric oxide–derived species in the key intracellular compartments of each cell that populates the atherosclerotic vessel wall influences signaling mechanisms that could contribute to the progression of CAD. For example, this delicate balance influences the expression of adhesion proteins and inflammatory cell activation, redox processes that regulate the production of oxidants by other oxidases, and the function of antioxidant systems, and decisions made by cells related to contractile function, proliferation, responses to stress, apoptosis, and necrosis. Thus, it is highly likely that mutations causing even minor changes in the function of p22phox-containing NAD(P)H oxidases could influence the progression of CAD. Individual ethnic groups could have other genetic variances or dietary and lifestyle customs, which modify the function of oxidant signaling and antioxidant defense systems that influence the progression of CAD in a manner similar to the mechanisms proposed for fluvastatin. Thus, there may be logical explanations for observations made in a Japanese patient group that associate the histidine 72 to tyrosine mutation with reduced risk of CAD. In addition, HMG-CoA reductase inhibitors may suppress vascular O$_2^-$ production by preventing mevonate-dependent isoprenylation of the G-protein Rac and assembly of the active form of NAD(P)H oxidases.

References


Key Words: atherosclerosis ■ coronary artery disease ■ NAD(P)H oxidase ■ oxidant stress ■ redox signaling
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