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NADPH oxidación y stress oxidativo en las enfermedades cardiovasculares

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The NADPH oxidase (NOX) gene family has been recently defined based on homology with the phagocyte respiratory burst oxidase, a well known multicomponent enzyme system that plays a critical role in antimicrobial host defenses. The essential components of the phagocyte oxidase (designated *phox*) include a membrane-bound flavo-heme catalytic subunit comprised of a gp91^{phox}-p22^{phox} heterodimer, as well as the cytosolic co-factors p47^{phox}, p67^{phox}, and the small GTPase Rac 1 or Rac 2. The gp91^{phox} protein contains two heme groups associated with transmembrane segments, and binding sites in its cytoplasmic domains for FAD, NADPH, and the cytosolic co-factors. Stimulus-dependent assembly of the complete oxidase complex leads to catalyzed electron transport from cytosolic NADPH to molecular oxygen, producing the free radical superoxide anion ($O_2^{\bullet -}$). Superoxide then serves as an intermediate for the formation of other reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\bullet}$).

The NOX gene family has 5 members, all homologous to gp91^{phox}, which is also designated NOX2. Although the members of the family exhibit structural similarity, they differ greatly in their range of tissue expression, co-factor and activation requirements, rate of superoxide formation, and apparent physiologic functions. For example, NOX1 is highly expressed in colon epithelium, NOX2 in phagocytes, and NOX4 in kidney. The preferred cytosolic co-factors for NOX1 are homologues of p47^{phox} and p67^{phox}, designated NOXO1 (O = organizer) and NOXA1 (A = activator), respectively. NOX5 has an N-terminal extension containing Ca^{2+}-binding EF-hand domains and is directly activated by calcium. EF-hand domains are also found in the NOX-related DUOX proteins, which in addition, have an extracellular peroxidase domain. The highest rates of superoxide formation are observed with the phagocyte oxidase, presumably due to the need to generate toxic concentrations of ROS for microbial killing, the main function of this NOX family member. A similar function has been postulated for NOX1 in colon cells. In contrast, other NOX family members appear to produce much lower superoxide fluxes, compatible with their putative roles in cell signaling.

There is abundant evidence for the expression of NOX family members and co-factors in vascular tissues. Early studies focused on the *phox* system and generally concluded that all of its components are detected in endothelial, adventitial, and vascular smooth muscle cells, albeit at considerably lower levels than in phagocytes. More recent work has indicated that NOX4 is broadly expressed in vascular tissues and that NOX1 and NOX5 may be present, but are more restricted. The rate of superoxide formation by vascular NADPH oxidases is generally rather low, in keeping with a signaling function. Whether this is due strictly to low NOX protein expression levels or in part to differences in activation and regulation of catalytic function is unknown. Vascular NOX systems appear to be regulated under a variety of circumstances. For example, angiotensin II, which stimulates superoxide production in vascular cells, upregulates the expression of a number of NOX proteins and co-factors. Experimental evidence has implicated ROS generated by vascular NADPH oxidases in such highly prevalent diseases as atherosclerosis, hypertension, and diabetes.