

## **Pathophysiology of redox processes in vascular diseases**

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Redox processes emerged as important mediators of physiological or pathological vascular events ranging from mechanical stress to atherosclerosis. Endothelial dysfunction, a condition underlying most vascular diseases, sums up to a dysfunction of redox signaling, i.e., the transduction of cellular processes integrated by a network of electron transfer reactions involving free radicals or related species. Disturbed redox signaling leads to oxidative stress, which can activate vicious pathophysiological circuits in several vascular diseases. Our data suggest that intracellular oxidative stress connected to such cell processes may even dominate over stress due to LDL oxidation and inflammatory cell influx in atherosclerosis and aortic valve disease. It is now clear that cellular reactive oxygen species (ROS) production is a controlled enzymatic process, and that such enzymatic ROS source is a key element of redox signaling cascades and a likely integrator to overall cellular stress responses. Vascular isoforms of the phagocyte NADPH oxidase (Nox) appear to be the most prominent source of basal as well as agonist-induced ROS. Known Nox agonists in vessels include angiotensin-II, growth factors, thrombin, arachidonic acid, and shear stress changes. Nox overexpression/activity occurs in vascular injury, atherosclerosis, diabetes mellitus and hypertension. Structures of Nox subunits differ among endothelium, smooth muscle cells (VSMC) and adventitial fibroblasts and likely play a major role in overall oxidase regulation. Our group has searched for the role of redox thiols in oxidase regulation and focused into the thioredoxin superfamily enzyme protein disulfide isomerase (PDI), a multifunctional dithiol/disulfide oxidoreductase chaperone from the endoplasmic reticulum (ER). Our recent data indicate that PDI displays spatial and functional interaction with NAD(P)H oxidase and strongly affects its activation by angiotensin II in cultured VSMC. In particular, PDI closely co-localizes with p22phox and Nox subunits. Such a possible regulatory role of PDI on NAD(P)H oxidase may occur and share common features with ER stress, a condition in which PDI migrates to the membrane. Our recent data suggest that NAD(P)H oxidase(s) can be activated by ER stressors and that vascular repair after injury displays severe ER stress, which may contribute to sustain oxidative stress and apoptosis. Overall, such findings can lead to novel paradigms of vascular oxidative stress and new ways to its manipulation.