Redox Control of Vascular Function

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In the past several years, a significant body of work has been published in *ATVB* about new research in the field of vascular biology and redox signaling. We would like to highlight new publications that have enriched our understanding of redox signaling in the context of vasculopathy. Although redox balance and perturbation involve a plethora of proteins and signaling molecules, the focus of recent research has involved the examination of chemically reactive oxygen species (ROS), reactive nitrogen species (RNS), and the interactions with other molecules or enzymes that lead to vascular pathology.[1,2] There are often a variety of downstream targets and mechanisms of cross-talk that can lead to pathologies observed in the vasculature as a result of redox imbalance. The objective of this article is to underscore the novel research in the field devoted to vascular redox physiology and disease.

Reactive Oxygen Species

The main sources of vascular ROS are NAD(P)H oxidase (NOX),[3] mitochondrial-derived superoxide (O_2^-),[4] uncoupled nitric oxide synthase (NOS),[5] and to a lesser extent xanthine oxidase,[6] cyclooxygenase,[7] and myeloperoxidase.[8,9] A delicate ROS balance exists within the vascular wall that can be either beneficial or deleterious, depending on the source of ROS or the mechanisms of ROS capture or quenching, and these topics have been extensively discussed in previous reviews.[10–12] ROS-associated proteins and their expression profiles vary in depending on vessel location within the vascular tree and tissue origin. Indeed, vascular smooth muscle cells (VSMC), endothelial cells, immune cells, and other hematopoietic cell types have vastly different expression patterns for the various ROS-related proteins. Moreover, these molecules readily change in response to stimuli and disease state.[13–19]

The balance between NOX protein expression and their role in disease is highly context and tissue dependent. There are 4 isoforms of NOX proteins found in vasculature (NOX1, NOX2, NOX4, and NOX5), and their impact on specific disease states has been broad. Consequently, much of the recent research has focused on NOX's 1, 2, and 4 as the expression of these proteins have been found to change because of pathology and play a causal role in disease.[14,20]

One major point of debate has been the role of NOX4 in vascular disease. A significant body of work indicates that NOX4 is a causative agent in vascular pathology, for example, NOX4 facilitates the progression of late stage of vasculopathies like atherosclerosis and age-related inflammation.[21–23] Inhibiting NOX4-mediated ROS may have therapeutic implications, as demonstrated by recent findings. Administration of the small n-terminal fragment of adrenomedullin-2 (intermedin$_{1-53}$) was found to significantly reduce both angiotensin II–induced apolipoprotein E knockout and $CaCl_2$-induced abdominal aortic aneurysm in mice. It was also shown that intermedin$_{1-53}$ reduces both NOX4 protein and mRNA in vivo, suggesting transcriptional regulation of NOX4 by the small peptide.[24] Moreover, NOX4 overexpression in cultured mouse aortic VSMC's induced changes toward a senescent phenotype with higher susceptibility to apoptosis, which in atherosclerosis was found to be harmful for plaque stability in NOX4-overexpression mice.[25] Novel findings on the molecular mechanisms involved in NOX4-induced stress implicate the induction of endoplasmic reticular stress through activation of the eukaryotic translation initiation factor 2α pathway.[26] NOX4, which is known to produce both hydrogen peroxide (H_2O_2) and O_2^-,[27] can also induce DNA damage because the higher chemical stability of H_2O_2 prevents rapid interaction, allowing for nuclear translocation and DNA modification.[28] It should be noted that not all NOX4 bioactivity creates pathological consequences. Some research has shown a protective role for NOX4 using apolipoprotein $E^{-/-}$ mice and $LDLR^{-/-}$ (low-density lipoprotein receptor) mice.[29–32] Brown adipose-derived H_2O_2 from NOX4 protein was shown to protect the vasculature through activation of protein kinase G,[33] and adipose tissue–derived NOX4 was also shown to slow the progression of type II diabetes mellitus and inflammation in obesity.[34] Taken together, more investigation in this area is necessary to elucidate the role that NOX4-produced ROS plays in accumulation of atheromatous plaque and maintenance of the structural integrity of the vascular wall.

NOX2, in contrast to NOX4, is not a constitutively active NOX isoform.[35] NOX2 is more highly expressed in fibroblasts and immune cells,[36] participating in recruitment of other macrophages to sites of inflammation that is beneficial during removal of infectious pathogens.[37] When NOX2 was overexpressed in the endothelium, increased inflammation and infiltration of leukocytes ensued.[38] NOX2 protein upregulation is often observed in infiltrating fibroblasts and leukocytes. Pharmacological inhibition of NOX2 using atorvastatin reduced thrombotic stress in the vasculature.[39,40] Administration of mesenchymal stem cells resulted in reduction of NOX2 and increased matrix stability, and both NOX2 null mice and mesenchymal stem cell–treated mice showed a lower incidence of abdominal aortic aneurysm, apparently through a NOX2 downregulation-mediated pathway.[41]

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Because multiple cell types contribute to thrombotic stress,[42] and because NOX2 seems to play a role in pathological ROS production by leukocytes and fibroblasts, identification of the mechanistic details will help to combat potential NOX2-derived ROS pathologies.

Oxidized low-density lipoprotein–induced migration of macrophages and endothelial cells seems to be NOX dependent. Constitutive activation of focal adhesion kinase and inactivation of protein tyrosine phosphatase nonreceptor type 11 (aka SHP-2), which are proteins required for CD36-facilitated macrophage migration, is dependent on NOX-mediated ROS production. Park et al[43] established this phenomenon that oxidized low-density lipoprotein was dependent on NOX-produced ROS. Conversely, ROS-mediated activation of CD36 in extracellular vesicles was found to inhibit migration of endothelial cells.[44] Although the exact role of extracellular vesicles remains to be determined, this contrasting finding for ROS in endothelial cell migration needs further investigation.

NOX1 protein has also been shown to be upregulated in similar pathological conditions to those found with NOX4 in both endothelial cells and VSMCs.[45–47] Myocyte-enhancing factor-2B was identified as an important transcription factor in proliferation, growth, and differentiation.[48,49] Another study showed that engagement of the matricellular protein thrombospondin-1 with CD47 activated NOX1,[50] an important finding, given that vascular matrices contribute heavily to the progression of diseases.[51] Cyclic stretch in vessels induces myocyte-enhancing factor-2B, which subsequently induces NOX1, and this has been identified as a necessary pathway for cyclic stretch-induced phenotypic switching of VSMC's to a proliferative state.[52] Similarly, both NOX1 and NOX4 isoforms are upregulated by high plasma glucose concentrations. Excess NOX1 and NOX4 production of ROS led to PKC (protein kinase C)-dependent downregulation of protein kinase G protein and mRNA, which caused blunted nitric oxide (NO)-soluble guanylate cyclase (sGC)-cGMP-protein kinase G response in vitro and in vivo.[53] Interestingly, human clinical data indicate that obese, sedentary individuals have elevated ROS in the blood and NOX proteins in skeletal muscle, both of which were significantly lower in lean and active subjects. These data suggest that exercise and fat accumulation heavily contribute to the regulation of ROS in the vasculature through NOX protein expression in adjacent tissues.[54]

Mitochondrial-derived ROS have also been identified and studied as a major contributor to vasculopathy when ROS generation goes untempered by other cellular mechanisms. ROS production is a continual process that occurs under normophysiological conditions and is estimated to produce ROS with ≈1% to 2% of the molecular oxygen consumed by the mitochondria.[55] This production is distinct from an upregulation of NOX proteins as a response to potential pathogen or danger associated molecular patterns.[37] The perivascular neutrophil microenvironment has been identified as a malleable niche, influenced by the presence of excess O_2^- generated from mitochondria.[56] Likewise, lysophosphatidylcholine has been implicated in mitochondrial ROS production and endothelial cell activation likely because of electron leakage across mitochondrial membranes.[57] Both of these conditions have been implicated in the progression of atherosclerosis through surplus mitochondrial ROS. Heart muscle produces ≈95% of its ATP from oxidative phosphorylation in mitochondria.[58,59] The energetic need for oxygen is much higher in coronary blood vessels than in other tissues to accommodate myocardial oxidative metabolism demands. As a result, cardiomyocyte oxygen consumption and aerobic respiration dominate oxidative production of H_2O_2 in the cardiac microcirculation.[60] Studies have also shown that H_2O_2 derived from mitochondrial O_2^- alters human coronary resistance artery diameter.[61–63] Healthy mitochondrial metabolism is responsible for the turnover of damaged mitochondria, but excess mitochondrial ROS can lead to depressed respiratory capacity.[64] Production of ROS in coronary arteries is coupled to myocardial metabolism and, by extension, mitochondrial respiration. In sum, these data suggest that excess mitochondrial ROS and downstream manifestations are tightly regulated and may be useful as predictors for progression of atherosclerosis and other diseases of lipid accumulation.

Other sources of excess ROS production can produce pathology with subclinical indications. For example, women have been shown to have a higher incidence of vascular stiffness and increased levels of plasma uric acid.[65–68] Pharmacological inhibition of xanthine oxidase was shown to increase vasoreactivity and reduce aortic hardening in female mice fed a Western diet.[69] In a similar manner, COX-2 (cyclooxygenase) is a responsive element to other forms of ROS and can exacerbate hypertension through feed-forward chronic production of inflammatory or vasoconstrictive prostaglandin synthesis and increase the magnitude of hypertension and ROS production in patients with ROS-induced vasculopathy.[70]

Many other ROS-sensitive mechanisms have been further elucidated, giving the field additional mechanisms and pathways to target for treatment of the most common vasculopathies. It has been established that HIF-1α (hypoxia inducible factor) expression correlates with lipid-laden plaques,[71] and it has recently been demonstrated that loss of HIF-1α in mouse models of atherosclerosis reduced lesion size because of decreased macrophage recruitment and infiltration.[72] It was found that HIF-1α was highly expressed in hypoxic compartments of the plaques and that HIF-1α induction associated with increased M1 differentiation. In accordance with previous findings, mice given bone marrow transplants from HIF-1α–deficient mice were less likely to show the same progression of atherosclerosis.[73] These results are consistent with the finding that ROS are capable of stabilizing HIF-1α.[74] Another vital ROS regulatory mechanism involves Nrf2 (nuclear factor [erythroid-derived 2]–like 2) activation.[75] Indeed, reduction of Nrf2 with siRNA (small interfering RNA) reduces production of antioxidant genes and proteins, promoting smooth muscle cell hyperproliferation and differentiation. This finding is consistent with the protective role for the Nrf2 pathway in atherosclerosis.[76] Foam cell formation by macrophages was prevented by inhibition of the Ca^{2+} uptake channel Orai1, resulting in decreased lesion size, infiltration, and markers of inflammation in apolipoprotein $E^{-/-}$ animals.[77] Importantly, it was found that secretion of proinflammatory markers in atherosclerosis remains elevated throughout all stages, aggravating progression of the disease irrespective of foam cell senescence or proliferative capacity.[78]

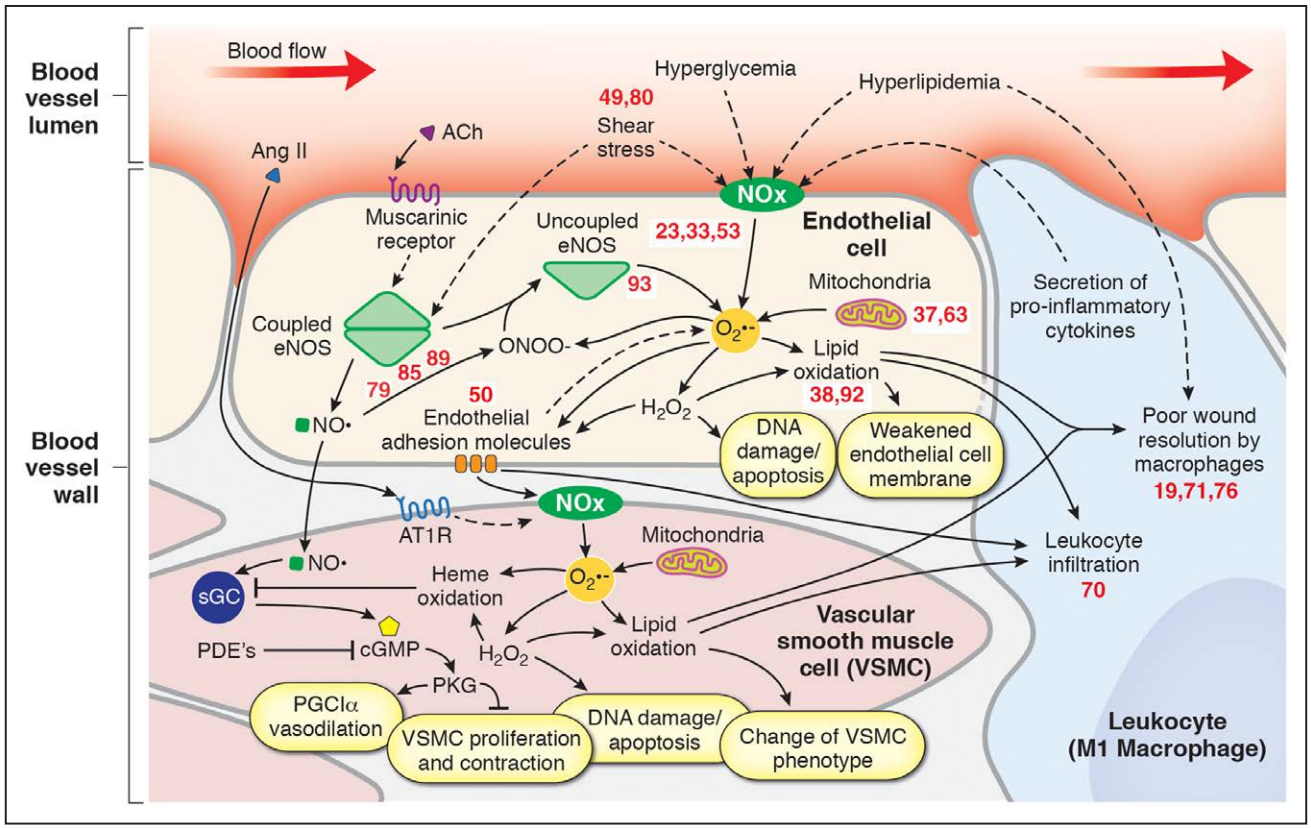

Figure. Numbers correspond to a reference in the bibliography from recent literature published in *ATVB* that has added to this area of the field and aided in our understanding of this pathway. Ach indicates acetylcholine; AngII, angiotensin II; AT1R, angiotensin II receptor type 1; cGMP, 3′,5′-cyclic-guanosine monophosphate; eNOS, endothelial nitric oxide synthase; NO·, nitric oxide; NOx, NAD(P)H oxidase; O_2^-, superoxide; PDE, phosphodiesterase; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1-α; and sGC, soluble guanylate cyclase.

Reactive Nitrogen Species

Similar to ROS, RNS, specifically NO and its derivatives, play vital roles in vascular function. NO is necessary for vascular tone regulation and control of blood pressure in muscular arteries throughout the vascular tree. NO signaling also participates in numerous vasculopathies, depending on the microenvironment in which it is produced and chemical reaction partners, neither of which need be mutually exclusive. As with ROS, NO generation requires tight regulation to avoid pathologies of insufficient or excess RNS for homeostasis.

Locale of NOS expression and NO generation is an important determinant of NO fate and activity. Differential localization of endothelial NOS (eNOS) expression leads to distinct downstream responses, with apical stimulation depressing adhesion of circulating leukocytes to the vascular wall and basal stimulation resulting in higher cGMP-dependent vasodilation of blood vessels. Localization and activity of eNOS are affected by lipid enrichment and enhanced kinetic stimulation of protein kinase C–meditated phosphorylation of eNOS at S1177.[79,80] Shear stress-induced PKC-mediated phosphorylation of endothelial eNOS at S1177 is also affected by glycolysis-dependent purine signaling and autophagy,[81] indicating that eNOS stimulation occurs via multiple mechanisms. Where eNOS and vasodilator-stimulated phosphoprotein—a protein kinase G target—have been genetically deleted in mice, inflammatory cytokines, monocyte adhesion, and macrophage infiltration have been observed in adipose tissue.[82,83] Indeed, the regulation of intimal proliferation through downregulation of M1-macrophage markers like matrix metalloproteinase-13, is a major function of NO.[84] Novel research using cross-transplanted eNOS knockout chimeras to investigate the role of eNOS in circulating blood cells established that hematopoetic cells are an important source of circulating NO within the blood.[85] A specific role for erythrocyte eNOS seems to be important for the regulation of nitrite homeostasis and systemic blood pressure.

Homeostatic regulation of NO production and signaling is of widespread importance to normophysiological processes. As with ROS, excess NO production can have harmful effects on the vasculature. In both transgenic mice overexpressing eNOS and endothelium-specific caveolin-1 knockout mice, excess NO production promotes cardiovascular imbalance.[86] Genetic deficiency of caveolin-1 induces cardiac hypertrophy, and overexpression of eNOS results in hypotension, which is a similar result to sepsis-associated hyperproduction of NO by inducible NOS.[87,88] Additional research has shown that excess NO, often because of inducible NOS, leads to loss of endothelial integrity in diseases like atherosclerosis,[89] despite the fact that exercise was shown to promote healthy arteriogenesis in an inducible NOS–dependent manner.[90]

Recent studies have focused on identifying mechanisms of NO inactivation by pathological O_2^- generation. It

was shown that perivascular adipose tissue of obese mice promotes uncoupling of eNOS, converting the protein to a O_2^- generator that exacerbates the underlying pathology.[91–93] Similar findings were reported in obese mice fed a high-fat diet, wherein cardiovascular dysfunction associated with NO deficiency driven by perivascular adiposity which was reversed by L-arginine supplementation and arginase inhibitor treatment therapies.[94]

A new area of research has focused on hemoproteins in endothelium and VSMC's and how heme oxidation state (ferric versus ferrous) modulate NO signaling. It was shown that the redox state of hemoglobin α (Hbα) at the myoendothelial junction regulates NO signaling. When in the ferric state, Hbα has a reduced binding affinity for NO, allowing the gaseous molecule to diffuse between the endothelium and the VSMC. By contrast, when Hbα is in the reduced ferrous state, NO is intercepted and signaling between endothelium and smooth muscle cells types is blunted, decreasing NO-sGC-cGMP–mediated vasodilation.[95–97] Studies have demonstrated that disruption of Hbα coupling to eNOS with a Hbα-mimetic peptide enhanced NO-sGC-cGMP–dependent dilation of resistance arteries in both the systemic and pulmonary circuits.[96,97] In endothelial cells, pharmacological inhibition of flavoprotein NADH cytochrome B5 reductase 3, otherwise known as methemoglobin reductase, facilitates NO signaling via the myoendothelial junction.[95,98] In VSMC's, a recent study showed a new role of cytochrome B5 reductase 3 where it functions to reduce sGC from its ferric to its ferrous state. This reduction of the sGC heme iron allows for NO sensing needed for cGMP production and dilation of arteries. Indeed, this finding represents the first insight into an enzymatic mechanism for regulating heme iron redox state of sGC.[99] Innovative research using fluorescence resonance energy transfer techniques has allowed for visualization of cGMP movement in real-time, revealing that not only is the breakdown of cGMP by phosphodiesterase isoforms 3 and 5 important but also cellular export of cGMP plays an important role as well.[100]

Conclusions

When taken together, these new studies have led to valuable insight emphasizing the importance of redox equilibrium needed for vascular health and how an imbalance promotes cardiovascular pathology (Figure). As the field leverages new techniques to measure the kinetics of production and quantify the amount of ROS/RNS needed for basic cell signaling, the nuances of this relationship will become clearer. Finally, as new discoveries surface, emphasis should be placed on developing innovative strategies to therapeutically target redox imbalance in cardiovascular disease.

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Disclosures

None.

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