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EDITORIAL

The Endothelium as Metabolic Conductor: Orchestrating Interorgan Metabolic Communication

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Vascular endothelial cells reside at the interface between the circulation and tissues, detecting mechanical, inflammatory, and nutrient signals and coordinating responses. Traditional models of metabolic disease emphasize nutrient excess and tissue-specific dysfunction, largely overlooking endothelial signaling as a mediator of systemic energetic stress. However, growing evidence suggests that endothelial cells actively influence interorgan metabolic communication by regulating reactive oxygen species (ROS), nitric oxide (NO), and other mediators. In this issue of *Circulation Research*, Huang et al[1] identify endothelial NOX (NADPH oxidase) 1 as a redox node, promoting the concept that the endothelium acts as a systemic metabolic conductor and reframing metabolic disease as a disorder of endothelial redox signaling, where specific redox nodes help set the tone for coordinated metabolic responses across tissues.[1] These findings raise an important mechanistic question: which endothelial redox enzymes coordinate metabolic signaling across tissues?

See Article by Huang et al

Huang et al first established a system-wide phenotype: global NOX1 deletion prevents high-fat diet-induced obesity, glucose intolerance, and resistance to insulin and leptin, while deletion of NOX2 or NOX4 does not confer similar protection. Although NOX1 has been extensively characterized in vascular smooth muscle cells,[2] its function in endothelial cells remains uncertain because its basal expression is lower than that of NOX2 and NOX4. However, endothelial NOX1 can be induced by proinflammatory cytokines, oxidized LDL (low-density lipoprotein), and disturbed flow, conditions that increase superoxide production, decrease nitric oxide bioavailability, and impair endothelial function.[2,3] As a result, endothelial NOX1 has generally been considered an amplifier of oxidative stress. Huang et al expand this perspective by showing that endothelial NOX1 acts upstream of metabolic dysfunction during nutrient overload, positioning it not just as a mediator of vascular injury but also as a redox regulator that influences interorgan metabolic communication.

Huang et al further highlight the endothelium as a metabolic conductor by asking whether endothelial NOX1 can directly regulate metabolism, utilizing complementary genetic approaches that identify it as a key regulator of systemic metabolic dysfunction. The current study found that endothelial-specific NOX1 deletion recapitulates the protective phenotype observed in a global knockout, while smooth muscle-specific deletion has no effect. Conversely, overexpression of endothelial NOX1 worsens metabolic dysfunction. Together, these complementary gain- and loss-of-function models establish endothelial NOX1 as a primary regulator of metabolic dysfunction rather than a secondary consequence of metabolic disease.

A central mechanistic insight from Huang et al is that endothelial NOX1 signaling affects skeletal muscle mitochondrial function. Endothelial-specific deletion of NOX1 restores spontaneous activity, preserves mitochondrial cristae structure, reduces calcium-induced swelling, and lowers mitochondrial superoxide levels in skeletal muscle, while these effects are reversed by endothelial NOX1 overexpression. These findings suggest that endothelial NOX1 signaling can directly impact skeletal muscle mitochondrial health. This concept aligns with a parallel literature identifying endothelial NOX4 as a vasculoprotective and redox-adaptive signal that mediates physiological communication between the endothelium and muscle.[4–7] During recovery from acute exercise, endothelial NOX4–derived hydrogen peroxide (H_2O_2) promotes glucose and fatty acid oxidation in

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skeletal muscle, suggesting that endothelial H_2O_2 can rapidly influence mitochondrial substrate use in nearby muscle fibers.[6] Huang et al's study broadens this framework from physiological to pathological stress. Whereas NOX4-dependent signaling supports adaptive metabolic responses during exercise, activation of endothelial NOX1 during nutrient excess is associated with impaired mitochondrial integrity and decreased energy expenditure. Overall, these results support a model in which endothelium-centered redox signaling, mediated by different NOX members, coordinates interorgan metabolic communication, promoting adaptive responses to physiologic stress while driving metabolic dysfunction during nutrient overload as shown in the Figure.

If endothelial NOX enzymes act as redox rheostats, an important question is how endothelial redox signaling affects local and systemic metabolism. Several nonmutually exclusive mechanisms may link endothelial redox signaling to metabolic regulation in nearby tissues. First, direct redox signaling may occur at the endothelial/parenchymal interface. Endothelial cells release ROS into the perivascular space, shaping the local signaling environment. H_2O_2, with its relatively high membrane permeability and longer half-life, is well suited for short-range signaling and can modify the activity of phosphatases, kinases, and other redox-sensitive targets that control vascular tone and metabolic pathways. In contrast, superoxide is short-lived and spatially restricted, with effects mostly confined to its site of production. Therefore, the balance between H_2O_2-dominant and superoxide-dominant signaling may determine whether endothelial ROS promotes adaptive metabolic tuning or oxidative stress.[8,9]

Second, changes in NO bioavailability may link endothelial redox imbalance to tissue energy metabolism. Superoxide rapidly reacts with NO, decreasing its availability while generating peroxynitrite, which interferes with NO-dependent signaling in both the endothelium and nearby tissues. Because NO controls mitochondrial respiration, cGMP signaling, and S-nitrosylation of metabolic enzymes, decreases in NO bioavailability could alter mitochondrial function and substrate use.[10]

Third, the endothelium functions as a gatekeeper for substrate delivery. Capillary endothelial cells regulate fatty acid transport through systems such as CD36 and coordinate glucose transport via transporters influenced by hypoxia-responsive pathways.[11,12] An ROS-dominant endothelial environment that disrupts transporter function or energy microdomains can change fatty acid availability, leading skeletal muscle to depend more on glucose, which, in turn, affects mitochondrial structure and function. These mechanisms are not mutually exclusive. Through redox-mediated paracrine signaling, modulation of NO levels, and regulation of substrate flux at the capillary interface, the endothelium is positioned to connect its redox state to local mitochondrial function and systemic metabolic balance.[13]

Together, these mechanisms point to a broader organizing principle: where the metabolic consequences of endothelial redox signaling depend on 3 main variables: NOX member type, the primary ROS species produced, and the microdomain from which the signal originates. NOX specificity influences both the chemical nature and subcellular localization of ROS, while the specific species (eg, H_2O_2 versus superoxide) and its site of production (such as the luminal surface, caveolar domains, or organelle-specific compartments) determine the signal's range, reaction partners, and reaction kinetics. These factors provide a framework for understanding how endothelial NOX signaling can lead to adaptive metabolic responses in some situations and harmful outcomes in others.

This framework proposes additional layers of regulation. Endothelial NOX1 could modify the endothelial secretome (ie, peptides, lipid mediators, and extracellular vesicles) that affect skeletal muscle metabolism. Redox-mediated changes in microvascular tone and perfusion may further impact nutrient and oxygen exchange. Anchoring endothelial outputs to NOX family specificity, ROS type, and spatial localization can help explain the varied metabolic effects of endothelial redox signaling and clarify how endothelial NOX enzymes coordinate interorgan metabolism. Beyond these mechanisms, endothelial

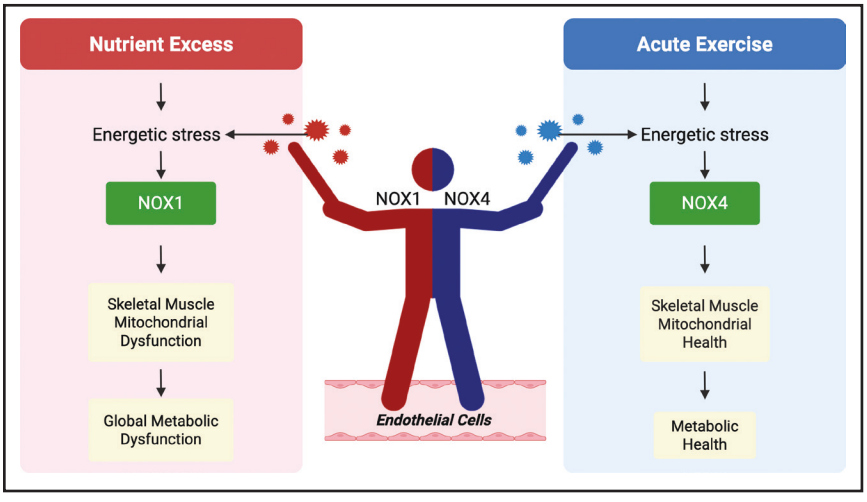

Figure. The endothelium: a metabolic conductor.
Schematic illustrating how endothelial redox signaling coordinates divergent metabolic outcomes in response to energetic stress. Created in BioRender. NOX indicates NADPH oxidase. Created in BioRender. Craige, S. (2026) https://BioRender.com/oegod8y.

redox signaling might also influence gene expression in nearby tissues.[8,14] Huang et al suggest that communication between endothelial cells and muscle could involve transcriptional reprogramming within skeletal muscle. RNA-seq analysis identified [8,14]*Cntnap4* and *Col9a1* as skeletal muscle genes disrupted by endothelial NOX1, implying that changes in endothelial redox signaling alone can affect gene expression in neighboring tissues. While these findings remain associative and require functional validation, they indicate that endothelial redox signaling extends beyond mitochondrial effects to regulate transcriptional responses. Supporting this idea, Specht et al[6] similarly found that deleting NOX4 in endothelial cells affected skeletal muscle gene expression after exercise. Whether these transcriptional changes are driven by ROS diffusion, altered nitric oxide signaling, secondary mitochondrial ROS production, or circulating intermediates still needs to be clarified.

Despite these advances, several important questions remain regarding how endothelial NOX signaling is initiated and transmitted across metabolic tissues. What upstream signals specifically activate endothelial NOX1 in response to nutrient overload? How might sex influence endothelial ROS–dependent metabolic signaling, considering previous reports of sex differences in redox responses to energy stress?[15] Mechanistically, does skeletal muscle dysfunction mainly stem from transcriptional reprogramming, or does endothelial NOX1 directly raise mitochondrial oxidative stress through intermediary signaling pathways? These questions emphasize the complexity of endothelial-driven metabolic regulation.

Huang et al's findings also suggest that endothelial NOX1 could be a therapeutic target for metabolic disease. They report that endothelial-specific deletion of NOX1 reverses diet-induced obesity and insulin resistance while restoring endothelial-dependent vasorelaxation. Consistent with this idea, NOX1 expression is higher in coronary arteries from obese individuals, indicating potential translational relevance. However, any therapeutic approach targeting endothelial redox pathways must be precise about NOX family members and cell types. NOX4 often promotes adaptive redox signaling and supports beneficial endothelial–muscle communication in response to exercise. Broad NOX inhibition could disrupt protective pathways.

Evidence from various energetic stressors now positions the vascular endothelium at the center of metabolic coordination, acting as a conductor rather than just a bystander. Understanding how NOX member specificity, ROS identity, and redox microdomains influence endothelial signaling will be crucial for developing therapies that precisely target NOX1 while maintaining other beneficial redox pathways. In this new framework, the vascular endothelium does not merely respond to metabolic disease; it actively helps coordinate systemic metabolism.

ARTICLE INFORMATION

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Disclosures

None.

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