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Perspectives

PERSPECTIVES

Endothelial Cell Metabolism and Vascular Function: A Paradigm Shift?

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A Perspective on: "Mitochondrial ATP Production Is Required for Endothelial Cell Control of Vascular Tone"

Metabolism dictates how cells, tissues, and organs operate—the vasculature is no exception. There is extensive research on how blood vessels fulfill the metabolic demands of the tissues they supply. However, how the metabolic state of the vasculature itself affects vascular function remains unclear. Several investigations used proliferative cell culture systems to study endothelial cell (EC) metabolism, leading to the dogma that the endothelium is unique in its dependence on glycolysis, rather than oxidative phosphorylation.[1] Even though most ECs do not proliferate, metabolism studies using native nonproliferative vascular cells, tissues, and whole animals are insufficient. A recent study in *Function*[2] challenges the current dogma and presents strong evidence for the critical involvement of mitochondrial oxidative phosphorylation in endothelial metabolism and vascular function (Figure 1).

The Glycolysis Dogma in EC Metabolism

Most cell types rely on mitochondrial ATP production as the primary energy source. However, the dogma has been that mitochondrial oxidative phosphorylation is dispensable in ECs. The concept that ECs are glycolytic in nature is supported with several observations using cell culture experiments in addition to the lower mitochondrial content in ECs compared with other metabolically active cell types.[3] While glycolysis predominates proliferative EC metabolism during vascular development and angiogenesis,[1] most ECs (≥90%) are nonproliferative and nonmigratory. Whether glycolysis or oxidative phosphorylation dictates EC energy production in mature blood vessels and whether EC metabolism affects vascular tone control are not fully understood.

Mitochondrial EC Metabolism

Cell culture environment alters metabolic pathways. The appreciation that oxidative phosphorylation is crucial for endothelial metabolism has recently gained traction with the increased use of freshly isolated ECs and arterial segments. Metabolic flux analyses, for example, showed that mitochondrial ATP production predominates in isolated brain microvasculature.[4] Mitochondrial ATP synthesis inhibition suppressed endothelium-dependent vasodilation.[5] Further, transcriptomic analyses revealed distinct metabolic profiles in vascular bed- and physiological function-dependent manners.[6] Recent evidence showed that mitochondrial ATP production is upregulated in renal ECs during water deprivation, and that glycolytic ATP production predominates in cardiac ECs in response to ischemic events.[7,8] These observations collectively highlight the flexibility of EC metabolism and its inherent ability to switch between mitochondrial and glycolytic pathways.

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Wilson and colleagues set out to test the impact of mitochondrial ATP production on endothelial function. Building on the

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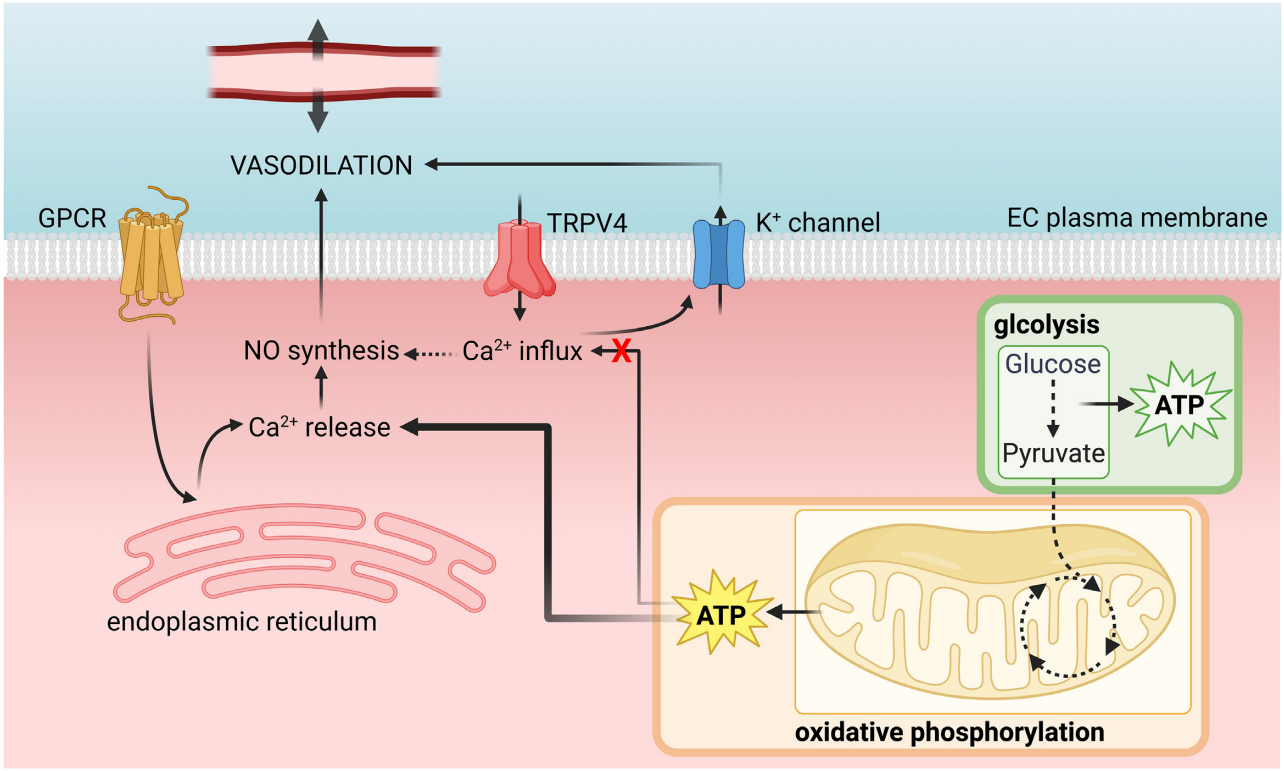

Figure 1. Endothelial metabolism and vascular tone: a schematic highlighting the key role of ATP production in sustaining Ca^{2+} signaling in ECs. G protein-coupled receptor (GPCR) activation causes Ca^{2+} release, and this release is dependent on oxidative phosphorylation. Mitochondrial production of ATP is not crucial for TRPV4-mediated Ca^{2+} influx. Ca^{2+} signaling leads to nitric oxide (NO) production and/or the activation of Ca^{2+}-sensitive K^+ channels, both effects ultimately causing vasodilation.

crucial role of endothelial Ca^{2+} signaling in vascular tone control, the authors used Ca^{2+} and diameter measurements in freshly isolated rat arteries along with pharmacological tools to assess whether inhibiting mitochondrial respiration disrupts Ca^{2+} signaling and arterial tone. The study presents compelling evidence for a 2-fold discovery: (1) oxidative phosphorylation in the endothelium is crucial for ATP production and the ability of ECs to control vascular tone; and (2) distinct EC-vasodilatory pathways are differentially regulated by mitochondrial ATP production.[2]

Oxidative Phosphorylation and Endothelial Ca^{2+} Signaling

First, the study demonstrated that inhibiting mitochondrial respiration reduced endothelial ATP levels and attenuated EC-mediated vasodilation. In particular, the complex V inhibitor, oligomycin, suppressed endothelium-dependent vasodilation induced by muscarinic receptor activation with acetylcholine (Figure 1), but had no effect on endothelium-independent vasodilation. The authors elegantly showed that oligomycin's effects were due to the inhibition of EC mitochondrial respiration, rather than a direct effect on smooth muscle contraction, increased production of reactive oxygen species, or increased cell death.

Mitochondrial ATP Controls Ca^{2+} Release

Second, Wilson and colleagues showed that mitochondrial ATP production is crucial for distinct endothelium-dependent vasodilatory pathways. Oligomycin suppressed acetylcholine-induced dilation but failed to affect vasodilation mediated by endothelium-dependent hyperpolarization. Acetylcholine evokes vasodilation through the activation of muscarinic receptors, downstream Ca^{2+} release from intracellular stores, and the generation of the potent vasodilator NO (Figure 1). Endothelial TRPV4 channel mediates vasodilation through Ca^{2+} influx and downstream activation of Ca^{2+}-activated K^+ channels, which, in turn, hyperpolarizes ECs and dilates arteries. Intriguingly, the findings in this study showed that mitochondrial ATP fuels endothelial Ca^{2+} release and subsequent vasodilation but has minimal effect on Ca^{2+} influx, downstream hyperpolarization, and vasodilation. The inhibitory effect of oligomycin on endothelium-dependent vasodilation is consistent with a recent study showing that ATP depletion inhibited endothelial- and NO-dependent vasodilation, but not endothelium-independent vasodilation.[5] The lack of effect for oligomycin on TRPV4-mediated Ca^{2+} influx is consistent with previous studies showing that ATP is dispensable or even inhibitory for TRPV4 channel activity.[2,9]

Outstanding Questions

The study by Wilson and colleagues supports the paradigm shift from the dogma that glycolysis solely fuels EC energy production. The work also invites new questions that await future investigations. EC metabolism shows plasticity under different conditions.[7] Whether a shift from mitochondrial to glycolytic metabolism—or vice versa—occurs in cardiovascular disease is not completely understood and could inspire novel therapeutic approaches. This is significant when considering recent

observations that EC metabolic dysfunction could underlie blood flow deficits in small vessel diseases.[10] Another important point inspired by the present study is that metabolic alterations can differentially affect different signaling modalities. Disease conditions affecting ATP production in ECs could therefore disrupt the balance between Ca^{2+} release and Ca^{2+} influx mechanisms, by suppressing one (e.g., IP_3R) and favoring the other (e.g., TRPV4). Additionally, it is important to appreciate that different vascular beds may have differences in basal EC ATP levels and may rely on specific ATP-production mechanisms. While Wilson and colleagues tested a few vascular beds in male and female animals, a more systematic investigation could unravel vascular bed and/or sex differences. Future research will be required to answer these questions and others that arise from this study.

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Conflict of Interest Statement

The author has no conflicts to declare.

Data Availability Statement

This article doesn't include data.

Concluding Remarks

The paper by Wilson and colleagues[2] provides compelling new information that highlights the importance of mitochondrial respiration for endothelial metabolism, Ca^{2+} signaling, and vascular function (Figure 1). This work further supports the paradigm shift from ECs being exclusively glycolytic to a more complex context in which oxidative phosphorylation and glycolysis work together to support endothelial function and vascular function.

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