READING BEYOND THE RED: What Fellows Are Reading in Other Journals

Role of Cellular Metabolism in Pulmonary Diseases

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Kim B, *et al.* Glutamine Fuels Proliferation but Not Migration of Endothelial Cells. *EMBO J* (1)

Reviewed by David Wu

Endothelial cells (ECs) are central actors in many disease processes, ranging from atherosclerosis to tumor angiogenesis. In the realm of diseases important to pulmonary and critical care medicine, sepsis, acute respiratory distress syndrome, pulmonary hypertension, and chronic obstructive pulmonary disease stand out, each of which has a component of endothelial dysfunction critical to disease initiation or progression.

ECs have recently been discovered to exhibit aerobic glycolysis (the Warburg effect) similar to tumor cells (2). This high glycolytic rate is critical for angiogenesis, although why the endothelium, in the presence of high oxygen tension, consumes so little of it is unknown. Another similarity between ECs and tumor cells is that they are both highly avid for glutamine, which is the most abundant circulating nonessential amino acid.

Using carbon-tracing experiments, Kim and colleagues demonstrated that glutamine is critical for EC proliferation (1). Glutamine serves as the major precursor to tricarboxylic acid (TCA) cycle intermediates, as compared with glucose, which contributes 20%. Glutamine is processed by glutaminase-1 (GLS1) into glutamate, which enters the TCA cycle as α -ketoglutarate. TCA intermediates are critical building blocks for cellular growth. Removal of glutamine or loss of GLS1 function inhibited EC proliferation, which was restored by replacement with α -ketoglutarate. An endothelium-specific knockout of *GLS1* confirmed that glutaminolysis is required for angiogenesis *in vivo*.

Kim and colleagues also discovered that glucose is critical for EC migration, whereas glutamine is dispensable. They postulated that ATP-dependent migration requires glycolysis, which is

localized along the migrating edge of cells, whereas GLS1 is localized to the center of the cell, critical for cell biomass production. This hypothesis that the cell can compartmentalize metabolism for subcellular use makes conceptual and energetic sense.

How glutamine is regulated by shear stress is unknown. ECs can dynamically regulate their metabolism between quiescent and active glycolysis. Hemodynamic flow is also known to affect cell metabolism, with high shear stress repressing EC glycolysis, through transcription factor KLF2 (Krüppel-like factor 2)-mediated cell quiescence and repression of glycolytic enzyme PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase-3) (3). In contrast, low shear stress increases endothelial glycolysis in a hypoxia inducible factor 1 α -dependent manner (4). Given that shear stress affects many genes and pathways and may modulate cellular respiration, endothelial use of glutamine under hemodynamic flow suggests further investigation.

Interestingly, ECs in pulmonary hypertension are known to have increased glycolysis and proliferation, and blockade of glutaminolysis has been shown to reduce pulmonary hypertension in animal models (5). Thus, targeting glutaminolysis to affect cell proliferation may be an effective adjunct to current therapies. Medications directed against metabolic pathways have started to make inroads in treatment of dysregulated tumor metabolism; however, it is not known whether targeting endothelial metabolism to treat nonmalignant vascular conditions is feasible or effective.

Cell metabolism is an integral part of disease diagnosis and monitoring because glucose and lactate, the input and output of glycolysis, are key determinants of mortality in critical illness. Whether monitoring glutaminolysis can also be used to monitor endothelial health is unknown. However, given the lack of endothelium-specific treatments for many diseases, understanding how cell metabolism contributes to specific cell functions can open new targets for therapy.

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Thwe PM, et al. Cell-Intrinsic Glycogen Metabolism Supports Early Glycolytic Reprogramming Required for Dendritic Cell Immune Responses. *Cell Metab* (6)

Reviewed by Parker S. Woods

During lung infection, both resident and infiltrating immune cells encounter varying oxygen and nutrient conditions, which may negatively affect their effector function. Moreover, immune cells must compete with pathogens for nutrients, which are often limited locally at infection sites. Thus, to overcome these metabolic stresses and to build an adequate effector response, immune cells need to have the flexibility to substantially alter their metabolic activity.

It is increasingly recognized that immune cells mount a proinflammatory response by using aerobic glycolysis, a state in which cells rely on glycolysis in the presence of adequate oxygen concentrations. Aerobic glycolysis provides not only an immediate source of ATP but also precursors needed for nucleotide, fatty acid, and amino acid synthesis (i.e., cellular biosynthesis). Both lymphocytes and myeloid cells upregulate glucose transporters to facilitate enhanced uptake of extracellular glucose to meet glycolytic demands (7, 8).

The majority of studies that investigated the role of glycolytic reprogramming were focused on the use of extracellular glucose to support immune cell effector function, but little is known regarding the role of intracellular glucose stores in these processes. In their article published in *Cell Metabolism*, Thwe and colleagues demonstrated that dendritic cells (DCs) use intracellular glycogen stores to support effector responses under Toll-like receptor stimulation (6). More specifically, they demonstrated that DCs express glycogen machinery and that pharmacologic inhibition or genetic loss of the rate-limiting enzyme involved in glycogenolysis, PYG (glycogen phosphorylase), impeded DC maturation, proinflammatory cytokine secretion, and antigen uptake.

Others have shown that glucose consumed by DCs enters the TCA cycle to generate citrate. Citrate metabolism is linked to endoplasmic reticulum and Golgi expansion, a process believed to enhance cytokine production in DCs (9, 10). Thwe and colleagues showed that PYG inhibition reduced citrate production while

having little impact on other TCA and glycolytic intermediates, suggesting that glycogen stores preferentially support citrate generation under Toll-like receptor stimulation. Interestingly, inhibiting glucose transport did not impact the immediate glycolytic reprogramming observed in DCs, but it did affect longer-term DC maturation. This suggests that intrinsic glycogen metabolism is critical in driving early DC maturation and that extracellular glucose may play an important role after the exhaustion of intracellular glycogen stores.

The findings reported by Thwe and colleagues, though rooted in basic scientific discovery, have broader clinical implications. Aberrant inflammatory processes can contribute to acute respiratory distress syndrome and sepsis. Understanding the metabolic fate of nutrients in activated immune cells may enhance the ability to treat and/or prevent such conditions by targeting distinct metabolic pathways. Moreover, it may be necessary to consider the metabolic needs of cells within a distinct tissue location when treating a disease or infection. For instance, cells in the lung interstitium likely have a vastly different set of metabolic requirements from those in the alveolar space. This knowledge can be exploited in cell-based therapeutics to treat disease more effectively.

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Dumas SJ, et al. NMDA-Type Glutamate Receptor Activation Promotes Vascular Remodeling and Pulmonary Arterial Hypertension. *Circulation* (11)

Reviewed by Heng T. Duong

Current therapies for pulmonary arterial hypertension (PAH) do not target the excessive proliferation of pulmonary vascular cells that leads to pulmonary vascular remodeling, which is a hallmark of disease. Growing evidence suggests that pulmonary vascular remodeling may be driven by metabolic reprogramming characterized by increased aerobic glycolysis, also known as the Warburg effect, and increased glutaminolysis leading to increased glutamate production (5, 12). Glutamate, a pleiotropic molecule that can be used in an anaplerotic fashion to generate α -ketoglutarate in the TCA cycle, has been implicated in the

pathogenesis of PAH, but the mechanisms are unknown. As the main excitatory neurotransmitter in the central nervous system (CNS), glutamate exerts its effects via different types of receptors, including the *N*-methyl-D-aspartate (NMDA) receptor. Interestingly, the NMDA receptor is also present in aortic endothelial and smooth muscle cells, suggesting that glutamate may also exert its effects via NMDA receptors in the pulmonary vasculature (13).

Dumas and colleagues examined whether the glutamate–NMDA receptor axis contributes to vascular remodeling in PAH (11). These authors first present evidence of increased glutamate, NMDA receptor expression, and glutamatergic signaling along the NMDA receptor axis in arteries from humans with PAH, suggesting this pathway is upregulated in PAH. Next, they demonstrate that the mechanism of increased glutamate release in the pulmonary vasculature may resemble that in the CNS. In neurons, glutamate is released from vesicles across the synaptic cleft in a rapid, calcium-dependent manner. The authors show that in both pulmonary microvascular ECs and pulmonary artery smooth muscle cells (PASMCs), glutamate release is similarly driven by intracellular calcium influx.

Dumas and colleagues found that ET-1 (endothelin), via endothelin receptor type A, stimulates glutamate release and increased membrane expression of NMDA receptor in PASMCs. Furthermore, they discovered a link between NMDA receptors and platelet-derived growth factor (PDGF), which is known to exert proliferative effects on PASMCs (14). PDGF exerted its proliferative effects on PASMCs via the NMDA receptor. Collectively, the authors linked the convergence of two pathways known to influence pulmonary vascular remodeling (ET-1 and PDGF) to the glutamate–NMDA receptor axis in human PASMCs.

Last, the authors confirmed the importance of glutamate–NMDA receptor axis in two rodent models of pulmonary hypertension. Genetic loss or pharmacologic inhibition of NMDA receptors attenuated pulmonary hypertension,

pulmonary vascular remodeling, and endothelial dysfunction in these models.

In summary, this is a well-done study delineating a new pathway in PASMCs linking cellular metabolism to canonical PAH signaling pathways, which influence pulmonary vascular remodeling. The study raises future avenues for research, including the potential role of other glutamate receptors such as AMPA, the role and mechanism of glutamate signaling in other cell types, and the cross-talk between endothelial and smooth muscle cells in glutamatergic signaling. The animal data should be interpreted with caution, given that the rodent models presented do not adequately model PAH in humans and because the NMDA receptor antagonists also exert CNS effects that may alter vascular tone and remodeling indirectly. Nevertheless, this work presents the glutamate–NMDA receptor axis as a potential signaling hub in PAH and a compelling potential new therapeutic target for PAH treatment. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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