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Cross-talk between signaling and metabolism in the vasculature

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ABSTRACT

The link between signaling and metabolism was first recognized with insulin signal transduction. Efficient glucose uptake by the endothelium requires insulin receptor activation to deliver GLUT receptors to the cell surface. More recently however, additional evidence has emerged for a broader crosstalk as signaling events have been shown to regulate a large number of metabolic enzymes. Changes in the metabolic status of endothelial and smooth muscle cells are observed at times of increased proliferative activity and these coincide with activation of cell surface receptors. Intriguingly, a rise in glycolysis appears to be associated with remodeling of the actin cytoskeleton during migration and angiogenesis. Overall, understanding how do signaling and metabolic pathways intersect and cross-regulate each other has become an important question and an emerging cornerstone in vascular biology.

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1. Introduction

To meet their bioenergetic needs, cells rely on glucose as one of the primary sources of energy. Through glycolysis, glucose is metabolized into pyruvate in the cytosol. Pyruvate can then either enter the tricarboxylic acid (TCA) cycle in the mitochondria, where it undergoes

oxidative phosphorylation (OXPHOS) in a process that requires oxygen, or it can be further converted into lactate (anaerobic glycolysis). OXPHOS is a very efficient process, generating a total of 32–36 ATPs per glucose molecule and therefore it is not surprising that the path is used by most mammalian cells [1]. In contrast, glycolysis only generates a total of 2 ATPs per glucose molecule, and thus, it is much less efficient than oxidative phosphorylation. The relative use of OXPHOS versus glycolysis varies in cells, and while it was originally thought that only cancer cells switch their metabolism to glycolysis, several examples in the recent literature highlight instances in which normal cells opt for glycolysis even in the presence of high levels of oxygen, a process called

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aerobic glycolysis, and in response to cell surface signaling. Why normal cells, in oxygenated tissues, would select a less efficient mode for ATP generation is an interesting puzzle and it has revealed that aerobic glycolysis is intertwined with signaling pathways that regulate anabolic metabolism, proliferation, and cytoskeletal regulation.

2. The Warburg effect is not exclusive to cancer cells

The switch from OXPHOS to aerobic glycolysis was first described by Otto Warburg. He discovered that cancer cells mainly use aerobic glycolysis even in the presence of oxygen to sustain their rapid and unlimited growth [2]. This phenomenon became quickly recognized as the “Warburg effect” and it has been prevalently studied in cancer cells [3, 4]. However, the Warburg effect is not exclusive of transformed cells; normal cells also upregulate aerobic glycolysis, especially in situations of rapid growth (Table 1). In fact, increased glycolytic metabolism was recently described in proliferating lymphocytes [5–7], activated macrophages [8], proliferating thymocytes [9–11], proliferating fibroblasts [12,13] and regenerating skeletal muscle cells [14]. In the absence of proliferation most of these cell types have a low baseline level of

glycolysis that increases by 20- to 30-fold (in the case of lymphocytes) upon activation [15,16].

A common link between the examples cited above is proliferation. Interestingly, endothelial cells (EC) even in a quiescent state are highly glycolytic despite their close proximity to oxygen. Importantly, while all ECs are glycolytic [17], there seem to be differences in the extent of glycolysis used by ECs from different vascular beds. Parra-Bonilla et al. described that rapidly proliferating pulmonary microvascular ECs are highly glycolytic, while the slower growing arterial ECs are less glycolytic and consume more oxygen [18]. Changes in rates of glycolysis were also described at times of vascular expansion. The endothelium has been shown to double glycolytic rates when switching from quiescence to an angiogenic phenotype [17]. Angiogenic ECs generate more than 80% of ATP through glycolysis, converting glucose into lactate, but less than 1% using OXPHOS in the TCA cycle [19,17]. Oxidative pathways only account for 15% of the total amount of ATP generated in ECs [17]. It is thus not surprising that, compared to other cell types, ECs have a rather small mitochondrial volume fraction (5% vs. 30% in oxidative hepatocytes) that mainly serves as signaling hubs rather than for generating energy/ATP [20].

The preference of ECs for aerobic glycolysis might seem surprising considering the abundance of oxygen in the blood and the direct and unlimited access of blood vessel-lining ECs to oxygen. Using glycolysis as the major metabolic pathway to generate energy might be beneficial when ECs sprout into avascular tissue. Furthermore, a low-oxidative metabolism limits the formation of reactive oxygen species (ROS) and potential ROS-mediated damage. Another advantage of glycolysis over OXPHOS is the fact that it can generate ATP much more rapidly, facilitating adaptation to quickly changing energy-demands of proliferating/migrating cells. Finally, by using less oxygen, more oxygen is available for perivascular cells [21]. But are these the only reasons for the preferential use of glycolysis by endothelial cells and what are the underlying signaling pathways?

3. Crosstalk between signaling and metabolism

It seems obvious that cell signaling and metabolism are linked events, but their cross-talk and regulatory pathways are poorly understood. Insulin signaling was the first of such links, as this pathway is required for the uptake of glucose by glucose transporters (GLUT). In the absence of insulin, GLUT is efficiently sequestered intracellularly in vesicles that are only recruited to the plasma membrane upon phosphorylation of the insulin receptor [22]. In turn, the insulin receptor activates phosphatidylinositol 3-phosphate kinase (PI3K)/AKT protein kinase [23], which subsequently activates AS160, a GTPase-activating protein (GAP) specific for RAB that facilitates anchorage of GLUT vesicles to the plasma membrane (Fig. 1). In fact, inactivating mutations of AS160 result in attenuation of GLUT translocation [23]. Importantly, PI3K and AKT also contribute to regulation of glycolysis through alternative mechanisms described below, further intertwining signaling and metabolism.

A recent publication has demonstrated that PI3K activation increases glycolysis in epithelial cells by enhancing cytoplasmic availability of aldolase A (Fig. 2) [24]. This activity is independent of AKT because specific inhibition of AKT through MK2206 had no effect on NADH/NAD⁺ ratio and extracellular acidification rate (ECAR), which are both proxies for glycolysis [24]. In contrast, the pan inhibitor BKM120 or the specific PI3K- α inhibitor BYL719 resulted in significant attenuation of glycolysis. Importantly, blockade of PI3K was found to be the direct result of a decreased release of aldolase A from the actin cytoskeleton [24]. Therefore, it appears that signaling that activates PI3K unifies several important activities in the cell notably glucose uptake, actin cytoskeletal dynamics, and glycolysis (Fig. 2). While these effects downstream of PI3K are yet to be demonstrated in other cell types, it is likely that the same outcome would be observed in vascular cells. It should be stressed that PI3K is one of the main pathways activated downstream of multiple

Table 1
Aerobic glycolysis in non-transformed cells.

Cell type	Experimental setup	Reference
Hematopoietic cells, lymphocytes	Cytokine stimulation (IL-3) of immortalized murine hematopoietic cells (FL5.12); IL-2 stimulation of primary human T-cells; IL-7 stimulation of immortalized murine B cell progenitors	Bauer et al. [6]
Lymphocytes	Rat thymus lymphocytes stimulated with concanavalinA	Hume et al. [5]
Lymphocytes	Primary human T cells co-stimulated with CD28 and insulin	Frauwirth et al. [15]
Lymphocytes	Primary murine T cells activated with CD3 and CD28	Wang et al. [16]
Macrophages	Bone marrow derived macrophages activated with LPS	Palsson-McDermott et al. [8]
Thymocytes	Primary rat thymocytes stimulated with concanavalinA and IL-2	Brand and Hermisse [11]
Thymocytes	Primary rat thymocytes stimulated with concanavalinA and IL-3	Greiner et al. [10]
Thymocytes	Primary rat thymocytes stimulated with concanavalinA and IL-4	Guppy et al. [9]
Adipocytes	Differentiation of human bone marrow mesenchymal stem cells (MSCs)	Meleshina et al. [42]
Stem cells	Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs)	Varum et al. [43]
Stem cells	Reprogramming of derived induced pluripotent stem cells	Folmes et al. [44]
Stem cells	Human bone marrow mesenchymal stem cells	Fillmore et al. [45]
Stem cells	Hematopoietic stem cells	Simsek et al. [46]
Stem cells	Hematopoietic stem cells	Takubo et al. [47]
Stem cells	Osteogenic differentiation of human mesenchymal stem cells (hMSCs)	Chen et al. [48]
Stem cells	Human embryonic stem cells (hESCs)	Turner et al. [49]
Stem cells	Mouse embryonic stem cells	Schieke et al. [50]
Stem cells	Human embryonic stem cells and hematopoietic stem cells	Ochocki et al. [51]
Fibroblasts	Primary human dermal fibroblasts, proliferating vs. quiescent (contact-inhibited)	Lemons et al. [12]
Smooth muscle cells	Human carotid artery vascular smooth muscle cells stimulated with PDGF	Lambert et al. [33]
Smooth muscle cells	Primary rat aortic vascular smooth muscle cells stimulated with PDGF	Perez et al. [34]
Myoblasts	Differentiation of immortalized mouse skeletal muscle cell line C2C12	Leary et al. [52]
Endothelial cells	EC spheroids, mouse retina, zebrafish	De Bock et al. [21]
Endothelial cells	Primary rat pulmonary microvascular endothelial cells (PMVECs) and primary rat pulmonary artery endothelial cells (PAECs)	Parra-Bonilla et al. [18]
Endothelial cells	Primary pig aortic endothelial cells	Culic et al. [19]

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