EDITORIAL COMMENT

Metabolic Suppression of HIF-1α Contributes to Susceptibility of Ischemic Injury in Diabetic Hearts*

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Hypoxia is a potent regulator of cellular metabolism and growth. Earlier works have identified hypoxia inducible factor (HIF) signaling as the molecular pathway responsible for such adaptation (1-3). The key component of this signaling pathway consists of 2 proteins, the constitutively expressed HIF-1β (also known as aryl-hydrocarbon receptor nuclear translocator or ARNT) and a labile binding partner (HIF-1α or HIF-2α). Under normoxia, oxygen-dependent prolyl hydroxylases (PHDs) catalyze the hydroxylation of HIF-1α and HIF-2α, which is a prerequisite for their degradation (4). Additionally, asparagine hydroxylation by factor inhibiting HIF-1 (FIH1) prevents the interaction between HIF-1α and core transcription machineries (5). Both PHDs and FIH1 require oxygen, iron, and α-ketoglutarate to carry out their functions. During hypoxia, HIF-1α and HIF-2α proteins accumulate and dimerize with ARNT; this complex then translocates into the nucleus (6), where it induces expression of genes involved in glucose metabolism, mitochondrial function, cell proliferation, and viability (6-8). Thus, HIF signaling coordinates a cellular program that protects the organism from the adverse consequences of oxygen deprivation.
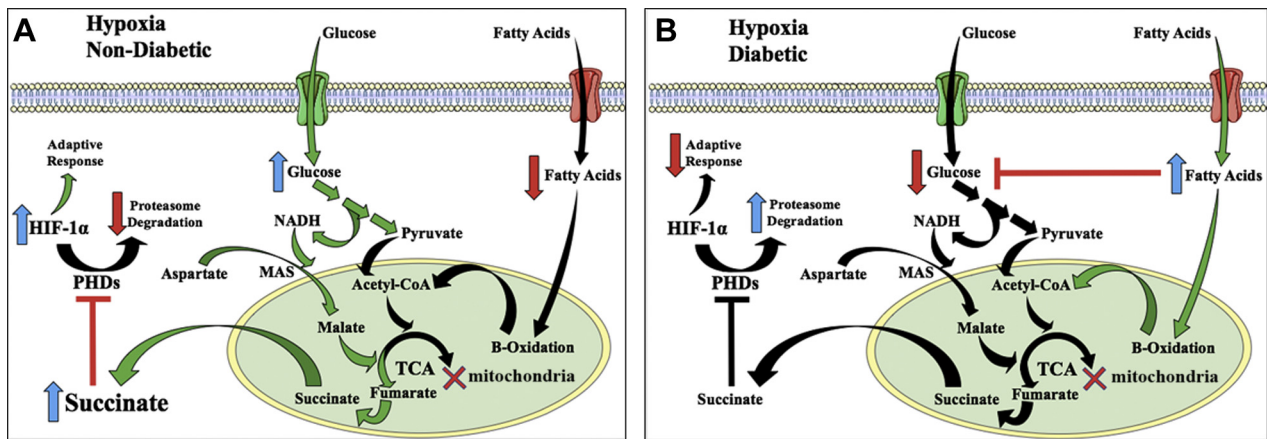
Downstream effectors of HIF have been extensively studied in cardiovascular disease and diabetes. HIF signaling regulates angiogenesis and vascular remodeling. Additionally, HIF-1α increases glycolytic gene expression, thereby ensuring adenosine triphosphate (ATP) production from anaerobic glycolysis (8,9). These effects have great implications in ischemic and pressure overload heart diseases (9). In addition to cardiovascular disease, altered HIF signaling has been implicated in diabetes. In patients with diabetes, the expression of ARNT is lower in the pancreas and liver and genetic deletion of this protein in these 2 organs results in diabetic phenotypes (10,11). Cardiac expression of ARNT is also reduced in the hearts of mice with genetic and diet-induced diabetes. Cardiac-specific deletion of ARNT leads to increased peroxisome proliferator-activated receptor-α expression, thereby resulting in heightened lipid uptake and oxidation. The imbalance between lipid uptake and oxidation causes lipid accumulation and spontaneous cardiomyopathy (12). This evidence demonstrates that diabetes may influence HIF signaling; at the same time, HIF signaling can modulate diabetic phenotypes.

In the heart, diabetes shifts cellular metabolism in favor of increased utilization of fatty acids (FAs) with a concomitant inhibition of glycolysis and glucose oxidation (13,14). FA-mediated suppression of glucose oxidation was first described by Randle et al. (15) in muscle and fat tissue. Increased FA oxidation results in higher levels of mitochondrial acetyl-coenzyme A and nicotinamide adenine dinucleotide hydride (NADH) and cytosolic citrate. These metabolic intermediates can allosterically inhibit 2 key glycolytic enzymes: phosphofructokinase-1 and

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FIGURE 1   Aberrant HIF Signaling in Diabetic Hearts

(A) In normal hearts under hypoxia, succinate levels increase dramatically because of increased glycolysis and MAS activity. Increased succinate levels inhibit PHD activity, thereby facilitating HIF-1α stabilization. **(B)** In diabetic hearts under hypoxia, the aberrant increase in fatty acid metabolism inhibits glycolysis. Reduced NADH influx into mitochondria through MAS blunts the increase in succinate during hypoxia, resulting in the inability to stabilize HIF-1α. CoA = coenzyme A; HIF = hypoxia inducible factor; MAS = malate-aspartate shuttle; NADH = nicotinamide adenine dinucleotide hydride; PHD = prolyl-hydroxylase; TCA = tricarboxylic acid. Figure adapted from Servier Medical Art (28).

pyruvate dehydrogenase (16). The inhibition of phosphofructokinase-1 in turn leads to accumulation of glucose-6-phosphate, which inhibits hexokinase (16); therefore, overall glycolytic flux is reduced. Although diabetic hearts are still able to generate adequate amounts of ATP through FA oxidation under normoxia, they are less capable of producing energy under hypoxia because of reduced anaerobic glycolysis. These defects may contribute to the worse outcome of patients with diabetes and acute myocardial infarction and explain why cardiovascular complications are the primary cause of death in patients with type 2 diabetes (17,18). Nevertheless, precisely how the metabolic derangement controls cellular response to hypoxia beyond energy production remains to be answered.

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The article by Dodd et al. (19) in this issue of *JACC: Basic to Translational Science* brings a novel insight into the susceptibility of diabetic hearts to ischemic injury by demonstrating that they fail to accumulate HIF-1α under hypoxia through a proteasome-dependent mechanism. Under hypoxia, the heart normally accumulates high levels of succinate; however, this increase is attenuated in the diabetic heart (**Figure 1**) (20). Succinate is a potent repressor of PHDs, and a reduced succinate to α-ketoglutarate ratio allows for increased activity of PHDs under hypoxia (21). In cell culture,

supplementation of insulin-resistant cells with dimethyl fumarate (which can be converted to succinate) restores the HIF-1α protein accumulation under hypoxia. A similar effect was achieved through treating cells with DMOG, a PHD inhibitor. Additionally, administration of DMOG to diabetic rats results in better functional recovery after cardiac ischemia/reperfusion in an ex vivo heart perfusion system.

More important, the authors mechanistically link increased FA oxidation to the failure of succinate accumulation in diabetic hearts under hypoxia. In hypoxia, the forward flow of electron transport chain is inhibited. Anaerobic glycolysis thereby becomes a vital source of ATP production, generating NADH as a byproduct. However, if the electron equivalents cannot be used, excessive cytosolic NADH would bring anaerobic glycolysis to a halt. In addition to lactate production, malate/aspartate shuttle allows for the transport of electron equivalents into the mitochondria, thus restoring cytosolic NADH/NAD$^+$ ratio. Increased mitochondrial malate and fumarate in this situation can drive succinate dehydrogenase in reverse and result in succinate accumulation (**Figure 1**) (20). Supplementation of cell culture media with FA forces cultured cells to use FA, which results in inhibition of glycolysis and reduced HIF-1α accumulation. Importantly, the authors demonstrated that both palmitate and oleate have similar inhibitory effects; therefore, the change in cellular