



EDITORIAL COMMENT

Diabetes, hypoxia and cardiovascular disease: From molecular mechanism to treatment[☆]



Diabetes, hipóxia e doença cardiovascular: do mecanismo molecular ao tratamento

João Vasco Ferreira^{a,b}

^a *Proteostasis and Proteolytic Signalling Lab, CEDOC, NOVA Medical School, NOVA University, Lisboa, Portugal*

^b *Group of Ubiquitin-dependent Proteolysis and Intercellular Communication, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal*

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Cardiovascular disease (CVD) is the leading cause of death in diabetic patients. Recent statistics from the American Heart Association show that 68% of people aged 65 or older with diabetes die from some form of heart disease. Around 50% of all adults with diabetes die of CVD; diabetic patients are two to four times more likely to die from heart disease than non-diabetic individuals. The high mortality of these patients is even more striking considering that diabetes is one of the most manageable risk factors for CVD. Indeed, even if glucose levels are under control, diabetic patients still suffer higher CVD-related mortality than non-diabetic individuals. In this context, a better insight is required into what might be happening in the heart under high glucose concentrations.

Hypoxia controls all steps of postischemic revascularization in all organs of the body, a process that is of cardinal importance in patients with myocardial ischemia. It occurs in part by activation of the transcription factor hypoxia-inducible factor 1 alpha (HIF-1 α) and other molecular partners.^{1,2} Perhaps the most important mechanism regulated by HIF-1 α in this context is transcription of vascular

endothelial growth factor (VEGF), a major player in the growth of new blood vessels.¹ Studies have shown that in the presence of elevated glucose concentrations, cells and tissues are subjected to increased levels of advanced glycation end products (AGEs),³ which are known to downregulate HIF-1 α function.^{1,2} AGEs are formed by the reaction of sugars such as glucose with the free amino group of certain amino acids, via reversible intermediates of a Schiff base and an Amadori product.³ This is similar to glycosylation, but requires no enzymatic activity and therefore is not regulated. Often, glycated proteins eventually lose their original functions, which makes the process toxic to the cell. Methylglyoxal (MGO), a byproduct of glycolysis that is elevated in diabetic patients, has a ~20 000-fold higher reactivity than glucose⁴ and has been shown to inhibit the HIF-1 α pathway by a number of different mechanisms.^{1,2} Nonetheless, the most likely cause of loss of cell response to hypoxia in most diabetic complications is destabilization of HIF-1 α , through direct modification of the transcription factor by glucose or MGO, leading to an irreversible conformational change of the protein and subsequent elimination by the cell's proteolytic systems.⁵ This hypothesis is supported by the loss of HIF-1 α in hypoxic tissues of patients with hyperglycemia.¹ In this issue of the *Journal*, Ramalho et al. show that this is also true for cardiac muscle cells, in this case the HL-1 cell line, in a time- and dose-dependent manner.⁶ Interestingly, even though there are reports that degradation of the HIF-1 α protein after glycation occurs through ubiquitination and subsequent

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E-mail address: joao.ferreira@nms.unl.pt

degradation of HIF-1 α by the proteasome,⁵ Ramalho et al. show that, at least in cardiac cells, proteasome inhibition is not sufficient to prevent HIF-1 α destabilization in the presence of MGO.⁶ Furthermore, degradation of HIF-1 α by a proteasome-independent pathway has been described.⁷ HIF-1 α is degraded in the lysosome by a mechanism called chaperone-mediated autophagy (CMA), a process that is particularly important under low oxygen concentrations.⁷

Strategies to reverse the loss of HIF-1 α under hyperglycemia have been shown to improve wound healing in diabetic mice.⁸ Most studies have focused on the use of prolyl hydroxylase (PHD) inhibitors such as dimethyl-oxalylglycine or the iron chelator deferoxamine.⁸ These compounds act by hindering the hydroxylation of HIF-1 α by PHDs, since hydroxylation is the initial step that triggers ubiquitination and degradation of HIF-1 α by the ubiquitin proteasome system. During hypoxia this pathway is inactive because PHDs use oxygen for hydroxylation of HIF-1 α . In this context the new data point toward CMA as a more suitable therapeutic target for the rescue of HIF-1 α function in diabetes. There is thus now strong evidence indicating that future research should focus on the role of CMA in the degradation of HIF-1 α under hyperglycemia, both in cultured cells and in animal models of diabetes. Compounds inhibiting degradation pathways that use the lysosome, like CMA, are well known and efforts are being made to find new ones.⁹ Moreover, the lysosome inhibitor hydroxychloroquine is already used in malaria patients. Therefore, in view of Ramalho et al.'s new findings, it is reasonable to hypothesize that the lysosome might be a suitable target for the prevention of HIF-1 α destabilization and promotion of postischemic revascularization, in particular in diabetic patients with myocardial ischemia in the context of CVD.

Conflicts of interest

The author has no conflicts of interest to declare.

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