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HYPOXIA-INDUCIBLE FACTOR-1 α IN STEM CELL PRECONDITIONING: MECHANISTIC ROLE OF HYPOXIA-RELATED MICRO-RNAs

To the Editor:

Since its inception more than 2 decades ago, ischemic preconditioning (IP) is considered as the most powerful cytoprotective stimulus and is being devised as a potent strategy to promote stem cell survival post-engraftment in the infarcted heart.¹ The elegant study from Hu and colleagues² is a step forward toward the use of low oxygen culture conditions to trigger activation of survival signaling pathways in the cells before their engraftment in vivo. The authors showed significantly improved survival of the hypoxia-treated (0.5% oxygen for 24 hours) mesenchymal stem cells after engraftment in the infarcted heart. Unlike many of the previous studies, an important aspect of the study protocol was cell engraftment during the acute phase of myocardial infarction to assess the effectiveness of a preconditioning approach. Acute phase engraftment exposed the engrafted cells to the harsh, cytokine-rich microenvironment of the infarcted myocardium, which was aggravated even more because of the infiltration of inflammatory and progenitor cells as a part of the intrinsic repair process. The authors attributed the effectiveness of the hypoxic preconditioning approach to up-regulation of hypoxia inducible factor (HIF)-1 α , a heterodimeric master switch of a hypoxia-responsive array of genes

that enable the cells to acclimatize and survive in low oxygen conditions. Although a low-level presence of HIF-1 α has been reported in the cytoplasmic compartment of cells grown under normoxia, hypoxia stabilizes HIF-1 α against degradation and promotes its translocation to the nucleus, where it forms functional complexes for gain of functions. As a part of our continuing endeavor to precondition donor cells for their better survival in the infarcted heart and that too with clinical relevance,³ we share our experience of extrapolating the classic IP strategy of exposing the cells to multiple sublethal ischemia/reoxygenation cycles of short duration to promote mesenchymal stem cell survival (unpublished data). This approach represents an extension of the one-time, long-term exposure to sublethal hypoxia approach suggested by Hu and colleagues.² Our results showed significant up-regulation of HIF-1 α in an Akt-dependent manner in the cells preconditioned by 2 cycles of ischemia-reperfusion of 30 minutes each. These molecular events successfully attenuated donor cell attrition on subsequent exposure to lethal ischemic insult. The participation of hypoxia-associated micro RNAs (miR), miR-107 and miR-210,⁴ downstream of HIF-1 α in translation of cytoprotective effects of IP was another important observation in our study. HIF-1 α -specific RNA interference abrogated both miR-107 and miR-210 in the preconditioned cells transfected with HIF-1 α -specific siRNA with a concomitant increase in preponderance of apoptotic cells. Our in vivo experimental results in a rodent model of acute myocardial infarction showed that transplanted preconditioned cells survived significantly better compared with their nonpreconditioned counterparts. Moreover, transplantation of preconditioned cells promoted miR-107 and -210 expression in the infarcted heart at the site of the cell graft. These novel findings necessitate more in-depth studies to elucidate whether

the effect of IP can be duplicated by manipulation of the cells for hypoxia-related miRNAs to promote donor cell survival.

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THE IMPLICATIONS OF OUTCOME PREDICTORS WHEN TRANSITIONING FROM ARTERIAL TO DOUBLE-SWITCH SURGERY

To the Editor:

I read with great interest the fate of the systemic ventricle after double-switch surgery among those who had left ventricle (LV) training.¹ The authors concluded that LV training with pulmonary artery (PA) banding resulted in a worse outcome after the double-switch procedure. I would like to add a few potential explanations for their findings. One of the important aspects of the decline in function can be related to the coronary circulation and its aberrant network in patients with corrected transposition of the great arteries.² This has been