LETTER

Promising antiapoptotic effects of helix B-surface peptide (HBSP) for treatment of heart diseases

We read with great interest the recent paper in PNAS by Ueba et al. (1) concerning the cardioprotection by helix B-surface peptide (HBSP), a nonerythropoietic, tissue-protective peptide mimicking the 3D structure of erythropoietin. The authors showed that HBSP protects cardiomyocytes from apoptosis in vitro and in vivo. Cardioprotection by HBSP presented in the paper was fascinating and complements other works concerning cardiomyocyte survival by erythropoietin (EPO) alternatives. The authors analyzed the effects of HBSP on cardiomyocyte apoptosis by using TUNEL and annexin V. The authors also attempted to analyze HBSP signaling in cell survival. Their conclusion that HBSP protects cardiomyocytes from apoptosis and leads to a favorable outcome in failing hearts through an Akt-dependent pathway is biologically relevant. EPO has been shown to cause antiapoptotic effects in a variety of cell types, including cardiomyocytes (2). In addition, the authors used TNF-α to induce apoptosis in their investigation. TNF-α is expressed in the heart during ischemic injury and inflammation and it provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways. Importantly, caspase activation plays a central role in TNF-α–induced apoptosis (3).

In recent years, there were significant advances in our understanding of antiapoptotic intracellular signaling events in response to EPO in cardiomyocytes. These efforts need to be continued, but it is important to use appropriate experimental tools that provide answers relevant for the known mechanisms of both EPO and TNF-α. The authors’ conclusion that HBSP can substitute EPO in cardioprotection is misleading, because EPO is known to trigger various networks including JAK-STAT activation, Bcl-2, caspase activity, protein kinase B (i.e., Akt1), and modulation of mitochondrial membrane potential to ensure myocardial cytoprotection (4, 5). To claim that HBSP can substitute EPO in cardioprotection, further demonstrations of, at least, more mechanisms of EPO cardioprotection are needed. In addition, caspase activation, the hallmark of TNF-α–induced apoptosis, was not investigated. Besides, there can be occasional increase in cleaved caspase-3 activity in a higher percentage in cardiomyocytes compared with TUNEL staining. Thus, the measurement of known apoptosis components of EPO and TNF-α apoptotic machinery may offer further information about the role of HBSP in cardiomyocyte apoptosis.

What we do find helpful is that, in figure 1 (1), the authors should consider the use of different time points. In figure 2 (1), it is not sufficiently discussed why the bands of Akt phosphorylation appear only transiently, and why the authors used different time points from the ones used for apoptosis analysis elsewhere in the paper. Although the relationship between cell death and cardiac function remains largely unclear, it is possible that one or more of these EPO pathways plays a significant role in modulating cardiac dysfunction through an apoptotic mechanism. Thus, identification of other players in the HBSP pathway may improve the benefits associated with therapeutic implication of apoptosis regulators in heart injuries.

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