Letter to the editor: “Cyclosporin A in left ventricular remodeling after myocardial infarction”

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TO THE EDITOR: We read with great interest the article by Khomukhamedov et al. (4) published in the American Journal of Physiology-Heart and Circulatory Physiology. The authors demonstrated that the immunosuppressant cyclosporin A (CsA) decreased apoptosis in remote (not at risk) regions of the myocardium after myocardial infarction (MI) but did not improve cardiac function or prevent necrosis. Though the authors attributed the absence of the protective effects of CsA to mitochondrial permeability transition pores (mPTPs) in post-MI remodeling, we believe that an alternative explanation may clarify the results.

Indeed, mitochondria and mPTP opening play a complex role in cardiac remodeling, hypertrophy, and heart failure resulted from MI. First, it should be pointed out that mPTPs play a critical role in necrosis, not apoptosis. Cyclophilin-D knockout cells demonstrated similar resistance to apoptotic factors but higher resistance to necrotic factors (5) compared with wild-type (control) cells. Although mPTP opening at high conductance induces matrix swelling and rupture of the outer mitochondrial membrane, leading to the release of cytochrome c from the inner mitochondrial membrane and depletion of ATP, cells likely die via necrosis, rather than apoptosis. mPTP opening requires Ca\(^{2+}\), ATP depletion (high P\(_i\)), high reactive oxygen species levels, and a neutral intracellular pH, as would occur in the heart during reperfusion. However, these alterations do not severely develop during chronic post-MI remodeling, as results from permanent (no reperfusion) coronary artery ligation (CAL). Actually, our previous studies demonstrated less mPTP opening in rat hearts subjected to permanent CAL for 12 or 18 wk when compared with those subjected to ischemia-reperfusion (1). Therefore, we think that the apoptosis observed in the post-MI, remote myocardium may result from mPTP-independent mitochondrial membrane permeabilization caused by Bax oligomerization, Bax/voltage-dependent anion channel interaction, or other unknown pathways. Second, drug delivery to the infarction (necrotic) area may have been obscured by low collateral flow in rodent hearts and/or delayed (48 h after CAL) CsA administration. In previous studies, CsA exerted cardioprotective effects when administered intravenously (bolus or multiple injections) before MI (ischemia) and/or upon reperfusion [reviewed in (2)]. Perhaps this explains why the authors did not observe a difference between control and CsA-treated post-MI groups with regard to the size of the necrotic area or cardiac function.

We would like to propose an alternative mechanism by which CsA could reduce apoptosis. CsA, a nonspecific mPTP inhibitor, binds to cyclophilin A in the cytoplasm and inhibits the calcium-dependent protein phosphatase, calcineurin (6). This inhibition, which is also caused by FK506, blocks cardiomyocyte hypertrophy, whereas overexpression of cardiac calcineurin produces cardiac hypertrophy, leading to heart failure in vivo (7). In addition, recent studies demonstrated that CsA inhibits a rise in intracellular Ca\(^{2+}\) (3), for example, through stimulation of Ca\(^{2+}\) uptake by the sarcoplasmic reticulum. Thus the antiapoptotic effects of CsA observed in rats with post-MI remodeling can be explained by inhibition of cytoplasmic Ca\(^{2+}\) and downregulation of apoptotic pathways through phosphorylation, perhaps similar to those involved in the cytoprotective actions of immunophilin-based drugs. In this scenario, CsA likely acts in a non-mPTP-dependent manner to prevent apoptosis in the remote post-MI myocardium.

In conclusion, in parallel to the authors’ attractive hypothesis that implicates mPTP in antiapoptotic effects of CsA, an alternative explanation should also be considered. We agree with the authors that further studies are required to clarify the contribution of mPTP to post-MI remodeling in the necrotic (infarction) area and remote myocardium using the mPTP-specific inhibitors such as sanglifehrin A or derivatives of CsA (i.e., NIM811), which do not inhibit calcineurin.

References


Author Contributions

S.J. edited, revised and approved final version of manuscript.

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