Connexin 43 phosphorylation in subsarcolemmal mitochondria: a general cardioprotective signal targeted by fibroblast growth factor-2?

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Online publish-ahead-of-print 16 May 2014

This editorial refers to ‘The FGF-2-triggered protection of cardiac subsarcolemmal mitochondria from calcium overload is mitochondrial connexin 43-dependent’ by W. Srisakuldee et al., pp. 72–80, this issue.

During the last years, our knowledge on the role of connexin 43 (Cx43) in myocardial pathophysiology has expanded substantially. Initially thought to participate only in propagation of the electrical impulse, Cx43 gap junction channels were later shown to mediate metabolic coupling between neighbouring cells, and to associate their fates during ischemia and reperfusion.1 Cx43 was then found outside gap junctions, forming unopposed hemichannels with paracrine signalling functions,2 and more recently has been found in locations other than the plasma membrane. Cx43, or its carboxyterminal domain, can translocate to the nucleus, where they may modulate cell growth and gene expression,3 and interact with intracellular signalling cascades involved in important functions as glucose metabolism.4 We know now that Cx43 is also present at the inner mitochondrial membrane of subsarcolemmal mitochondria (SSM) of cardiomyocytes,5 that it modulates mitochondrial K+ uptake,6 complex I respiration,7 and radical oxygen species generation,8 and that this localization is important for preconditioning protection.9 In a recent study, ischemic preconditioning protected SSM submitted to ischemia–reperfusion.10 The study by Srisakuldee et al.11 published in the current issue of *Cardiovascular Research* provides evidence, indicating that the cardioprotective effect of fibroblast growth factor-2 (FGF-2), previously described by these and other authors, is indeed mediated, at least in part, by mechanisms depending on Cx43 present in SSM. The authors found that treatment with FGF-2 attenuates calcium-induced mitochondrial permeability transition (MPT) in Langendorff-perfused rat hearts, measured as cyclosporine A-preventable mitochondrial swelling in SSM, and that this protective effect could be prevented by the Cx43-hemichannel blocker Gap27. The modulation of MPT by mitochondrial Cx43 is consistent with previous studies in rat brain mitochondria.12 Moreover, the authors demonstrated that the effect of Cx43 on MPT did not require an increased translocation to mitochondria, but was dependent on its phosphorylation at S262 and S368, as it could be reproduced by phorbol 12-myristate 13-acetate stimulation.

These results are relevant as they suggest that Cx43 at SSM may not only be important for ischemic or diazoxide-induced preconditioning, but a key signalling element in different forms of cardioprotection. The results provided also hints on the molecular mechanisms involved. The fact that FGF-2 protection can be inhibited by a hemichannel blocker is consistent with the hypothesis that Cx43 forms, indeed, hemichannels at the inner mitochondrial membrane.8 Furthermore, the importance of phosphorylation at S262 and S368 may help to identify the molecular mechanisms involved, and may help to define new pharmacological targets. On the other hand, the effects of FGF-2 on fibroblast activation, myocardial fibrosis, and hypertrophy may limit the direct translation of treatment with FGF-2 to patients as a cardioprotective agent against myocardial ischemia reperfusion, and further research is needed in this regard.

These exciting results should be confirmed and expanded by future research. A critical point will be to reinforce the evidence of a cause–effect relationship between phosphorylation of Cx43 at S262 and S368 and protection against MPT. In this regard, it will be interesting to know if protection of SSM by FGF-2 occurs also in transgenic models with reduced or absent Cx43 expression or with reduced Cx43 translocation to mitochondria. It will be also important to characterize the intracellular kinetics of Gap27, a connexin mimetic peptide acting on the second Cx43 extracellular loop, as the carboxyterminal domain of mitochondrial Cx43 is oriented towards the intermembrane space, and Gap27 should reach the mitochondrial matrix to exert its action.

As it usually happens, although it is not always clearly recognized, the results from Srisakuldee et al.11 are not completely linear. The protective effect of FGF-2 against MPT was also observed at a smaller scale, in IFM, containing little Cx43. The protective effects of FGF-2 were

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associated with increased levels of PKCε, pPKCε, and Tom20 in both mitochondrial populations, and GSK-3β and pS9-GSK-3β in IFM. No clear explanation is given to the increased resistance of IFM to calcium-induced MPT after FGF-2 treatment. FGF-2 acts by binding to plasma membrane tyrosine kinase receptors (FGFR1-4) that are widely expressed in the myocardium.13 The 18 kDa isoform of FGF-2 is a potent mitogen and a powerful angiogenic agent, and it is up-regulated in the myocardium in response to injury and chronic stress, including that of ischaemia, at both the transcriptional and translational levels.13 Binding of FGF-2 to FGFR1 receptors is followed by internalization and nuclear translocation of the complex. Activated nuclear FGFR1 may then directly activate gene expression.14 However, stimulation of FGF-2 receptors also leads to activation of downstream signals. Some of these signalling cascades have been involved in cardioprotection, including activation of the RISK, MAPK, phospholipase C-PKC, and Src-associated pathways.13 Involvement of nitric oxide signalling and including activation of the RISK, MAPK, phospholipase C-PKC, and Src-associated pathways.13 Involvement of nitric oxide signalling and including activation of the RISK, MAPK, phospholipase C-PKC, and Src-associated pathways.13 Involvement of nitric oxide signalling and including activation of the RISK, MAPK, phospholipase C-PKC, and Src-associated pathways.13

References

Conflict of interest: A.R.-S. is a recipient of a contract from the Generalitat de Catalunya (Programa d’Estabilització d’Investigadors, Departament de Salut, Direcció d’Estratègia i Coordinació).