A TRiP to heart failure

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This editorial refers to ‘Blockade of sarcolemmal TRPV2 accumulation inhibits progression of dilated cardiomyopathy’ by Y. Iwata et al., pp. 757–765, this issue.

Transient receptor potential (TRP) channels constitute a somewhat eclectic family of ion channels that share structural similarities and some functional properties, especially cation permeability and weak voltage sensitivity. TRP channels are expressed in virtually every cell type present in the heart, including cardiomyocytes, fibroblasts, endothelial cells and vascular smooth muscle cells.1

In the current issue of Cardiovascular Research, Iwata et al.2 describe a potential role for TRPV2 in the progression of dilated cardiomyopathy (DCM). TRPV2 is a Ca$^{2+}$-permeable cation channel which is activated by temperatures $>$30°C, and might also function as a mechanosensitive channel.3 Both in sensory neurons and atrial myocytes, TRPV2 has been proposed to function as a stretch-activated channel. However, it seems now relatively established that TRPV2 has no physiological role in sensing of physical stimuli such as pressure or temperature, since thermal and mechanical responses of the Trpv2−/− mouse are identical to those of WT mice. Notably, a cardiac phenotype of Trpv2−/− mice has not been reported yet.4 Chemical agonists of the channel include endocannabinoids, 2-APB, and probenecid, but caution should be taken. It is a common theme in the TRP channel field that pharmacologic agents are notoriously non-selective. Thus, the response of Trpv2−/− neurons to either of these compounds was not distinguishable from WT neurons.4 Likewise, inhibitors of TRPV2 include promiscuous compounds such as SKF96365, amiloride, ruthenium red, trivalent cations, and citral. Recently, Tranilast has emerged as a TRPV2-specific blocker although it is clear that this compound also affects other targets (see below).3

An important theme in the understanding of the cellular role of TRPV2 is the subcellular localization of the channel protein and the trafficking from internal cytosolic pools towards the plasma membrane. TRPV2 was originally cloned as a calcium-permeable channel that, when overexpressed in a cell line, translocates to the plasma-membrane in response to insulin-like-growth factor 1.5 In cultured and primary β-cells TRPV2 expression at the plasma membrane is increased by insulin, after binding to the insulin receptor and activation of PI3 kinase.6

In the heart muscle, TRPV2 was proposed to be responsible for the positive inotropic effect of probenecid, which has no effect on cardiac contractility in Trpv2−/− mice.7 These authors show that TRPV2 mediates Ca$^{2+}$ release for the sarcoplasmic reticulum, and probenecid does not activate a transmembrane current in healthy cardiomyocytes. Iwata et al.2 show in this issue of Cardiovascular Research that in three different animal models of DCM and human cardiac tissue from DCM patients TRPV2 is increasingly present at the sarcolemma. The same authors have shown before that cardiac overexpression of TRPV2 in mice leads to cardiomyopathy due to Ca$^{2+}$-overloading. In this study, it was proposed that TRPV2 is activated by membrane stretch, and that increased presence of TRPV2 in the sarcolemma of subjects with Duchenne muscular dystrophy would be a crucial mechanism for dystrophy of cardiac (and skeletal) muscle.8 Now they show that when myocytes are isolated from DCM patients, β-sarcoglycan-deficient hamsters, sialytransferase overexpressing mice, and doxorubicin-induced DCM mice, TRPV2 is accumulating in the sarcolemma, as opposed to (unknown) intracellular compartments or the intercalated disks in healthy tissue. To probe TRPV2 as a therapeutic target, Iwata et al. apply different strategies to interfere with TRPV2 function. First, they overexpressed part of the N-terminus of the TRPV2 protein in cardiomyocytes of DCM animals, which effectively removed TRPV2 from the sarcolemma and prevented the further development of DCM, ameliorated contractile dysfunction and improved survival of the affected animals. Secondly, they inhibited TRPV2 function with Tranilast, which markedly suppressed DCM progression. Tranilast is a drug, which is already used in clinical practice for the treatment of allergic reactions. Several studies have suggested that it blocks TRPV2 function, but its effects might also be related to other targets. Indeed, it was also shown that the drug affects ATP-sensitive K+ channels, up-regulates the expression of microRNA 133, and influences gene expression of TGF-β1 and Rac1.9–11 Thus, to delineate the effects of Tranilast to TRPV2 inhibition, experiments with Trpv2−/− mice seem essential. The same remark stands for the strategy to over-express part of the TRPV2 N-terminus. This part of the protein has been implicated in several protein–protein interactions, and is an important site for the regulation of other related TRP channels.3 Thus, the overexpression of part of the N-terminus of TRPV2 does not necessarily affect only the translocation of TRPV2, but might also change the regulation of other proteins in the cardiac muscle. Bearing these precautions in mind, it is unclear from the available data whether the development of DCM induces TRPV2 translocation, or whether TRPV2 translocation induces DCM progression. What would be the role of the TRPV2 channel in healthy cardiac myocytes, and how its translocation to the sarcolemma is regulated in cardiomyocytes remains equally elusive.

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TRPV2 is not the only TRP channel that is implicated in cardiac function. A great deal of attention has already been paid to the TRPC channels that, by allowing Ca\(^{2+}\) influx, are able to activate calcineurin-NFAT-mediated cardiac hypertrophy.\(^ \text{12}\) Mutations in the human TRPM4 gene are linked with progressive familial heart block type I and isolated cardiac conduction block, through an as yet unknown mechanism.\(^ \text{13}\)

Recently, it was shown that knockout of TRPM7 leads to a complex cardiac phenotype, depending on the time point in cardiac development when the gene is inactivated. Early in embryogenesis (<E9), TRPM7 gene knockout leads to congestive heart failure and death by E11.5 due to decreased proliferation of the myocardium. Late in development (E13), TRPM7 knockout hardly produces any cardiac phenotype. At an intermediate stage, knockout of the TRPM7 gene results in the development of cardiomyopathy associated with heart block, impaired repolarization and ventricular arrhythmias in 50% of Trpm7\(^{-/-}\) mice.\(^ \text{14}\)

Considering that Ca\(^{2+}\) (mis)handling in the cardiomyocyte is an essential trigger for the development of heart failure, arrhythmias and cardiac remodelling,\(^ \text{15}\) it is unsurprising that Ca\(^{2+}\) permeable TRP channels might play an essential role in these processes. The challenge lies in the extension of this idea to human disease and the development of specific strategies to target these channels specifically in the cardiac muscle. Indeed, TRP channels are broadly expressed, and the available pharmacological tools might be too promiscuous. It is in this respect that article by Iwata et al. in this issue of *Cardiovascular Research* provide intriguing clues for the potential of TRPV2 as a drug target in DCM.

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