Cellular mechanisms of failure and arrhythmia in the diseased heart

N.A. Beard,[1] A. Denniss,[1] K. Walweel,[2] D.R. Laver,[2] P. Molenaar[3,4] and A.F. Dulhunty,[5] [1]Health Research Institute, Faculty of Education, Science, Technology and Mathematics, University of Canberra, Bruce, ACT, 2617, Australia, [2]School of Biomedical Sciences and Pharmacy, University of Newcastle and Hunter Medical Research Institute, Callaghan, NSW 2308, Australia, [3]Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, 4000, Australia, [4]Northside Clinical School of Medicine, University of Queensland, The Prince Charles Hospital, Chermside, QLD, 4032, Australia and [5]John Curtin School of Medical Research, Australian National University, Canberra, ACT 0200, Australia.

The RyR2 ligand-gated Ca^{2+} release channel is found embedded in the membrane of the intracellular Ca^{2+} store (the sarcoplasmic reticulum; SR), within the heart. It forms the hub of a large macromolecular complex that plays a vital role controlling cellular Ca^{2+} handling and specifically in SR Ca^{2+} release leading to systole. Maintaining a highly regulated and robust release of Ca^{2+} during systole and minimizing Ca^{2+} release, or leak, through the RyR2 during diastole is essential to healthy heart function. In heart failure, excess Ca^{2+} release or leak through RyR2 during diastole is prevalent. This leak is an arrhythmic substrate (Shannon *et al.,* 2002), which can be induced by changes in channel sensitivity to Ca^{2+} (Marx *et al.,* 2000; Terentyev *et al.*, 2008; Walweel *et al.,* 2017), the loss of regulatory co-factors and covalent modification by stress-induced reactive oxygen/nitrogen species and enhanced phosphokinase activity (reviewed in Dobrev *et al.*, 2014).

We have previously shown that RyR2 is hyperphosphorylated at S2808 and S2814 and redox modified in human heart failure (Walweel *et al.,* 2017). There is a reduction in the association of regulatory phosphatases with RyR2, which in part can account for the hyperphosphorylation observed in human heart failure patients (Walweel *et al.,* 2017). These phosphor/redox-dependent changes correlate with a loss of channel responsiveness to Ca^{2+}, and to a reduced association of the regulatory co-factors FKBP12 and FKBP12.6 from the channel (Walweel *et al.,* 2017). Our results illustrate that changes in Ca^{2+} sensitivity are also observed in a number of other cardiac pathologies, including a model of RyR2-linked arrhythmogenic right ventricular cardiomyopathy and viral induced-myocarditis. Very recent data show a changed pattern of Ca^{2+} handling protein expression between atrial and ventricular healthy human heart tissue. Comparing failing heart atria and ventricle, we find not only very varied protein expression patterns, but also differences in phosphor/redox- RyR2 modification and RyR2 calcium handling.

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