The Role of LRRC10 in Cardiac Excitability and Regeneration

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Abstract

LRRC10 is a cardiac-specific protein whose function in the heart remains poorly understood both in health and disease. Our prior studies showed that LRRC10 is a potent regulator of L-type Ca^{2+} channel current, but the mechanism underlying that regulation remains poorly understood. Furthermore, LRRC10 has been linked to cardiac regeneration in zebrafish and related species. Using whole-cell patch clamp studies of HEK cells expressing $Ca_v1.2$, β_{2CN2}, and $\alpha_2\delta$ subunits encoding for L-type Ca^{2+} channels, we demonstrate that co-expression of patient-specific variants in LRRC10 exhibit a remarkable range of effects channel function. Further studies explore the key regions of $Ca_v1.2$ involved in channel reguation by LRRC10. We next examined the role of LRRC10 in neonatal mouse heart regeneration. Wild type and *Lrrc10*$^{-/-}$ neonatal mice underwent surgically induced myocardial infarction by occlusion of the left coronary artery one day after birth. In contrast to wild type mice which showed complete cardiac regeneration at 28 days, *Lrrc10*$^{-/-}$ mice exhibited impaired cardiac regeneration with resulting scar formation. Characterization of the WT and *Lrrc10*$^{-/-}$ hearts showed comparable activation of cell cycle genes but impaired cytokinesis. AAV9-LRRC10 delivery on day 1 rescued regeneration in *Lrrc10*$^{-/-}$ hearts following injury. Overall, these results demonstrate that LRRC10 finely regulates L-type Ca^{2+} channel function and is essential cardiac regeneration in neonatal mouse hearts. Ongoing studies are examining the interface between LRRC10 regulation of L-type Ca^{2+} channel function and cardiac regeneration.