Staying Connected Without Connexin43
Can You Hear Me Now?

Barry London

As popular cellular telephone commercials suggest, we place considerable value on our ability to remain connected to our friends and neighbors. The same principals ring true in cardiovascular physiology. Connexin (Cx) proteins are located at cardiac gap junctions and form low resistance pathways for the intercellular spread of electrical excitation and small molecules. Within each cell, six connexin subunits coassemble to form hemichannels that then dock with their counterparts on neighboring cells. Ventricular myocytes express Cx43 along with lower levels of Cx45, atrial myocytes express Cx40 and Cx43, and conduction system cells express Cx45 and Cx40. Thus, both heteromeric channels (with variable mixtures of Cx subunits in each hemichannel) and heterotypic channels (formed from asymmetric hemichannels in neighboring cells) are expected.

Gene-targeted mice have greatly advanced our understanding of the roles of individual connexin genes. Homozygous Cx45 knockout mice have abnormal cardiac development and die as embryos. Homozygous Cx40 knockout mice have impaired conduction with prolonged PR intervals, bundle branch blocks, and a propensity toward atrial arrhythmias. Studies on heterozygous Cx-targeted mice (Cx43+/−) show decreased protein levels and decreased conduction velocity, although these findings have been the subject of some controversy. Homozygous Cx43 knockout mice (Cx43−/−) die in the early postnatal period with cardiac defects, making a detailed analysis of the impact of Cx43 ablation on ventricular impulse propagation difficult. To circumvent these difficulties, a conditional Cx43 knockout mouse using the Cre-lox system was engineered. These conditional knockout mice have marked decreases in Cx43 protein and sudden death due to ventricular tachyarrhythmias. Of note, some ventricular myocytes express normal levels of Cx43 and the conduction velocity within the ventricular myocardi- um of the Cx43 conditional knockout mice was decreased by only 50%.

Synthetic stands of plated neonatal cardiac myocytes allow the study of impulse propagation and arrhythmia formation in a controlled 2D environment. In the current issue of Circulation Research, Beauchamp et al use this technique with Cx43 knockout myocytes to study conduction. They report an absence of Cx43 protein, marked decreases in cell coupling (<5%), and very slow propagation (~2 cm/sec or 4% of normal). Thus, there does appear to be a large safety factor for impulse propagation in the heart, consistent with arguments based on computer-modeling studies. In addition, the residual conductance is consistent with Cx45 channels, although the distribution of Cx45 within the gap junctions is markedly altered in immunohistochemical studies of the knockout strands. Finally, uncoupling of residual gap junctions with heptanal eliminates conduction, arguing against the efficacy of field effect transmission and in support of the requirement for gap junctions to support electrical propagation in this preparation.

As is always the case, some questions do remain. The properties of the remaining connexins in the Cx43 knockout strands are consistent with Cx45, but this has not been directly tested. Such experiments could be done by comparing synthetic strands of the Cx43+/−/Cx45+/− myocytes used here to Cx43−/−/Cx45−/− myocytes. Alternately, Cx45 knockdown techniques such as RNAi could be used. These experiments would also provide the lower limit of coupling that allows propagation. In fact, direct communication failure from one cell to another is already evident in the Cx43−/− strands, with activation of some cells by circuitous routes.

The conditional Cx43 knockout mouse is one of the few transgenic mice that actually dies of ventricular fibrillation. A logical interpretation of this finding related reduced coupling to an increased risk of sudden death. It may be, however, that the relatively preserved conduction velocity in that mouse is related to heterogeneities at the cellular level, and that these heterogeneities rather than uncoupling and/or conduction slowing are responsible for the murine sudden death phenotype.

Every model system carries its own limitations. Synthetic 2D strands of neonatal myocytes may not adequately represent 3D adult cardiac muscle. Thus, the findings do not eliminate the possibility of field effect transmission in the intact heart. Relating findings from mouse myocytes to humans also remains difficult, given the marked differences in heart rate, repolarizing currents, and action potential duration between the species.

In summary, Beauchamp et al circumvented perinatal lethality in the Cx43−/− mouse to advance our knowledge of connexin function. Additional studies of this type will take advantage of other transgenic and gene-targeted mouse models. The findings published here, however, represent a clear advance in our understanding of the wireless communication used by the heart.
References


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