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Roles of HCN2 channels in congenital heart diseases

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Congenital heart diseases (CHDs) affect 80,000-120,000 newborns in US annually. CHDs encompass a wide spectrum of cardiovascular malformations, and remain the major cause of infant mortality among all types of birth defects. To date, molecular mechanisms underlying CHDs remain elusive, largely owing to the complexity of the diseases and lack of animal models that can reproduce the disease conditions in a laboratory setting.

The hyperpolarization-activated, cyclic nucleotide-gated cation channels (HCN) are responsible for generating spontaneous pacemaker activities in both cardiac and central nervous systems. These channels are present in other tissue or cell types to perform multiple essential biological functions. We recently characterized two HCN2 knockout (HCN2KO) mouse lines, in which the full-length HCN2 is disrupted. The first line died at approximately 6-weeks of age while the second line could live beyond adulthood with a special diet. Maternal echocardiography data on the KO hearts revealed a markedly underdeveloped left side since embryogenesis, suggesting that HCN2KO mice developed hypoplastic left heart syndrome (HLHS) and subsequent fetal arrhythmia. The survived line remodeled their hearts to permit harder blood pumping, leading to improved survival %. The average size of the survived line was half of WT control at birth; they exhibited a significantly retarded growth rate and were "arrested" at 5-weeks of age. Other additional data further indicates that the HCN locus is a hot spot for HLHS onset. Our novel findings suggest that the HCN2 gene is indispensable in cardiogenesis and these new KO models are therefore innovative platforms for CHD studies.

Biography

Nian-Qing (Nan) Shi has completed her Ph.D. in Microbiology in 2000 from The University of Wisconsin-Madison. After she finished an industrial post-doctoral training in mitochondrial redox regulation with Tate and Lyle, she returned to academia to investigate the molecular composition and structure/function of a mitochondrial ATP-sensitive potassium (mitoKATP) channel in cardioprotection. Her team identified and cloned the cardiac mitoKATP channel, which had been pursuing by the field since 1991. In her recent studies, she started exploring the roles of HCN2 channels in congenital heart diseases. She serves as editorial members for 3 journals and reviewers for several major cardiac journals.

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