



Quality control in the secretory pathway and congenital heart diseases.

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Congenital heart malformations represent the single largest class of birth defects in human and are the leading cause of death in infants under one year old. Despite this the regulatory networks responsible for the heart formation remain poorly understood. Focus of this presentation is on the role of calreticulin, a critical component of the quality control mechanisms of the secretory pathway, in congenital heart diseases. Calreticulin deficiency in mice is lethal due to defects in heart development. The calreticulin gene is tightly regulated during cardiac development and up-regulation of calreticulin expression leads to a complete heart block reminiscent of human disease suggesting that calreticulin may play a role in the development of pacemaker activity in postnatal heart. In the adult, the heart rate is driven by spontaneous and repetitive depolarizations of pacemaker cells to generate a firing of action potentials propagating along the conduction system and spreading into the ventricles. We have engineered pacemaker cells from ES cells, a model that recapitulates early stages of heart development, and showed that calreticulin and InsP₃-dependent calcium homeostasis are essential for a proper generation of pacemaker activity during early cardiogenesis and fetal life. These studies underscore the importance of calreticulin during the early stages of cellular commitment, cardiogenesis and pacemaker development.

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Host: Dr Henry Mok