Establishing a Model for Congenital Atrioventricular Block using Human Embryonic Stem Cells

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Congenital heart block (CHB) is an autoimmune disease caused by transplacental passage of maternal anti Ro/La antibodies (Abs) in Lupus, Sjogren and asymptomatic mothers. CHB carries a high mortality and a need for permanent pacing. Two proposed theories regarding CHB pathogenesis exist: the electrophysiological (inhibition of calcium channels) and the chronic apoptosis hypotheses.

Aims: To establish an *in-vitro* model for CHB using human embryonic stem cells derived cardiomyocyte (hESC-CMs) and to investigate the potential mechanistic contribution of the electrophysiological theory.

Results: Specific IgG's from 3 mothers of children with CHB reactive to Ro/ La antigens were used. Staining of the hESC-CMs with anti-Ro/La Abs revealed intense nuclear staining, confirming their expression by these cardiomyocytes. Whole-cell patch-clamp recordings following Abs application showed significant slowing of the hESC-CMs' action-potential frequency followed by complete cessation of beating, which was reversible after Abs washout. Laser-confocal Ca2+ imaging was utilized to record Ca2+ transients. Abs application led to complete quiescence of Ca2+ transients in 55% of tested hESC-CM and a decrease in frequency in 43%, findings that were partially reversible by Abs washout. The Ab effect was also noted at the multicellular level, using the multielectrode array mapping system. Spontaneous beating frequency was reduced by 64±14% initially and stopped in 66%. Moreover, marked conduction slowing was noted by 2.6±0.2 fold, with partial recovery after washout. Finally, Abs application led to reduced contractility of the hESC-CMs and to increased apoptosis (TUNEL staining) 24h later.

Conclusions: Our study suggests that the hESC-CMs may serve as a unique model to study CHB, and as such it represents the first description for the use of hESC to study acquired diseases. Moreover, our results support the direct electrophysiological hypothesis as an important contributing mechanism to CHB.