Modeling congenital heart defects with pluripotent stem cells: insights from human embryonic stem cells with trisomy 21

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Down syndrome is the most common human chromosomal disorder caused by the presence of all or part of an extra human chromosome 21, which occurs in approximately 1 in 750 of live births (Letourneau A et al., 2012; Reeves RH et al., 2001). Congenital heart defects affects 40-50% of patients with Down syndrome (Sailani MR et al., 2013; Williams AD et al., 2008) and represent a leading cause of morbidity. While it is known that gene-dosage imbalances disrupt prenatal development, the underlying mechanisms and the cellular pathways involved in congenital heart defects associated with Down syndrome remain to be determined. In order to understand how this chromosomal disorder evolves in early cardiac development and leads to perturbations possibly responsible for congenital heart defects, we used human embryonic stem cells induced to differentiate toward the cardiac lineage, a valuable model to recapitulate native stages of cardiogenesis and analyse the defects arising from errors in the morphogenetic program. Using two unrelated human embryonic stem cell (hESC) lines exhibiting complete trisomy 21 (T21), one of which was fraternal sibling of two additional euploid lines, we investigated gene and protein expression, both over a time-course of early development, and specifically in cardiomyocytes. Investigations also included functional studies in isolated beating cardiomyocytes, whose properties are closely determined by diverse ion channels and regulatory proteins expressed during cardiogenesis in a temporal specific manner (Sartiani et al., 2007). T21-hESC displayed many significant differences in expression of genes involved in early differentiation process, a point in development which would have major implications for mesodermal lineage development. More notably, the reduced number of ISL1(+) progenitor cells giving rise to the secondary heart field development, is expected to affect the formation of cardiac outflow tract and chambers, resulting in a global perturbation of heart development. Furthermore, we provided evidence for two candidate genes located on chromosome 21, ETS2 and ERG, whose overexpression during cardiac commitment likely account for the disruption of secondary heart field development. Finally, we reported an abnormal electrophysiological phenotype of differentiated cardiomyocytes from T21-hESC, similar to that seen in early fetal echocardiograms, suggestive of a global derangement of electrophysiological maturation attained by T21-cardiomyocytes. Together these analyses provide insight into the complex developmental patterns at the basis of congenital heart defects in Down syndrome.

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