Abstracts

Molecular medicine and development

Program/Abstract # 311
Mesenchymal β-catenin regulates Tbx1 expression and causes DiGeorge-like phenotypes
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DiGeorge syndrome is one of the most common genetic diseases in humans affecting 1 in 4000 people. This disease is characterized by pharyngeal apparatus malformations causing outflow tract alignment and cardiac septation defects, thymus, parathyroid aplasia/hypoplasia, and craniofacial defects. Most cases of DiGeorge syndrome are caused by deletion of chromosome 22q11 and Tbx1 is the candidate gene for cause of the disease. Tbx1 heterozygous mice show minor cardiovascular defects. Whereas, Tbx1 null mice display the most severe features of the disease. Tbx1 over-expressing mice also exhibit DiGeorge-like phenotypes, indicating that the gene dosage of Tbx1 is critical. Here, we show that canonical Wnt/β-catenin signaling negatively regulates the Tbx1 gene and that mesenchymal deletion of β-catenin using Dermo1-cre causes a DiGeorge-like phenotype. Phenotypes include, abnormalities of the great vessels, including aberrant emergence of the right and left subclavian arteries, hypoplastic pulmonary arteries, aortic arch hypoplasia, major cardiac outflow tract abnormalities classified as double outlet right ventricle, overriding aorta, pulmonary truncus arteriosus, ventricle septation defect, atrial septation defects, micrognathia, thymus hypoplasia and detachment. Tbx1 expression is up-regulated in β-catenin conditional knockout embryos. Fgf8 expression and the FGF8/FGFR signaling downstream targets Erm and Pea3 are also increased. This finding indicates that Wnt/β-catenin signaling is important for modulating the level of Tbx1 expression and that disruption of this balance is a likely etiology of DiGeorge-like disease phenotypes.

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Program/Abstract # 312
The effect of embryo biopsy on gene expression and development in the preimplantation mouse embryo
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Preimplantation Genetic Diagnosis (PGD) is a form of prenatal screening done on embryos prior to the initiation of pregnancy so that only select embryos are transferred. PGD requires assisted reproduction, culture to the 8-cell stage, and an invasive embryo biopsy procedure which involves: 1) incubating embryos in divalent-cation-deficient medium to disrupt cell adhesion, 2) breaching the zona pellucida with Acidic Tyrode's, laser drilling, or mechanical force and 3) aspirating one or two blastomeres. Although PGD has been used successfully in the clinic, the risks associated with PGD for the health and well-being of the offspring have not been examined in an animal model. In this study we developed a mouse model of PGD to determine the effect of various aspects of the biopsy procedure (incubation in Ca2+/Mg2+-free medium, Acidic Tyrode's treatment, blastomere aspiration), performed individually or in combination, on preimplantation embryo development and global patterns of gene expression. There was no significant difference between the treatment groups in terms of preimplantation embryo development. However, a significant percentage of embryos that were subject to Acidic Tyrode's treatment hatched prematurely. Microarray analysis demonstrated that the treatment groups were more similar than different in terms of global gene expression. Multiple Statistical Analysis of microarray analysis showed that no genes were different among the treatment groups. These results suggest that there is not a correlation between the embryo biopsy procedure and alterations in preimplantation development and global gene expression.

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Program/Abstract # 313
Role of MESD in WNT signaling and lipoprotein metabolism
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Loss of mesd (mesoderm development) blocks gastrulation and mesoderm differentiation in mice. Polarity defects likely result from improper localization of WNT co-receptors LRP5/6. LRP5/6 are members of the LRP (low-density lipoprotein related receptors) family. We hypothesize that MESD functions more broadly to fold LRPs. Consistent with this hypothesis, mesd mutants are smaller than wnt3a−/− or lr p5/6−/− mutants. Using a cell culture secretion assay, we show that MESD is required for trafficking LRPs containing a beta-propeller/EGF motif. In mesd mutants, the scavenger receptor LR2 (megalin) is diffusely localized in the VE of mesd mutants compared to apical localization in wt embryos. LR2 is important for nutrient uptake in the visceral endoderm (VE), as well as for protein clearance by the kidney proximal tubule. Electron micrographs show that the VE in mesd mutants has a reduced number of vesicles, as compared to wild-type littermates. Further, uptake of dI-HDL is impaired in mesd mutants. This suggests that the growth defects result from impaired nutrient uptake as a result of improperly localized LRPs. If MESD is a general LRP family chaperone, MESD may have an additional, and novel, role as a regulator of cardiovascular health. LRP family members LR1, LDLR, and VLDLR have

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