Role of Transforming Growth Factor Beta2 in Congenital Heart Disease

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Congenital heart disease (CHD) represents the largest class of birth defects in the US and affects about 0.8% of all babies born. As a result of remarkable advances in the medical and surgical management of CHD, more than 75% of children born with CHD now live into adulthood. As such, discovery of the causes for CHD is not only a fundamental research endeavor, but is vital to the health care of this growing community. Inherited genetic mutations in Transforming Growth Factor Beta (TGFB) gene are found in the patients of Loeys-Dietz syndrome. Several cardiac (endocardial, myocardial) and extra-cardiac (second heart field, neural crest) cell lineages that express Tgfb2 contribute to heart development. To study the role of Tgfb2 in different cell types involved in heart development, we have generated Tgfb2 conditional knockout mice. These mice harbor Tgfb2 LacZ-tagged conditional-ready allele (also called tm1a). By using long range PCR (LR-PCR) we have confirmed the germline transmission of Tgfb2tm1a allele. Histological examination shows that Tgfb2tm1a/tm1a embryos develop several congenital heart defects. This indicates that Tgfb2tm1a allele is a knockout-first allele, which is consistent with the original design of our conditional gene targeting scheme. Next, by crossing to Flp recombinase mice we can generate mice with a Tgfb2 conditional-ready allele (also called tm1c). The presence of Tgfb2tm1c allele in the mice is confirmed by genomic PCR. In the future, we plan to use Tgfb2tm1c mice to conditionally delete Tgfb2 in different cardiac or extra-cardiac cell types using well-characterized Cre recombinase transgenic mice. Collectively, we have produced, generated, and validated mice harboring the Tgfb2 LacZ tagged knockout-first and conditional-ready allele. Our results from embryos carrying homozygous Tgfb2tm1a allele indicate that TGFβ2 is required for heart development. Future research will be crucial in expanding knowledge of the unknown cellular etiology of cardiac malformations in patients with TGFB2 mutations.

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