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Research Description

My research efforts have concentrated on delineating the molecular basis of vascular development in the mammalian embryo as an approach to understanding the etiology of congenital heart diseases. My laboratory efforts are based on the hypothesis that the developing vasculature provides important patterning information that directs subsequent cardiac and pulmonary morphogenetic events. We have focused our investigation on two areas: 1) the role of endothelial cell adhesion molecules, particularly PECAM-1 in regulating vascular ontogeny and 2) the role of NFATc-1, in specification of endocardial development during early organogenesis. PECAM-1/CD31 is the earliest endothelial specific adhesion molecule expressed in the developing embryo. In addition, it is expressed as multiple alternatively spliced isoforms which demonstrate dramatically different adhesion profiles. We are using in vitro cell culture, in situ whole mouse embryo culture, and transgenic approaches to define the specific role of PECAM-1 and its alternatively spliced isoforms in embryonic vascular ontogeny. To facilitate these studies, the laboratory has developed techniques for adenoviral mediated, tissue specific gene delivery in situ and in utero, during critical stages of cardiovascular development. Most recently, we have identified restricted expression of PECAM-1 to the inner cell mass of the pre-implantation embryo defining the first ICM specific cell adhesion molecule and suggesting a role for PECAM-1 in maintaining stem cell pluripotency. To this end, we have begun characterization of both the ICM and endothelial specific regulatory regions of PECAM-1. In addition, the laboratory has begun analysis of the first endocardial specific transcription factor identified to date, Nuclear Factor of

Activated T cells (NFATc1) and has demonstrated that it is required for normal aortic and pulmonary valve formation utilizing null mutations in the mouse. Strategies aimed at defining the "upstream" and "downstream" mechanisms by which NFATc regulates semilunar valve formation include chimeric analysis by ES cell blastocyst complementation, representational display with micro array screening, as well as quantitative anatomical and physiological assessment using high resolution ultrasound and MRI microscopy. Finally, we are developing strategies for endothelial specific gene mutations using the Cre-Lox system and defining inducible endothelial specific promoters to allow temporal a spatial gene manipulation throughout the vascular system. We are particularly interested in delineating the role of the receptor tyrosine kinase, Tie1, in pulmonary vascular development. We have documented that there is a burst of Tie1 expression in the pulmonary vasculature that is associated with rapid lung maturation in the neonatal period and are using whole lung bud culture and postnatal analysis to further determine the role Tie1 plays in pulmonary vascular maturation.

Publications

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