Department of Pharmacology & Toxicology

SECOND ANNUAL THEODORE M. BRODY DISTINGUISHED LECTURE

MICHIGAN STATE UNIVERSITY

JOEY V. BARNETT, PhD
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Department of Pharmacology
Vanderbilt University
Nashville, TN

DATE: October 28, 2009
TIME: 12:00 noon to 1:00 pm
LOCATION: B448-49 Life Sciences Bldg

...With Introductory Comments about Theodore M. Brody by Steven Brody

UNRAVELING CARDIOVASCULAR DEVELOPMENT - TGFβ IN VALVES AND VESSELS

HOSTS: SUSAN M. BARMAN

Cardiovascular disease is a major cause of mortality and morbidity. Revealing the cellular processes and molecules that regulate the formation and remodeling of the cardiovascular system is required to develop effective therapies for cardiovascular disease. The Transforming Growth Factor β (TGFβ) family of ligands are key regulators of development and disease. Three ligands, TGFβ1, TGFβ2, and TGFβ3, signal through three cell surface receptors The role of the Type I (TGFβR1 or ALK5) and Type II (TGFβR2) receptors in signaling has been well studied while less is known about the Type III TGFβ receptor (TGFβR3), or betaglycan. Our laboratory has focused on revealing the role of TGFβR3 in cardiovascular development. Using a combination of experimental embryology and mouse genetic approaches, we determined that TGFβR3 signals via noncanonical pathways distinct from those activated by TGFβR2/TGFβR1 and that TGFβR3 is required for specific events during cardiovascular development. During valvulogenesis TGFβR3 is required for endocardial cell epithelial-mesenchymal transformation (EMT) *in vitro* and mesenchymal cell differentiation *in vivo*. Loss of TGFβR3 results in enlarged cushions and altered remodeling of the valve leaflets. Unexpectedly, deletion of TGFBR3 in the mouse resulted in a failure of coronary vessel development. This was accompanied by alterations in epicardial, epithelial cell interactions with the extracellular matrix, increased apoptosis, and decreased proliferation. Relatively little is known concerning the signaling mechanisms downstream of TGFβR3. Using AVC endocardial cell EMT as an assay, we have identified TGFβR3-dependent downstream signaling pathways that are distinct from those stimulated by TGFβR2/TGFβR1. Specific C-terminal amino acids in TGFβR3 and interacting protein partners are required for endocardial cell EMT. Together, these studies reveal unique and nonredundant roles for TGFβR3 in cardiovascular development and TGFβ signaling.

Refreshments will be served