Similar Molecular Mechanisms Regulate Plasticity of Embryonic Endoderm and Stem/Progenitor Cells in Adult Endoderm Organs

Jennifer J. Kordich[1], Deborah Sinner[1], Kwon-Sik Park[2], Robert Opoka[1], Mildred Stahlman[3], Aaron M. Zorn[1], Jeffery Whitsett[2], and **James M. Wells[1]**

[1]Division of Developmental Biology, Cincinnati Children's Research Foundation, Cincinnati, OH
[2]Division of Pulmonary Biology, Cincinnati Children's Research Foundation, Cincinnati, OH
[3]Department of Pediatrics, Vanderbilt University, Nashville, TN

We have observed that numerous genes that are expressed by embryonic endoderm cells are also expressed in the stem cell niche of adult endodermally derived organs suggesting that embryonic and stem cell plasticity are controlled by similar mechanisms. For example the transcription factor Sox17, which is required for normal endoderm development in Xenopus and mouse, is expressed in the intestinal crypts, in a subset of ciliated cells in the conducting airway of the lung, in the pancreatic ducts, and in a subset of cells in the Islets of Langerhan's. Following naphthalene-induced injury in the lung, Sox17 becomes broadly expressed in the regenerating epithelial cells of the conducting airway. Furthermore, misexpression of Sox17 in the distal lung causes cells to adopt a proximal lung progenitor cell phenotype implicating Sox17 as a regulator of progenitor cell fate. Our studies suggest that Sox17 might regulate cell fate by antagonizing the canonical wnt pathway, which is known to regulate stem/progenitor cell proliferation in several organs. In colorectal carcinoma cells and *Xenopus* embryos, Sox17 antagonizes Wnt/TCF activity and depletion of endogenous Sox17 protein in embryos results in increased Wnt-target gene expression suggesting that Sox17 normally restricts TCF/β-catenin activity, *in vivo*. We have identified that Sox17 antagonizes this pathway utilizing a novel mechanism by which it directly binds to TCF transcription factors and β-catenin and targets these proteins for degradation via a non-canonical, GSK3β-independent mechanism. Our findings suggest that the ability of Sox17 to regulate cellular plasticity in the embryo is utilized by progenitor cells in adult endoderm organs during normal self-renewal and during regeneration following injury. Furthermore, we have implicated Sox17-mediated degradation of TCF/β-catenin proteins as a possible pathway to target for clinical strategies aimed at promoting stem cell mediated regeneration.