Dr. Jianwen Que

Abnormal separation of the respiratory system from the foregut leads to the common birth defect esophageal atresia/tracheoesophageal fistula (EA/TEF) which affects 1/2,500-3000 newborns. Although the anomaly can be corrected with surgical intervention, up to 72% of surviving adolescents and adults continue to suffer from respiratory problems throughout their lifetime, suggesting a connection between EA/TEF and lung abnormalities. Consistently, EA/TEF is always accompanied by abnormal lungs (e.g. lobe fusion) in animal models, although the underlying mechanism is unknown. We recently showed that an epithelial saddle formed at the lung-esophageal boundary moves upward to split the lung and trachea from the esophagus. However, several important questions remain to be answered. How is the lung involved in saddle formation and movement? What is the underlying cellular and molecular mechanism? We aim to use a combination of organ culture, frog, and mouse models to address these issues. Our lineage tracing data show that derivatives of respiratory progenitor cells (Nkx2.1 positive) integrate into the esophagus during separation. Moreover, our preliminary data suggest that a unique lung epithelial progenitor subpopulation (Sox2;Sox9;Isl1 positive) located at the lung-esophageal boundary plays critical roles in the formation of the saddle. We further found that the loss of the transcription factor Sox2 or Isl1 in the lung progenitors, including the subpopulation, leads to EA/TEF and abnormal lungs in both frogs and mice. Interestingly, these abnormalities are accompanied by a reduction of extracellular matrix (ECM) proteins including Fras family members Fras1 and Frem2 which are known to regulate lung development. We therefore **hypothesize that the Sox2/Isl1 axis regulates ECM proteins in a lung epithelial progenitor subpopulation (Sox2;Sox9;Isl1 positive) that is required for respiratory--esophageal separation and lung development.** We will test the hypothesis with three specific aims: **Aim1** to determine the contribution of the lung epithelial progenitor subpopulation to the saddle formation and respiratory-esophageal separation; **Aim2** to test the hypothesis that Sox2 regulates Isl1 in the lung epithelial progenitor subpopulation to control respiratory-esophageal separation; **Aim3** to test the hypothesis that Isl1 regulates the separation process and lung development through ECM proteins. Notably, chromosomal deletion of the region covering *ISL1* (and other genes) has been found in patients with EA/TEF. Our findings therefore will provide direct evidence and mechanistic insight into the role of Sox2/Isl1/ECM axis in the pathogenesis of this defect and associated lung abnormalities.