Mutations in SIN3A cause diaphragmatic hernia, lung hypoplasia, and pulmonary hypertension in humans and mice

Stokes, G1; Genthe, W1; Brix, M1; Wynn, J1; Shen, Y2; Chung, W2; McCulley, DJ1

1. University of Wisconsin-Madison, Madison, WI; 2. Columbia University, New York, NY

Background
- Congenital diaphragmatic hernia (CDH) is a common and severe congenital malformation affecting 1 in 3500 live births.
- The high mortality in CDH patients is due to lung hypoplasia and pulmonary hypertension.
- Our hypothesis is that a core group of genes is responsible for both diaphragm formation and development of the lungs and pulmonary vasculature.
- Whole exome sequencing in patients with CDH identified mutations in the SIN3A gene.
- SIN3A encodes a transcription factor required for cell cycle regulation, histone modification, muscle cell development, and lung epithelial cell development.

Objectives
1. Determine the role of Sin3a in the developing diaphragm and lung mesenchyme
2. Identify the mechanisms responsible for lung hypoplasia and pulmonary hypertension due to Sin3a loss of function

Methods: Tissue-specific conditional deletion of Sin3a in diaphragm or lung mesenchyme

Diaphragm and lung mesenchyme cell specific deletion

Results: Sin3a deletion in skeletal muscle results in defective diaphragm development

Results: Early Sin3a deletion causes CDH and lung hypoplasia

Results: Sin3a mutant mice have lung defects present at birth

Results: Loss of Sin3a causes defects in cell cycling and increased cell death

Results: Loss of Sin3A transcriptional regulation causes multiple gene expression changes

Conclusions
- Mutations in the SIN3A gene were identified in patients with CDH.
- Sin3a deletion in mice causes CDH, lung hypoplasia, defects in cell cycling, and pulmonary hypertension.

Future Directions
- Use Sin3a genetic targets as a guide to improve lung and pulmonary vascular defects in mice as a path toward future therapy for patients with CDH.

Acknowledgements
Projected supported by funding from the University of Wisconsin-Madison School of Medicine and Public Health, Department of Pediatrics, UW-ICTR, NICHD, and NHLBI

Many thanks to the members of the McCulley laboratory and collaborators
Giangela Stokes: gstokes@wisc.edu, David McCulley: dmcculley@wisc.edu