Abstract:

Introduction: Genetic variants in T-box transcription factor 4 (TBX4) cause pulmonary hypertension (PH), however, there are diverse phenotypes with respect to timing and severity of disease. Previous mouse studies demonstrated that germline TBX4 knockout is embryonic lethal, but knowledge gaps exist in how postnatal disruption of TBX4 signaling affects lung structure and PH.

Methods: A mouse model was used in which TBX4 was inactivated on day of life (DOL) 1. On DOL21, lung function was evaluated, and tissue was collected. Radial alveolar counts (RAC), vessel density, and right ventricular hypertrophy (RVH) were assessed. Downstream lung angiogenic (VEGF, KDR and eNOS) and inflammatory mediators (TNF-a and IL-1) were measured.

Results: TBX4 deficient mice exhibited decreased RAC compared to controls ($p < 0.05$). Total lung resistance was increased, and total lung compliance was reduced in the TBX4 deficient group ($p < 0.05$, $p<0.01$). Postnatal TBX4 deletion reduced lung vessel density ($p<0.001$) and caused RVH ($p< 0.01$). Lung pro-angiogenic and inflammatory cytokine expression were reduced in TBX4 deficient mice.

Conclusion: Postnatal disruption of TBX4 signaling is sufficient to impair lung function, reduce alveolar and vascular growth and cause RVH, which are associated with decreased lung expression of pro-angiogenic mediators but not enhanced inflammation.