Nuclear YAP inhibition impairs fetal lung development in an ex vivo murine model

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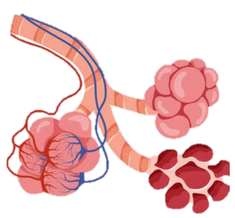
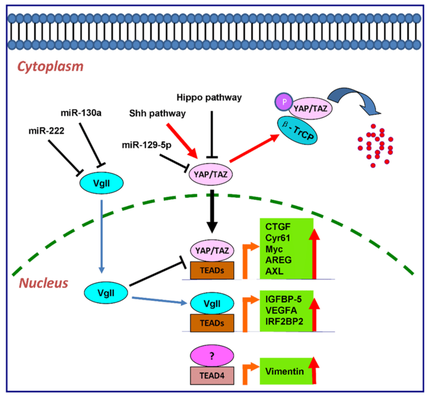
Background

- YAP/TAZ is a key mechanosensory signaling pathway during fetal development



- YAP activation promotes | normal lung branching and alveolarization
- Recent literature suggests a downregulation of the activated nuclear YAP (nYAP) with a corresponding upregulation in deactivated cytoplasmic YAP (cYAP) in the pathogenesis of congenital diaphragmatic hernia (CDH) lung hypoplasia

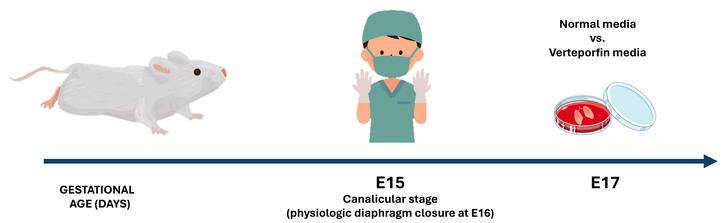


Aim

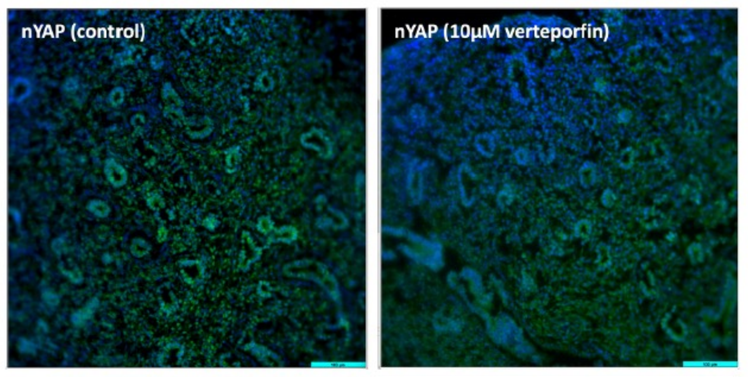
The purpose of this study was to determine the impact of nYAP inhibition in an ex vivo murine model of congenital diaphragmatic hernia fetal lung development, using verteporfin (a known YAP inhibitor).

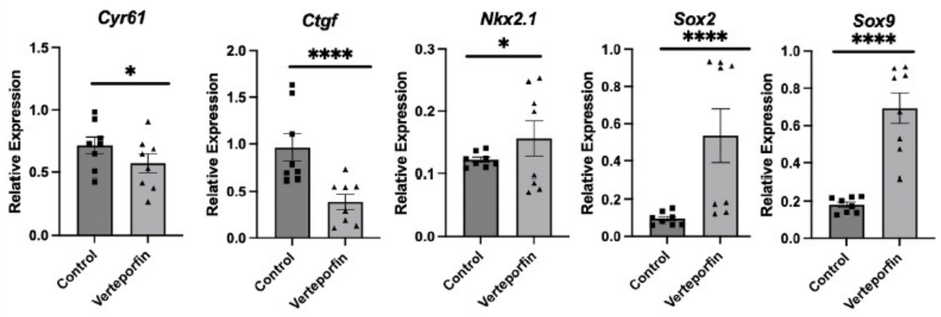
Methods

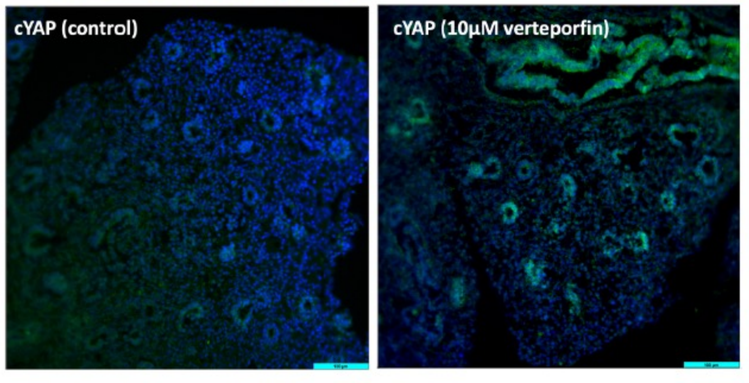
- Pregnant mice were **sacrificed at E15**, with **whole lungs removed** at time of harvest
- Lungs were **cultured x48hrs** in media with and without **10μM verteporfin**
- Tissue analysis**: qPCR** for gene expression, **immunohistochemistry** to localize nYAP and cYAP, and **whole mount** to visualize branching

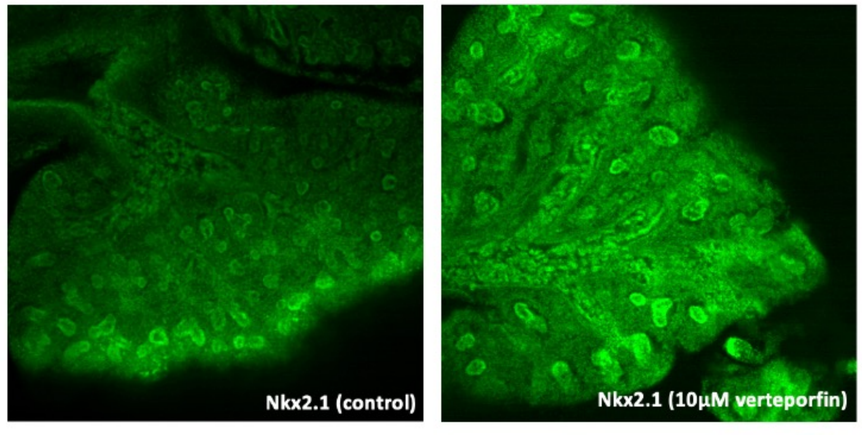


Results









Conclusion

This novel study suggests that nYAP inhibition during fetal lung development recapitulates many pathologic features of the CDH lung, including **reduced distal airway branching** and a **less mature pulmonary phenotype**. Modulation of the YAP/TAZ pathway may represent a possible novel molecular therapeutic target in fetuses with severe CDH.