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## **THE ARYL HYDROCARBON RECEPTOR (AHR) IS INVOLVED IN THE PATHOGENESIS OF CDH**

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### **Background:**

Environmental factors may contribute to 70% of congenital diaphragmatic hernia (CDH) cases. A specific class of environmental chemicals, similar to nitrofen, can activate the transcription factor aryl hydrocarbon receptor (AHR) to change gene expression.

### **Objective:**

Our objective is to determine how activated AHR can influence gene expression to contribute to the abnormal lung development seen in CDH. Therefore, we hypothesize that activation of AHR by nitrofen is involved in the pathogenesis of CDH.

### **Methods:**

Ethical approval was obtained prior to experiments (19-010 (AC11436)). We compared the response of AHR to nitrofen to known ligands - benzo[ $\alpha$ ]pyrene and resveratrol - in the BEAS-2B human epithelial cell line (n=3). AHR activity within a 24 hour exposure period was assessed with immunocytochemistry (ICC/IF). We compared the abundance of AHR in saccular lung sections (n=3) from human CDH patients (Week 39-40) and nitrofen-treated rat pups (E21) to age-matched controls using immunofluorescence (IF).

### **Results:**

AHR activation was induced in BEAS-2B cells within six hours of treatment. We saw all ligands induce of the translocation of AHR fluorescent signal from the cytoplasm (inactive) to nucleus (active), suggesting nitrofen activates AHR. After 24 hours of treatment, the AHR signal was strictly cytoplasmic and diminished. CDH patients and rat lung sections have increased AHR abundance in the mesenchyme and airways compared to controls.

### **Conclusion:**

We observed the activation of AHR using nitrofen, strengthening our argument that AHR is involved in the development of this disease. We saw similar changes in AHR abundance in both human CDH and nitrofen rat lungs; suggesting that similar pathological mechanisms are involved. This dysregulated expression of AHR may contribute to abnormal lung development in babies born with CDH. The results suggest that environmental chemicals structurally similar to nitrofen may activate AHR to induce CDH.