ABSTRACT SUBMISSION FORM

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Exploring the role of sex and gender on health research

CHRD
CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

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Title
THE ARYL HYDROCARBON RECEPTOR (AHR) IS INVOLVED IN THE PATHOGENESIS OF CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Background
Environmental factors may contribute to the abnormal lung and diaphragm development in 70% of congenital diaphragmatic hernia (CDH) cases. Certain environmental chemicals can activate the Aryl hydrocarbon receptor (AHR) to induce gene expression.

Objective
We hypothesize that activation of AHR by these chemicals is involved in the pathogenesis of CDH.

Methods
We used nitrofen to induce CDH in rodents and assessed the binding ability and response of nitrofen to AHR using induced-fit virtual docking and immunocytochemistry (ICC)(n=3). AHR mRNA abundance in nitrofen treated rats (E18, E21)(n=3); and human CDH lungs (Week 39-40)(n=3) were compared to age-matched controls using RNAScope. We used immunofluorescence (IF) to compare AHR protein in human CDH patients (Week 39-40)(n=3) and nitrofen treated lungs (E18, E21)(n=3) to age-matched controls. Ethical approval was obtained.

Results
Induced-fit virtual docking showed that nitrofen binds to AHR with a binding affinity of -8.4 kcal/mol which is very similar to that of the well-established AHR ligand TCDD (-8.6kcal/mol). We observed translocation of AHR from the cytoplasm (inactive) to the nucleus (active) in BEAS-2B cells through ICC within 6 hours; suggesting nitrofen activates AHR. AHR mRNA expression was greater in nitrofen lungs at E18 and control lungs at E21. In the human samples AHR mRNA appeared to be higher in control lungs. AHR protein abundance was greater in control lungs at E18 and in nitrofen lungs at E21. Human AHR protein was higher in CDH lungs at end point gestation.

Conclusion
Nitrofen binds and activates AHR. AHR is dynamic throughout development suggesting it may play contribute to the abnormal development seen in CDH. We see similar changes in AHR abundance in human CDH and nitrofen rat lungs; suggesting that similar pathological mechanisms are involved. Our results suggest that environmental chemicals structurally similar to nitrofen may activate AHR to induce abnormal lung development in CDH.

Theme:
Basic Science

Do you have a table/figure to upload?
Yes

Untitled
Figures for CHRD.pdf

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
Masters Student

What was your role in the project?
all of the above

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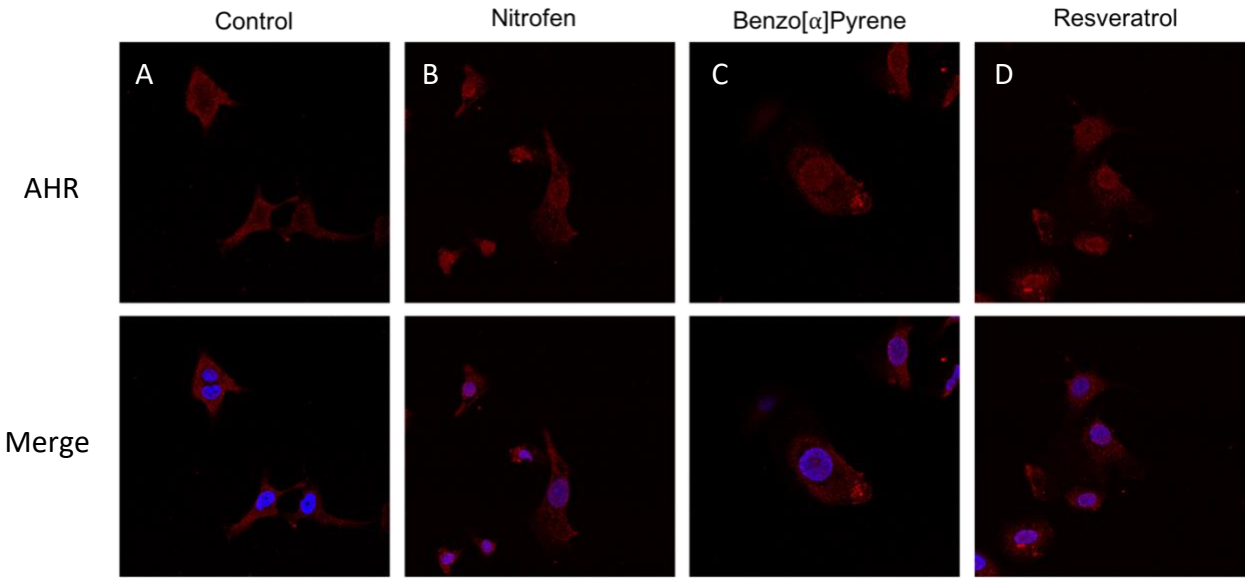

Figure 1. Immunocytochemistry shows nuclear translocation of AHR when treated with nitrofen. Cells were treated with normal media, 10uM nitrofen, BAP, or resveratrol. After 24 hours of incubation, nuclear translocation of the AHR signal was seen in the cells treated with nitrofen, BAP and resveratrol while it was not seen in the control cells, indicating that all three treatments induce nuclear translocation suggesting activation of AHR. (n=3).

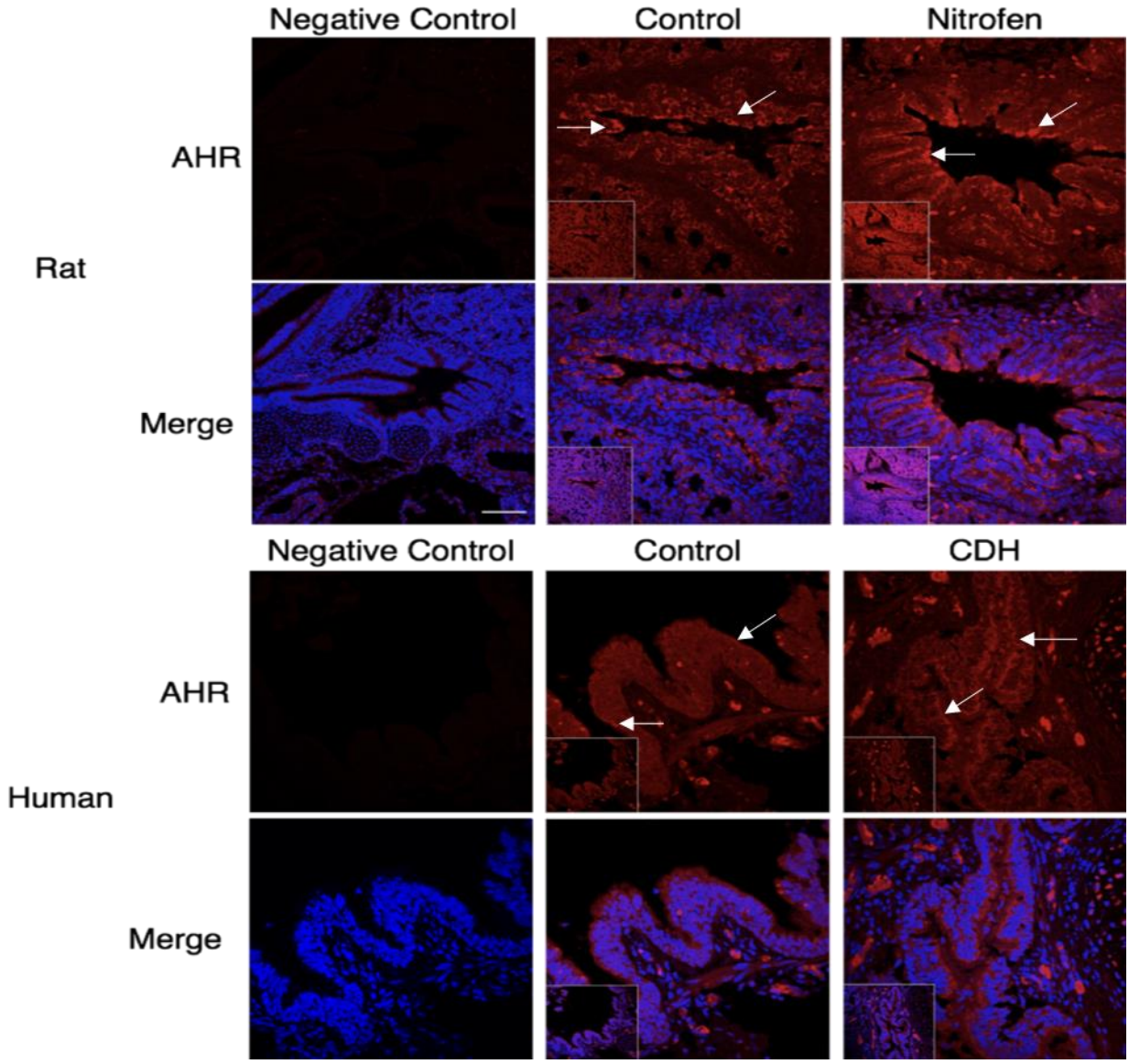

Figure 2. Increased AHR protein expression in rat nitrofen induced lung development at E21 and human CDH at 38 weeks. End point gestation immunofluorescence suggests an increase in AHR protein abundance in the airways of nitrofen induced rat lung development (E21)(n=3) and human CDH lungs (40 weeks) relative to control (n=3). Expression in both rat and human lungs appears to be cytoplasmic with the greatest difference in expression seen around the larger airways. Arrows indicate signal. Scale=100μm.