Benzene Metabolite, Hydroquinone, Activates the Aryl Hydrocarbon Receptor Pathway in Trophoblasts

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Benzene Metabolite, Hydroquinone, Activates the Aryl Hydrocarbon Receptor Pathway in Trophoblasts
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Introduction: Benzene is the 6th most produced chemical in the world and a major pollutant that has been shown to have adverse effects on pregnancy. We previously showed that maternal benzene exposure during pregnancy induces maternal immune activation and also leads to an increase in fetal reabsorptions. The molecular mechanism in which benzene induces these negative effects is poorly understood. Here we developed a cellular model of benzene exposure to understand the molecular effect of benzene on trophoblast cells. Specifically, cells were exposed hydroquinone, a major benzene metabolite, in order to determine the molecular mechanism behind the observed maternal immune activation during benzene exposure.

Method: Trophoblast cells (Sw.71) were exposed to 25μM of hydroquinone for 2, 4, 8, 16, 24 and 48 hours. Cells were collected at the time intervals specified above for RNA extraction and qPCR analysis.

Results: Our data has shown that: 1) hydroquinone treatment activates AhR pathway as CYP1A1 is significantly induced in trophoblast cells; 2) hydroquinone treatment leads to inflammation in the trophoblast cells, which is shown as the significant increase of IL-6 and IL1-β gene expression 24 hours after treatment; 3) hydroquinone treatment has a major impact on the ER stress that we reveal increased CHOP expression as early as 2 hours and in the later time points. Additionally, we see an initial increase in BIP. However, BIP is decreased at 24 hours of hydroquinone treatment. This expression pattern suggests that ER stress is being induced after hydroquinone treatment in a short time. 4) hydroquinone treatment induces interferon stimulated genes (ISGs) 24 hours after treatment, such as ISG20, Mx1.

Conclusion: Our findings indicate that exposure to the major benzene metabolite, hydroquinone, induces activation of the AhR pathway in trophoblast cells. Activation of this pathway is known to lead to inflammation and ER stress. These processes were observed here by increased levels of inflammatory cytokines (IL-6 and IL1-β) and transcription of genes associated with the unfolded protein response. Trophoblast cells exposed to hydroquinone also had higher levels of ISGs. The findings here suggest a potential molecular mechanism by which benzene and its metabolites exert detrimental effects on pregnancy.