Aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor, is a classic receptor of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). It is well established that perinatal exposure of TCDD increases fetal and neonatal mortality and decreases litter sizes, which in part could be via suppressing the placental vascular remodeling. However, AhR knockout in mice also leads to similar adverse phenotypes in the fetus and newborn as TCDD does, indicating a critical role of AhR in fetal and neonatal growth and development. We have reported the expression of AhR in human fetal tissues and in human placental endothelial cells. To examine the physiological roles of AhR in fetoplacental vasculature, we determined the effects of 2-(1’H-indole-3’-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE, a non-toxic, endogenous AhR ligand which is likely derived from tryptophan and cysteine via the condensation reaction) on placental endothelial proliferation and migration in vitro using human umbilical cord vein (HUVE) & artery (HUAE) cells as cell models. Methods: Cell proliferation and migration were assayed. Cell cycle progression was analyzed by flow cytometry. Western blotting was used to quantify changes in AhR levels. Real-Time PCR was used to determine mRNA expression of CYP1A1, CYP1B1, AhR, VEGFA, VEGFC, VEGFR1, VEGFR2, NP-1, FGFR1, and eNOS. Results: ITE at 1 μM and TCDD (serves as a control) at 10 nM inhibited (p < 0.05) HUAE and HUVE cell proliferation by ~ 30% on Day 6 without affecting the cell cycle progression. ITE and TCDD inhibited (p < 0.05) HUAE cell migration by ~ 40% and 30%, respectively, whereas did not affect HUVE cell migration. ITE and TCDD rapidly decreased (p < 0.05) AhR protein levels in HUVE (~ 80% by ITE at 2 hr and ~ 80% by TCDD at 8 hr) and HUAE (~90% by ITE and ~ 85% by TCDD at 8 hr) cells; ITE increased (p < 0.05) CYP1A1 and CYP1B1 mRNA in HUVE and HUVAE cells, indicating activations of AhR. Moreover, ITE and TCDD elevated (p < 0.05) VEGFA mRNA levels by 40% and 16% at 48hr in HUVE cells. ITE, but not TCDD, inhibited (p < 0.05) NP-1 mRNA levels by 14% and 16% at 24hr and 48hr in HUVE cells. Neither ITE nor TCDD altered the mRNA expression of VEGFC, VEGFR1, VEGFR2, FGFR1, and eNOS in HUVE and HUAE cells. Conclusions: These data indicate that ITE and TCDD inhibit HUVE & HUAE cell proliferation and while they suppress only HUAE, but not HUVE cell migration, implying differential angiogenic regulation of ITE and TCDD in HUVE and HUAE cells. Thus, upon activation by its endogenous ligands, AhR may suppress placental endothelial growth, preventing abnormal angiogenesis in placentas.
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**Other Presentations:**


Teaching and Mentorship:

09/2013-present: Sohum Mansukhani, undergraduate student in Department of Biology, UW-Madison. Mentorship in HUVEC & HUAEC primary cell culture, Western blotting, and data analysis.

11/2013-present: Lingpin Pang, MD, visiting scholar, mentorship in endothelial culture, immunohistochemistry, Western blotting, and data analysis.

06/2012-08/2012: Kevin Zhang, Dept. of Science and Technology, Academy for Advanced Technology Middle School, Chicago, IL, (Enrolled in Department of Biological Sciences, Dartmouth College, Hanover, NH). Mentorship in immunohistochemistry and Western blotting.

02/2011-02/2012: Pan San Chan, medical school student in UW-Madison. Mentorship in endothelial culture, Western blotting, and data analysis.

06/2010-08/2010 Roy Fang, high school student. Mentorship in endothelial culture.

ERP Service:

2011 ERP Service: ERP Symposium Committee Member.