The Soy and Spinach-Derived Phytoestrogen Coumestrol Impairs Trophoblast Cell Function and Causes Reduced Placental and Fetal Weights

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Introduction

Hypertensive pregnancy disorders including the devastating disease preeclampsia (PE) are a global problem in the world today, responsible for over 570,000 fetal and maternal deaths per year. Mothers diagnosed with hypertensive pregnancy disorders such as PE often experience hypertension and proteinuria, while the fetus often exhibits fetal growth restriction (FGR). Despite its severity, there is no cure, nor preventative therapy. Thus, there is an urgent need to identify novel pathways and therapeutic targets for PE. While diagnosed clinically after 20 weeks of pregnancy, PE has its developmental origins in the first trimester from failure of fetal-derived trophoblast cells to invade and remodel the maternal decidual tissue (figure below). Appropriate functioning of trophoblast cells includes aggressive invasion into the maternal tissue and remodeling of the maternal spiral arteries from contracted, low-volume vessels to high-capacity vessels, allowing for the efficient exchange of life-giving nutrients and gases for the fetus.

The trophoblast cells also recruit specialized immune cells, known as uterine natural killer (uNK) cells, which together promote remodeling by secreting cytokines, chemokines, and matrix metalloproteases. Abnormal trophoblast invasion results in the formation of a smaller placenta with constricted vessels, causing reduction of blood flow and nutrient delivery, ultimately leading to FGR and potentially the accumulation of reactive oxygen species (ROS). HTR8 immortalized trophoblast cells were subjected to invasion using a transwell membrane and migration via wound-healing assays described in schematic (A). Upon coumestrol administration (65μM), cell invasion was reduced (B-D). Coumestrol administration also caused slowed migration in a wound healing assay (E-I), which was determined by migration distance (J). Black lines represent mean with SEM.**p-value≤0.001

Coumestrol Impairs Trophoblast Cell Migration & Invasion

Coumestrol Administration Causes Reduced Embryo and Placental Weights at Day 12.5 of Pregnancy

Placental Compartment Ratios are Similar Between Coumestrol and Vehicle Treated Placentas

(A-B) DAPI, DBA-lectin, and PECAM staining of vehicle and coumestrol treated placentas. (C-D) Depicts example of highlighted placental regions used to perform ImageJ analysis. (D) Scatter plots depicting placental area percentages and lengths defined by compartment (decidua, chorion, labyrinth, juxta-placental zone). (E-G) uNK cell images from vehicle and coumestrol treated placentas with summary statistics. Black lines represent mean with SEM.

Conclusions

• HTR8 Trophoblast Cells Treated with Coumestrol
  - Decreased cell migration and invasion
  - Decreased mRNA levels of ROS inhibitors
  - Increased levels of ROS

• Coumestrol Exposed Wildtype Dams
  - Decreased placental and fetal weights
  - Reduced pregnancy plug rate
  - Reduced mRNA levels of ROS inhibitors, proliferation, angiogenesis
  - Similar placenta compartment organization and structure
  - Similar uNK cell count/density

References


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