Preeclampsia

- Hypertensive disorder unique to pregnancy
- Incidence: 6-8% of all pregnancies in the U.S
- Leading cause of maternal and neonatal morbidity and mortality
- Shallow implantation and reduced oxygenation of the placenta may lead to preeclampsia (Wang et al, Physiology, 2009)

![Diagram of normal and preeclampsia placenta with blood flow comparison]
Potential Roles of ERRγ in Pathogenesis of Hypertension

- ERRγ is an O$_2$-dependent transcription factor
- In studies of ERRγ knockout mice, ERRγ was found to regulate cardiac, gastric, and renal K$^+$ homeostasis via control of a number of hypertension-associated genes (Alaynick WA, et al, Mol Endocrinol, 2010).
- Placenta has the highest expression level of ERRγ among human reproductive tissues (Takeda et al., J. Biochem, 2009)
- ERRγ serves a critical role in the induction of aromatase (hCYP19) expression during human trophoblast differentiation (Kumar et al, Mol Endocrinol, 2011)
Objective

• **ERRγ regulation in human trophoblast**
  - Analyze the role of ERRγ in regulation of K⁺ channel genes and kallikrein in human placental cells in culture

• **ERRγ expression in preeclampsia**
  - Assess the expression of ERRγ in placentas from preeclamptic vs. normal pregnancies

• **ERRγ deficient pregnant mice**
  - Investigate the role of ERRγ in blood pressure regulation in ERRγ deficient pregnant mice
ERRγ mRNA & Protein Levels are Increased in Placentas from Preeclamptic vs. Control Women

**ERRγ mRNA Expression**

- Control: 1.0
- Preeclampsia: 2.5

*P = 0.0327

**ERRγ Protein Expression**

- Control: 0.5
- Preeclampsia: 1.5

*P = 0.0225
ERR_γ Expression & Activity are Related with Blood Pressure Regulation

**ERR_γ deficiency**
results in hypotension

**Increased ERR_γ activity**
causes hypertension in WT
Angiogenesis is Increased in Placentas of ERRγ Deficient vs WT Mice
VEGFR Signaling is Altered in Placentas of ERRγ Deficient vs WT Mice

**Placental VEGF mRNA**

- WT: n=8
- ERRγ Deficient: n=8

**Serum sFlt-1**

- WT: n=6
- ERRγ Deficient: n=6

*P=0.0028

*P=0.0087
Hyponatremia & Salt Wasting in ERRγ Deficient Pregnant Mice Result in Hypotension

**Total Urine Na⁺**

- WT
- ERRγ Deficient

**Blood Na⁺ (18.5 dpc)**

- WT: 140 ± 10
- ERRγ Deficient: 145 ± 10

**Systolic Blood Pressure**

- WT
- ERRγ Deficient

*P-values:*

- Total Urine Na⁺: *P=0.029*
- Blood Na⁺: *P=0.0112, *P=0.015, *P=0.025, *P=0.027, *P=0.028*
- Systolic Blood Pressure: *P=0.000*
Aldosterone Synthesis is Decreased in ERRγ Deficient vs. WT Pregnant Mice

**Serum Aldosterone**

- WT: 300 pg/ml
- ERRγ Deficient: 200 pg/ml

*P = 0.0289

**Cyp11b1 mRNA in Adrenal Glands**

- WT: 1.0
- ERRγ Deficient: 0.5

*P = 0.0382

**Cyp11b2 mRNA in Adrenal Glands**

- WT: 1.0
- ERRγ Deficient: 0.5

*P = 0.0169

**ChIP-qPCR for ERRγ Binding to Cyp11b2**

- Fold enrichment compared to IgG

- WT: 1.5
- ERRγ Deficient: 0.5

*P = 0.0419

**Cyp11b2**

- ERRE
- Exon 1

-242-AAGGTC-236
Summary

Preeclampsia

\[ \uparrow \text{ERR} \gamma \]

Maternal

- Cyp11b1, Cyp11b2 \( \uparrow \)
- Aldosterone \( \uparrow \)
- Serum \( \text{Na}^+ \) \( \uparrow \)
- Urine \( \text{Na}^+ \) \( \downarrow \)

Placental

- sFlt-1 \( \uparrow \)
- Vegf \( \downarrow \)

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Future Studies

• To investigate the role of ERRγ in placental angiogenesis by placenta-specific overexpression of ERRγ in transgenetic mice

• To analyze ERRγ expression in placentas of women with early vs late and mild vs severe preeclampsia
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