

ABSTRACT

MOLECULAR MECHANISMS INVOLVING PPAR γ IN THE PLACENTAL PATHOPHYSIOLOGY OF PREECLAMPSIA

By

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Preeclampsia (PE) is a hypertensive disorder of pregnancy that effects 5-7% of all pregnancies and is the main cause of maternal-fetal morbidity and mortality worldwide. Despite significant advancements in obstetric and neonatal care, the prevalence of PE has remained steady over the past thirty years. There is no cure for PE other than placental and fetal delivery. The exact etiology of the PE syndrome remains unclear however, maternal vascular malperfusion and placental ischemia are prominent features of the PE placenta that cause abnormal trophoblast differentiation and function. PE is considered a two-stage disease due to the ischemic-diseased placenta releasing altered secretion of placental proteins that negatively impact the maternal endothelium causing hypertension and end organ damage. The placental dysfunction is as well characterized by a reduction of the transcription factor, peroxisome proliferator activated receptor γ (PPAR γ) which normally promotes trophoblast differentiation and healthy placental function. This dissertation has aimed to understand the link between PPAR γ -driven trophoblast dysfunction and the imbalance of secreted proteins in PE. The restoration of these disrupted pathways by PPAR γ actions in the placenta could offer potential therapeutic pathways to reverse the disease, extend pregnancy duration, and dampen maternal sequelae. This dissertation has utilized a collection of first trimester and term healthy and preeclamptic placentas in addition to immortalized cell lines to understand the effect of PPAR γ activation by the drug, Rosiglitazone, during preeclamptic or in vitro

ischemic conditions. These studies revealed several molecules that are regulated by PPAR γ in the human placenta, including the anti-angiogenic soluble fms-like tyrosine kinase 1 (sFLT1) and the cytoprotective heme oxygenase (HO1). Both proteins were restored to normal levels in PE by treatment with the PPAR γ activating drug, Rosiglitazone. Furthermore, PPAR γ activation improved the anti-angiogenic environment in the PE placenta as shown by increasing the pro-angiogenic and growth factor proteins: placental growth factor, fibroblast growth factor 2, follistatin and heparin-binding epidermal growth factor. Placental activation of PPAR γ further restored the angiogenic balance in PE through significant reductions in the anti-angiogenic proteins, angiopoietin-2 and soluble endoglin. Using an endothelial cell model representing the maternal response to the placental protein secretion, these works revealed improved angiogenesis in endothelial cells during culture with conditioned medium from Rosiglitazone-treated PE placentas. These studies collectively show the beneficial effects of placental activation of PPAR γ to improve placental and vascular function in PE. Future works should aim to understand global changes from PPAR γ regulation in the human placenta and focus on compounds that hold promise to be safely used during pregnancy with the goal to improve pregnancy outcomes.