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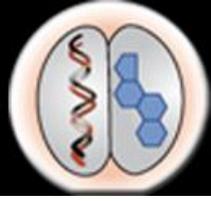
Degree Objective: Ph.D. Endocrinology and Reproductive Physiology

Background: BS Biology, University of Wisconsin-River Falls

Current Research Project:

Exploration of mechanisms associated with renal injury in preeclampsia using in vitro and in vivo models

Preeclampsia is a disorder of pregnancy causing serious maternal and perinatal morbidity and mortality. Hypertension and renal manifestations are the hallmarks of human preeclampsia. The renal manifestations are a potential pathway to understand the mechanism of preeclampsia. The renin-angiotensin system (RAS) has been well recognized to play a significant role in the pathogenesis of preeclampsia. Crossbreeding of hAGT and hREN transgenic mice carrying human genes has serendipitously identified development of preeclampsia/eclampsia-like syndrome in gravid hAGT ♀ crossbred with hREN ♂ with renin expression appearing in the placenta. We have re-established this model using departmental development funds. We have confirmed development of hypertension, proteinuria/proteinosis, placental necrosis, alterations in circulating sFlt1 and VEGF similar to human preeclampsia and development of glomerular endotheliosis in this model. This model, therefore, is very suitable to further investigate the specific mechanistic basis of renal injury in preeclampsia. Our data reveal a novel finding of increased VEGF binding, but not sFlt1 binding to the glomerular endothelial cells (GEnCs) in settings of glomerular endotheliosis. Since GEnCs do not produce VEGF, this finding suggests a role for VEGF and not sFlt1 in renal injury in this model. Increased VEGF immunostaining on GEnCs has also been described in human preeclampsia. In the kidney VEGF is produced by podocytes and glomerular endothelial cells express its cognate receptors. VEGF, sFlt1 and myriad of vascular dysfunction and hypoxemia associated mechanisms are known to increase VEGF receptor expression. VEGF is known, acting through VEGFR2, to disrupt glomerular endothelial adherens (AJ) and tight (TJ) junctions. Relevant representative molecules of AJs are VE-Cadherin and Alpha-Catenin and of TJs are ZO-1 and Connexin 43 (Cx43). Our model shows not just proteinuria but also increased excretion of VE-Cadherin in urine which is the evidence of glomerular endothelial barrier disruption in this model. Dr. Bird and colleagues have identified VEGF mediated Src activation mediated Cx43 gap junction disruption mediated endothelial dysfunction. Integrity of AJs and TJs is critical to maintain glomerular filtration barrier (GFB) function. Renal literature suggests role for VEGF, VEGFR2 and sFlt1 in the mechanism of renal injury disruptive of GFB function. Too much or too little VEGF causing disruption of GFB is known as VEGF paradox! We hypothesize that, in this model and in human preeclampsia, A) Increased VEGF binding to the GEnCs is due to change in the VEGFR2 (increased) expression and B) VEGFR2 mediated (Src) activation leads to disruption of GEnC adherens and tight junctions critical to the GFB function.



In this investigation we aim to to A) Demonstrate changes in VEGFR2 expression in PE vs control and compared to no change in VEGFR1 or sFlt1 expression via fluorescent imaging of mouse kidney sections and mouse glomerular endothelial cell (GEnC) cultures, and B) Demonstrate disruption of AJs and TJs by showing discontinuous co-immunostaining of VE-Cadherin, ZO-1, and Cx43. We have conducted all the animal experiments and have the necessary tissue samples to process as proposed in this investigation. We have procured high quality GEnCs, established our methods for *in vitro* experiments, and are in the process of data collection. We recognize that there are other potential factors involved in the mechanism of renal injury in this model and in human preeclampsia. The goal of this proposal is to establish the VEGF mediated biomolecular basis of the renal injury in this model. Our colleagues have recently discovered that CLA can rescue the Src activation and endothelial dysfunction. Therefore, in the future, we will propose to rescue glomerular injury in this model by treatment with CLA. Organic dairy products and beef are a rich source of CLA. There will be a need to establish safety of pharmacologic treatment using CLA before a clinical trial is conducted. There is a real potential for fast-tracking a specifically targeted treatment trial to reduce maternal and fetal morbidity and mortality in human preeclampsia.

Honors:

Science and Medicine Graduate Research Fellowship 2013-2016

Publications:

Degner, K., R. R. Magness, and D. M. Shah. "Establishment of the Human Uteroplacental Circulation: A Historical Perspective." *Reproductive Sciences* (2016). 12 Oct. 2016 [Epub ahead of print]

Posters and Presentations:

Science and Medicine Graduate Research Scholars Poster Symposium

Title: *A Potential Role for Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) in the Pathogenesis of Preeclampsia*

Wisconsin Institute for Discovery, September 2014

The UW Cardiovascular Center Annual Scientific Poster Fair

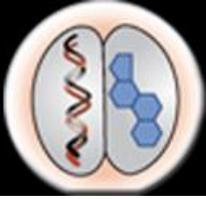
Title: *A Potential Role for Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) in the Pathogenesis of Preeclampsia*

Health Sciences Learning Center, December 2, 2014

Endocrinology and Reproductive Physiology Program Seminar

Title: *Exploration of Mechanisms of Renal Injury in a Mouse Model of Preeclampsia*

UW-Madison Biotechnology Center, March 19th, 2015



The Society for Reproductive Investigation Annual Conference 2015

Title: Expression of Vascular Endothelial Growth Factor Receptors in the Kidney of a Mouse Model of Preeclampsia

San Francisco, California March 26th 2015

The Society for Reproductive Investigation Annual Conference 2016

Title: A Potential Role for VEGF Signaling in the Development of Proteinuria in Preeclampsia

Montreal Canada, March 25th 2016

Teaching Experience:

BioHouse Learning Community Graduate Student Mentor 2014-2016

Science and Medicine Graduate Research Fellowship Outreach Committee 2014-2016

Grants and Awards

The University of Wisconsin-Graduate School Research and Development Award

Funding Support 2015-2016

National Institute of Health Training Grant (T32) Award

Funding Support 2016-2018