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ROLE OF SFLT-1 IN VASCULAR REGULATION IN PREGNANCY AND ITS EFFECT ON FETAL VASCULAR PROGRAMMING

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ROLE OF SFLT-1 IN VASCULAR REGULATION IN PREGNANCY AND ITS EFFECT ON FETAL VASCULAR PROGRAMMING

by

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Dedication

This dissertation is dedicated to the following people:

My parents, who have been taking care of my little girl and giving me endless love and support.

My husband, who has been sharing challenges and stress

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ROLE OF SFLT-1 IN VASCULAR REGULATION IN PREGNANCY AND ITS EFFECT ON FETAL VASCULAR PROGRAMMING

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Various angiogenic growth factors, such as the vascular endothelial growth factor (VEGF) and placental growth factors (PlGF), have been shown to play an important role in the vascular physiologic changes occurring during pregnancy; therefore inhibition of these factors by a circulating scavenger receptor, soluble VEGFR-1, also called sFlt-1, is believed to play a role in the pathogenesis of preeclampsia.

We created a mouse model of preeclampsia induced by administration of adenovirus carrying sFlt-1. We have shown that pregnant mice that over-express the sFlt-1 are hypertensive, deliver growth-restricted fetuses, have lower platelet counts compared with controls, and have other manifestations of a preeclampsia-like syndrome. In order to further investigate the underlying mechanisms in this validated mouse model, we evaluated maternal central and peripheral vascular function and found increased contraction in response to phenylephrine (PE) in both carotid arteries and uterine arteries, and impaired endothelium-dependent relaxation in uterine arteries of sFlt-1-treated group toward the end of gestation. In addition, pregnant mice over-expressing sFlt-1 displayed a

progression toward increased expression of HIF-1α and TGF β3 and decreased expression of GCM1 in the placenta, as well as increased expression of HIF-1α in the kidney, with a more pronounced difference at term.

In the last part, we demonstrated that only adult male offspring born to sFlt-1-treated pregnant mice were hypertensive, which confirms the role of the intrauterine environment in the developmental origins of adult disease, as well as a gender-dependent effect in fetal programming. Hence, this animal model provided an approach to study not only the pathogenesis of preeclampsia and but also fetal vascular programming.

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