ABSTRACTS

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Who let the dogs in: A canine trophoblast invasion model for pre-eclampsia

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Preeclampsia is a pregnancy-specific syndrome that affects 2-8% of pregnant women worldwide. It is the third leading cause of maternal mortality in the United States, accounting for 20% of maternal deaths, for which the only known cure is delivery of the placenta. Preeclampsia results from abnormal cytotrophoblast invasion of the endometrium and myometrium that morphologically is described as shallow. This superficial trophoblast invasion results in insufficient remodeling of the spiral arteries and hyperperfusion of the human placenta. Despite intensive investigation for more than 50 years, the causes of preeclampsia are largely unknown and the effectiveness of current models has been limited. An effective animal model is crucial to understanding the underlying causes of preeclampsia. It is easier and more ethical to obtain placental samples from early gestation in animals. Although preeclampsia can occur in higher apes, it does not occur spontaneously in most non-human primate models studied. Other animal models have struggled to be effective in the study of preeclampsia for a number of reasons. Rodents, such as mice and rats, have been commonly used to study the induction of clinical signs associated with preeclampsia (e.g. high blood pressure, proteinuria) through transgenic and knockout studies, but have proven to be less useful in studying shallow trophoblast invasion. To our knowledge, no existing model demonstrates the shallow trophoblast invasion observed in preeclampsia. A larger non-rodent animal model could be more easily manipulated to demonstrate changes in morphology, histochemistry, and gene expression throughout pregnancy.

Compared to other domestic animal models (e.g. sheep, pig) used to study human pregnancy-related disorders, the canine placenta is significantly more invasive therefore more like the human model. It is important to note that the morphologic and histologic similarities between normal canine trophoblast invasion and that of the preeclamptic trophoblast invasion are striking. In both types of placentation, cytotrophoblasts invade the endometrium (uterine epithelium) and the endometrial stroma (decidua) but do not completely invade the myometrium. Another feature of both forms of placentation is that transformation of the endometrium (decidualization) may play a role in regulation of trophoblast invasion. We believe that the canine model will be a useful improvement over the current efforts to investigate preeclampsia and other disorders of shallow trophoblast invasion. The long-range goal of our laboratory’s research is that with a canine model, new treatments (and possibly preventions) for the underlying cause of preeclampsia (e.g. shallow trophoblast invasion) can be developed. The central hypothesis to this approach is that canine trophoblasts display several cellular and molecular similarities to human preeclamptic trophoblasts. Our laboratory is currently working to identify time points during pregnancy when canine trophoblasts exhibit invasive properties. To do this, fresh placental tissue is collected from pregnant dogs, cytotrophoblasts are isolated and in vitro invasive properties are compared.

Canine pregnancy length is 65±1 days from the onset of the surge in luteinizing hormone (LH) and is not influenced by breed or litter size. Canine pregnancy can be divided into three stages: preimplantation (from day 0 to day 20), embryonic and placental development (day 20 to day 45), and fetal and placental maturation (day 45 to day 65). Our laboratory is comparing changes in trophoblast cellular behavior and gene expression at the beginning (48% of pregnancy; 31±1 days past the LH surge; n=8) and end (68% of pregnancy; 44±1 days past the LH surge; n=8), of trophoblast invasion in canine pregnancy as well as at two later time points, 88% of pregnancy (57±1 days past the LH surge; n=8) and at the end of pregnancy (65±1 days past the LH surge; n=8), which are important for comparison to published human studies where placentas are obtained at similar gestational ages. Most human studies of preeclampsia use placentas collected from the second and third trimester after delivery or C-section. Since matrix metalloproteinases (MMPs) are essential for the penetrative ability of human cytotrophoblasts in vitro and in vivo, the role of MMP2 and MMP9 in cultured canine trophoblasts and in culture media as well as from maternal serum concentrations throughout pregnancy are being investigated. In addition, MMP2 and MMP9 gene expression is being examined using RT-PCR at each of these time points during pregnancy from both whole placental tissues and isolated cytotrophoblasts.

We believe that investigation into these processes will advance scientific knowledge in the field of abnormal placentation with respect to trophoblast invasion and specifically relating to preeclampsia. Ultimately this line of research may lead to the discovery of new genes important in the regulation of trophoblast invasion and a novel therapeutic or preventive treatment. In addition, determining the gene involved with canine trophoblast invasion may identify causes of infertility relating to pregnancy loss and placental/trophoblast retention (e.g., subinvolution of placental sites).