O-6 Estrogen Regulates Vascular Permeability During Implantation Through the Kallikrein-Kinin System

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Background & Objectives: Implantation is initiated with the attachment of the blastocyst to the luminal epithelium of the receptive uterus. In the mouse, the first discernible sign of implantation is an increased vascular permeability at the site of blastocyst apposition. This incrased vascular permeability coincides with the attachment reaction between the blastocyst and the luminal epithelial cells of the uterus. Though it is critical in implantation, it is not clear how vascular permeability regulated at this time. To understand that, we did the molecular level studies.

Method: We employed a delayed implantation mouse model in which embryo attachment to uterus id dependent on estrogen administration to ovariectomized pregnant animals. Using DNA microarray rofiling, we identified genes and choosed one of the candidate genes, kallikren 5 (Klk5). Using several methodology, Northern blot, RIA, Immunohistochemistry, we conformed the expression patterns and the functions.

Results: We observed a high level of Klk 5 expression in the normal pregnant uterus at the time of implantation. Consistent with this observation, we found a significant level of mRNA encoding the lowm-olecular weight kininogen, a substrate of the kallikrein, during days 5 to 8 of pregnancy. In order to investigete further if E indeed regulates the generation of kinins, we monitored the level of bradykinin in the uterine fluids on day 4.5 of pregnancy before and after treatment with an antiestrogen ICI 182, 780. Our studies showed that the bradykinin level in the uterine fluid, which measured at 4427±85 pg/mg total protein on day 4.5 of gestation, declined by more than 50% upon administration of ICI 182,780. We also investigate the functional impact of blocking bradykinin action during implantation. Pregnant mice were treated with an agonist or antagonist for bradykinin receptros BR and B2R. Interestingly, our results showed that administration of an antagonist that blocked both B1R and B2R significantly reduced the number of blue bands in the vascular permeability assay compardto control animals that were treated either vehicle or an agonist of B1R and/or B2R.

Conclusions: Collectively, these results support the hypothesis that E induces vascular permeability during implantation through the kallikrein-kinin system.