MATERNAL LYMPHOCYTES AND ENDOMETRIAL ENDOTHELIUM ARE KEY REGULATORS OF THE ANGIOGENESIS THAT PROMOTES FETAL SURVIVAL

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INTRODUCTION: Spontaneous prenatal mortality is an unresolved issue that lacks strong animal models. Commercial meat pigs may be excellent models because they experience two waves of spontaneous fetal loss at early and mid pregnancy (term gestation is 114-days). Fetal demand in excess to placental blood supply is considered a contributing cause to failure of genetically normal porcine conceptuses. Early placental vascularization is mediated by vascular endothelial growth factor (VEGF) family members. We recently demonstrated that porcine peri-implantation endometrial lymphocytes (LY) are highly angiogenic and contribute to maintenance of successful pregnancy1. Here we report histological analyses of arresting and viable littermate implantation sites and extension of our molecular analyses to midgestation.

METHODS: Virgin gilts (young, first estrus females) or gilts at gestation days (gd) 20, 30 or 50 (n=4/group) were studied. Endometrial vessels were examined histologically using isolectin immunostaining for endothelial cells (EC), acid-orcein giemsa for elastin or Masson’s trichrome for collagen fibers. Gene expression was quantified in 500-laser capture microdissected LY and EC by real time PCR. Expression of VEGF, VEGF-receptor (R) 1, R2 and Placenta growth factor (PGF) was evaluated and compared with expression in whole endometrium, and, for pregnant animals, in fetal trophoblasts from the same implantation site.

RESULTS: Isolectin immunostained EC differed between healthy and arresting sites. In the latter, EC were discontinuous, irregular in shape and swollen. Arteries in arresting sites were narrower and had fragmented elastin and excessively deposited collagen fibers that might lead to the narrowing of arterial lumen. Both LY and EC expressed all VEGF family members studied but relative transcript numbers varied in abundance with gestational age and health status of the implantation site. LY and EC obtained from attachment sites of arresting fetuses expressed significantly fewer transcripts than LY and EC from sites containing healthy conceptuses. Dynamic changes in gene transcription also occurred in endometrial biopsies and in trophoblast as gestation progressed with significantly less angiogenic gene transcription in tissues from sites containing failing fetuses. Maternal cells (LY and EC) had significantly more transcripts for angiogenic factors than trophoblasts suggesting an important role for endometrial angiogenesis in determination of fetal outcome.
DISCUSSION:
These data indicate that expression of angiogenic factors is tightly coordinated between maternal and fetal environments and involves at least three cell types, LY, EC and trophoblast. Spontaneous fetal loss is associated with simultaneous deficits in maternal and fetal angiogenesis.

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REFERENCE: