

Cell Biology Symposium: The Immune System in Pregnancy

57 Tolerance of the maternal immune system to the fetal semi-allograft. M. G. Petroff*, S. M. Alam Khorshed, C. Linscheid, and S. Jasti, *Department of Anatomy and Cell Biology, University of Kansas Medical Center, Kansas City, KS.*

Pregnancy has often been likened to an allograft due to the genetic differences between the mother and her baby. Upon the discovery of the major histocompatibility complex antigens in the 1950s it was reasoned that in order for the mother to tolerate the fetus, the 2 must somehow prevent or suppress an immune response that could result because of their immunogenetic differences. Initial hypotheses of how the mother could tolerate the semiallogeneic fetus included maternal immune suppression, immunological immaturity of the fetus, and physical separation of the mother and fetus. The last 60 years of research have enlightened us greatly in the mechanisms by which this paradoxical situation flourishes; to varying degrees, all of Sir Peter Medawar's hypotheses regarding the fetal "allograft" are true. The trophoblast-derived placental trophoblast provides the physical interface between mother and baby, and although this tissue restricts expression of major histocompatibility complex molecules, there is no shortage of paternally-inherited minor histocompatibility antigens. These minor antigens, when mismatched between organ donor and recipient, cause chronic allograft rejection in transplantation; in pregnancy, minor antigens are expressed by the trophoblast, and are detected and robustly tolerated by the maternal immune system. We have hypothesized that paternally-inherited as well as placenta-specific antigens are detected by the maternal immune system as a result of trophoblast expression, and moreover, by virtue of shedding of copious amounts of trophoblast microvesicles and exosomes into the maternal blood. The detection of fetoplacental antigens by maternal CD4+ and CD8+ T lymphocytes occurs as a muted immune response that is controlled by placental factors co-expressed with the antigens. Despite this highly controlled lymphocyte response to the fetus, maternal memory T cells develop and can persist in women for decades. Although the physiological ramifications of these persistent T cells are not understood, they may include effects on long-term health of mothers. Supported by NIH R01HD045611 and P01HD049480.

Key Words: pregnancy, placenta, trophoblast

58 The immune system in CL formation/angiogenesis/lymphangiogenesis and its role in establishment of pregnancy. A. Miyamoto*¹, K. Shirasuna², S. Haneda¹, T. Shimizu¹, and M. Matsui¹, ¹*Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Japan,* ²*Jichi Medical University, Tochigi, Japan.*

The establishment of pregnancy needs a well-balanced regulation in endocrine and immune systems and involves interactions among conceptus, oviduct/uterus and CL. In particular, the optimal rate of increase in plasma P4 during the first 1 wk after ovulation is critical for the conceptus growth, leading to successful pregnancy in cattle. Events involved in maternal recognition of pregnancy (MRP) may commence before 1 wk after AI, as interferon-stimulated genes (ISGs) and IL10 mRNA expressions in circulating immune cells increase in pregnant cows. To regulate optimal endocrine condition in this narrow time window, CL should develop rapidly with active angiogenesis/lymphangiogenesis. Major angiogenic factors VEGF and FGF2 work in developing CL, but may also act as chemoattractant to PMN. Indeed, PMNs were observed at highest number in new CL with highest IL8 expression, and PMN secrete IL8 to induce active angiogenesis/lymphangiogenesis in CL. The findings led us to hypothesize functional

polarization of neutrophils (proinflammatory N1 vs. anti-inflammatory N2). It is interesting that on d 5 after AI circulating PMN exhibit upregulated expression of ISGs, and that PMN in CL are stimulating luteal angiogenesis, both of which are physiological prerequisites for occurrence of pregnancy. During later phase of MRP, the conceptus secretes a large amount of interferon-tau (IFNT), thereby preventing CL regression. Likely IFNT reaches CL and acts on acquisition of PG-resistance. New lymphangiogenesis stimulated by IFNT may occur at MRP without any new angiogenesis in cows. Taken into account that PGE2 is also upregulated in CL at MRP, some shifting of local immunity toward immune tolerance may occur in CL of early pregnancy. Interestingly, persistent CL (non-pregnant) and CL of early pregnancy showed similar mRNA expression, but differed in higher expression of Foxp3 mRNA in CL of pregnancy. Elucidating the immune system for earlier MRP together with local regulation of CL development utilizing immune system may help in understanding physiology and pathophysiology of early pregnancy in cows.

Key Words: corpus luteum, angiogenesis/lymphangiogenesis, early pregnancy

59 Effects of maternal obesity on placental and gut inflammation and immune function. M. Zhu*¹, H. Wang², M. Du³, and S. P. Ford², ¹*School of Food Science, Washington State University, Pullman,* ²*Department of Animal Science, University of Wyoming, Laramie,* ³*Department of Animal Science, Washington State University, Pullman.*

Obesity in pregnant women is a growing public health concern, which negatively affects fetal development and has long-term effects on offspring health. The placenta mediates nutrient transport to fetuses and is a source of inflammatory cytokines. Maternal obesity in sheep induces placental inflammation as indicated by enhanced expression of inflammatory cytokines including tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-8 and IL-18, and exaggerated c-Jun N-terminal kinase (JNK)/c-Jun and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) inflammatory signaling pathways. Accompanying placental inflammation, maternal obesity induces an inflammatory response in the late gestation fetal large intestine of sheep, manifested by elevated expression of TNF- α , IL-1 β , IL-6, IL-8, and monocyte/macrophage chemotactic protein-1 (MCP-1), as well as macrophage markers, CD11b, CD14, and CD68 in the fetal gut. In addition, we observed that inflammation persisted in offspring gut of obese mothers. Using non-obese diabetic (NOD) mice, we further demonstrated that offspring born to obese mothers had higher gut epithelial permeability, called "leaky gut," which is one of the main etiological factors for several common diseases including inflammatory bowel diseases, Type I diabetes and related autoimmune diseases. In agreement with increased gut permeability, we showed that maternal obesity resulted in an increased incidence of Type I diabetes, as evidenced by a severe lymphocyte infiltration and destruction of pancreas islets in the offspring of obese NOD mice. In summary, maternal obesity induces inflammation in the placenta and fetal gut, which has long-term effects on offspring gut immunity, likely pre-disposing offspring to inflammatory bowel diseases, type 1 diabetes and other autoimmune diseases. (Supported by NIH 7R15HD073864-02; USDA 2008-35203-19084; 2009-65203-05716).

Key Words: maternal obesity, offspring, placenta