Physiology and Endocrinology Symposium: Mediators of Effects of Stress on Reproduction, Growth, and Lactation

498 Consequences of leaky gut on the immune system, metabolism, physiology and animal performance. L. H. Baumgard1, S. K. Kvidera1, E. A. Horst1, M. J. Dickson1, E. J. Mayorga1, M. Al-Qaisi1, S. Lei1, J. A. Ydstie1, C. S. Shouse1, K. L. Bidne1, J. T. Seibert1, A. F. Keating1, J. W. Ross1, J. T. Selsby1, R. P. Rhoads2, 1Iowa State University, Ames, IA, 2Virginia Tech University, Blacksburg, VA.

Dairy cows are frequently immune challenged, and obvious infections include metritis and mastitis. An often-unrecognized source is compromised gastrointestinal tract (GIT) integrity; a consequence of stressors including dietary changes, hind-gut acidosis, systemic inflammation, heat stress, psychological stress, and feed restriction. Immunomodulation begins when immune cells recognize invading pathogens, eliciting inflammatory cytokine responses culminating in an acute phase response characterized by fever, leukocytosis, and hepatic acute phase protein synthesis. Paradoxically, endotoxemia (a catabolic condition) either causes insulin (a potent anabolic hormone) secretion or markedly enhances glucose stimulated insulin secretion. We recently demonstrated an in vivo lipopolysaccharide (LPS)-activated immune system consumes >1 kg of glucose within 12 h; a finding consistent with activated immune cells requiring glucose primarily for fuel and as a biosynthetic precursor. Despite increased glucose requirements, anorexia accompanies immunomodulation, which decreases diet-derived glucose precursors. Inflammation decreases milk synthesis and this presumably represents a strategy to spare glucose for the immune system. To further ensure an adequate fuel supply for the immune system, hepatic glucose output increases via both glycogenolysis and gluconeogenesis. Simultaneously, peripheral insulin resistance develops leading to decreased glucose uptake by skeletal muscle and adipose tissue. These metabolic adaptations are indicative of altered homeorhetic partitioning toward a new dominant physiological state of immunoactivation. GIT-derived endotoxin is also likely a key contributor to infertility as LPS and/or LPS-induced hyperinsulinemia markedly disrupts follicular, ovarian and uterine physiology. Additionally, gut-derived LPS also negatively affects the mammary epithelial barrier and causes hypocalcemia. Thus, leaky gut may be a common denominator that explains why transition cow disorders are strongly correlated with each other. It is becoming increasingly clear that GIT barrier dysfunction negatively affects many economically important dairy phenotypes.

Key Words: inflammation, leaky gut, glucose

499 Mechanisms linking metabolic stress with innate immunity and endometrial health. I. M. Sheldon*, Swansea University Medical School, Swansea, United Kingdom.

Bacteria infect the endometrium lining the uterus of cattle after parturition, and clearance of these microbes depends on robust host tissue defenses. Animals under metabolic stress are at increased risk of post-partum uterine disease, which often leads to infertility. One hypothesis is that metabolic stress impairs host tissue defenses. Innate immunity is a key component of endometrial defense against bacteria. Innate immunity is precipitated on host cell receptors that recognize pathogen-associated molecular patterns, and activated cells release inflammatory mediators. Cellular metabolism and innate immunity are highly integrated systems in tissues, and stressing one system might affect the other. Indeed, endometrial responses to the pathogen-associated molecular pattern, lipopolysaccharide, increases endometrial glucose consumption and induces aerobic glycolysis. Conversely, depriving endometrial tissues of their main energy substrates, glucose or glutamine, impairs their innate immune response to pathogen-associated molecular patterns. Furthermore, endometrial inflammatory responses to lipopolysaccharide are reduced by small molecules that modulate the intracellular sensor of energy, AMP-activated protein kinase. Metabolic stress also impacts lipid metabolism in cattle, and manipulating the mevalonate pathway, which precedes cholesterol synthesis, modulates inflammatory responses to pathogen-associated molecular patterns. However, other potential regulators of endometrial function, including mammalian target of rapamycin, insulin-like growth factor-1, and ovarian steroid hormones have limited impact on immunity. In conclusion, metabolic stress perturbs inflammatory responses to pathogen-associated molecular patterns in endometrial tissue, and fundamental regulators of cellular metabolism have the greatest impact on innate immunity.

Key Words: endometritis, metabolism, infertility

500 Physiology and pathophysiology of the microbiome and immune-related genes in development of the fetal brain. C. E. Wood*, M. B. Rabaglino, M. A. Zarate, and E. I. Chang, Department of Physiology and Functional Genomics, College of Medicine, University of Florida, Gainesville, FL.

Fetuses are commonly understood to develop in a sterile environment, and it is generally understood that bacterial invasion of the intrauterine environment predisposes the pregnancy to preterm birth. We have performed 2 studies that suggest that bacteria may play a role in the development of the fetus and preparation for birth and extrauterine life. To identify the major pattern of gene expression in the developing fetal sheep brain in the latter half of gestation, we used microarray technology to model gene expression in cerebral cortex, hypothalamus, hippocampus, and medullary brainstem at 80, 100, 120, 130, and 145 d gestation (term = 147 d) and 1 and 7 d postnatally. The differentially expressed genes (DEG) were analyzed using Supervised Weighted Gene Co-expression Network Analysis. The gene ontology analysis revealed that genes expressed by immune cells of the hematopoietic lineage (from the hematopoietic stem cells to more differentiated cells, for example macrophage, dendritic cells and T cells) are being transcribed at an increasing rate toward the last stage of gestation and transition to the extra-uterine life. We proposed that this gene expression pattern might be stimulated by the presence of bacteria in the fetal brain. qPCR experiments revealed an increasing abundance of bacterial 16S rRNA in the fetal brain in the latter half of gestation, approximating the rise in expression of the immune system within the brain. In other experiments, we discovered that maternal stress (ventilatory hypoxia) causes migration of bacteria into the fetal circulation and stimulates inflammatory pathways in fetal brain and other tissues. Bacterial populations appearing in fetal brain after maternal stress are relatively non-diverse: Staphylococcus simulans and other Staphylococcus species predominated. Together, our studies suggest that, in normal fetuses, there is a fetal microbiome. We propose that the presence of small numbers of bacteria may help direct fetal immune development and that the migration of bacteria into the fetus can be stimulated in conditions of maternal stress.

Key Words: fetal brain, microbiome
501 Effectors of immunometabolic adaptations to lactation: implications on physiology and performance. J. J. Loor*, F. Batis- tel, M. Vailati-Riboni, and Z. Zhou, University of Illinois, Urbana-Champaign, IL.

Immunometabolism represents the interface between immunology and metabolism, and is an emerging field of investigation in livestock biosciences. In human medicine, immunometabolism recognizes the link between obesity and the immune system, explicitly acknowledging that obesity-induced inflammation promotes onset of chronic disorders. More importantly, at the core of this concept is the recognition of “multilevel interactions between metabolic and immune systems,” implying “cross-talk” or “communication” among key cells and organs, which are orchestrated by unique mechanisms and their effectors. Such mechanisms correlate closely with health or disease status. The field of immunometabolism as it pertains to periparturient dairy cows is in its infancy. Classic studies before the 21st century defined the key metabolic, endocrine, and immune adaptations characterizing the transition into lactation. The advent of high-throughput technologies in the past decade further allowed the exploration of interrelationships among these systems. As a result of discoveries from that research, ongoing focus is on the bi-directional communication between immune and metabolic cells with signaling molecules derived intrinsically or as a result of intermediary metabolism or immune responses in tissues such as liver, adipose, and skeletal muscle. Both, macronutrients and micronutrients can be important effectors in the regulation of the immunometabolic response of the cow with effects often broad in nature. These responses are of great importance during the adaptation phase to lactation, as they seem to be key determinants of feed intake and milk production, reproduction, and health status. Management of total dietary energy supply and certain essential nutrients are examples of promising tools that can help regulate and enhance immunometabolic adaptations during the periparturient period and early lactation. A better understanding of the multilevel interactions among the various components of the metabolic and immune systems during the periparturient period has already led to identification of pathogenic mechanisms that underlie certain complications afflicting cows. Future research in this area should lead to promising therapeutic approaches.

Key Words: immunometabolism, nutrients, peripartum

502 Lipids as regulators of conceptus development: implications for nutritional regulation of reproduction. E. S. Ribeiro*, Department of Animal Biosciences, University of Guelph, Guelph, ON, Canada.

Pregnancy losses are substantial in dairy cattle and threaten reproductive efficiency. Approximately 60% of the fertilized oocytes are lost during development and fail to generate a live calf. Whereas early embryonic losses are more frequent, fetal mortality occurring later in development are more costly. The elongation phase of preimplantation conceptuses is critical in this context because 1) 39% of blastocysts fail to elongate and 2) events occurring during this period are important for subsequent maintenance of pregnancy. The onset of elongation is marked by dynamic changes in the transcriptome of trophectoderm cells. Peroxisome proliferator-activated receptor gamma (PPARG), a nuclear receptor activated by binding of fatty acids, coordinates a substantial portion of these changes. In addition to having its own transcript expression increased during elongation, PPARG also promotes transcript expression of genes related to uptake, oxidation, modification, and de novo biosynthesis of fatty acids and prostaglandins. Lipid droplets of epithelial cells in the endometrium seem to be the major source of lipids for conceptus utilization. Therefore, endometrial lipid profile is likely to regulate PPARG activity in conceptuses and the success of elongation. Formation of lipid droplets is induced by progesterone and its composition can be altered by diet and health status of the cow. About 40% of dairy cows develop inflammatory diseases postpartum, which impairs conceptus elongation and increases the likelihood of pregnancy loss. Uterine environment is a major contributor for this cause of subfertility because these outcomes are also observed following embryo transfer. Inflammation alters lipid composition of tissues because such molecules are used as inflammatory mediators. Thus, changes in composition of endometrial lipids might be involved in subfertility of cows developing postpartum inflammatory diseases. Targeting of uterine lipid metabolism and PPARG activity during preimplantation conceptus development through health postpartum and nutraceutical diets are good strategies to improve survival of pregnancy in dairy cows.

Key Words: conceptus, lipids, inflammation

503 Reduction in oocyte developmental competence by stress is associated with alterations in mitochondrial function. Z. Roth*, Department of Animal Sciences, Robert H. Smith Faculty of Agriculture, Food and Environment, the Hebrew University, Rehovot, Israel.

Stress can impact reproductive performance of lactating cows by targeting the ovarian pool of follicles and their enclosed oocyte. Among the documented stressors are heat, environmental and food toxins, metabolic stress and pathogens. Oocytes collected during the hot season are of lower quality than those collected in the winter, as expressed by reduced cleavage rate and lower blastocyst formation. A similar pattern has been reported for oocytes exposed to endocrine-disrupting chemicals or those collected from cows with mastitis or metritis. While the underlying mechanism might differ, accumulating evidence suggests that various stressors impair oocyte mitochondrial functioning. Within the oocyte, mitochondria are involved in ATP generation, calcium homeostasis, regulation of cytoplasmic redox, signal transduction and apoptosis. Summer heat stress is strongly associated with alterations in mitochondrial distribution, an increased proportion of highly polarized mitochondria, and impaired expression of mitochondrion-associated genes, in particular those encoding oxidative phosphorylation complexes for ATP production. Thus, it is proposed that stress reduces ATP levels below the required threshold, compromising the progression of oocyte maturation. Oxidative phosphorylation in mitochondria is the major source of reactive oxygen species (ROS). Under physiological conditions, ROS are essential for nuclear maturation; however, disequilibrium between ROS production and antioxidative capacity might lead to DNA damage and apoptosis, as documented for oocytes exposed to heat stress or environmental toxicants. The review provides new insights into the cellular and molecular responses of the oocyte to stress with an emphasis on the mitochondria. It discusses some strategies to mitigate the effects of stress on the mitochondria, such as incorporation of coenzyme Q10—a key component of the mitochondrial respiratory chain, administration of antioxidants and microinjection of healthy mitochondria. Exploring the oocyte’s cellular and molecular responses to a specific stress might enable the development of new strategies to mitigate its effects on fertility.

Key Words: stress, mitochondria, oocyte developmental competence