

0774 Utilizing 'omic' techniques to understand energy balance in the lactating dairy cow.

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Nutrigenomics describes how the amount and/or type of feed an animal receives, relative to its genetic and physiological requirements, affects its molecular phenotype, thus changing production, energy balance, reproduction, and health. For example, Holstein-Friesian cows (HF) bred almost exclusively for milk production have a more prolonged and severe negative energy balance in early lactation than HF cows bred on an index that includes traits related to longevity and health. This is due, in part, to a greater uncoupling of the somatotrophic axis and the level and duration of this uncoupling can be influenced by diet. In addition, the decline in reproductive success in recent decades has been associated with the increased negative energy balance associated with genetic selection for milk production. However, differences in the endometrial transcriptome indicate that genetic selection for milk production is also associated with a failure to recognize pregnancy as well as inadequate suppression of the local immune system and nourishment of the embryo, which are not necessarily related to energy balance. Nonetheless, some of the genes involved are epigenetically regulated and could be altered by nutrition. Factors that influence energy balance, such as nutrition and milking frequency, have different effects on the metabolism of the mammary gland, liver, and adipose tissue. For example, although once-daily milking and greater feeding levels improve energy balance, once-daily milking lowers milk production through reduced secretory cell activity and number, whereas, greater feeding levels increase milk production through the provision of more nutrients. These effects are independent and at least partially additive; if both strategies are used, the outcome is a combination of the two. Experimental results indicate that the molecular changes underpinning these effects can persist beyond the period of treatment. Less frequent milking results in an earlier recoupling of the somatotrophic axis post-partum and adipose accretion, physiological changes that are also influenced by energy balance, but are dependent on feed type as well as availability. A greater understanding of the effects of nutrition on the molecular phenotype is required to optimize cow management for productivity and welfare.

Key Words: nutrigenomics, energy balance, reproductive failure, genotype

0775 Systems biology of regulatory mechanisms of nutrient metabolism in lactation. J. P. McNamara*,
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The role of the dairy cow is to help provide high-quality protein and other nutrients for humans. We must select and manage cows with the goal of reaching the greatest possible efficiency for any given environment. We have increased efficiency tremendously over the years, yet the variation in productive and reproductive efficiency among animals is still quite large. In part this is because of a lack of full integration of genetic, nutritional, and reproductive biology both in research and management decisions. However, integration across these disciplines is increasing as biological research findings show more specific control points at which genetics, nutrition, and reproduction interact. An ordered systems biology approach that focuses on why and how cells regulate nutrient use and on how and why organs interact by endocrine and neurocrine mechanisms will speed improvements in efficiency. Nutrient metabolism is controlled by a number of factors, including type and amount of intake, stage of lactation, and amount of milk production, through a complex system of neurocrine and endocrine regulation. In turn, nutrient metabolism in the brain, liver, splanchnic organs, and muscle directly affect the efficiency of the animal. The metabolic efficiency of the mammary gland runs at its thermodynamic maximum unless there is a physiological disease or a massively imbalanced ration. The variation in efficiency of animals is a result of variations in metabolism in non-mammary tissues; including nutrient metabolism in the liver, protein turnover in the muscle, and lipid turnover in the adipose tissue. These metabolic paths are allotted to maintenance costs in practical application. Thus, using a systems biology modeling approach, we can design experiments specifically to integrate our knowledge on tissue metabolism, food intake, milk production and overall efficiency. Data from genomic studies, transcriptional arrays, endocrine and neural signals, tissue metabolism and animal level experiments can be integrated to clearly indicate which are the controlling factors. This approach can help focus our research to make faster and large advances in efficiency and show directly how this can be applied on the farms.

Key Words: systems biology, lactation, metabolism

0776 Insights provided by nutrigenomics into the effect of diet on metabolism and milk production.

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The impact of diet on metabolism and milk production has been well-appreciated by dairy nutritionist for many years. Nutrigenomics has provided tools and experimental approaches critical to identifying the functional mechanism of nutrients. First, nutrigenomics has led to the discovery of basic mechanisms using cell culture and rodent models that provide strong candidate

mechanisms for testing in the cow. Second, the application of nutrigenomics approaches in the cow has provided direct insight into novel mechanisms of the cow. The presentation will focus on the application of nutrigenomics to understanding diet-induced milk fat depression and dietary regulation of the circadian rhythm of the mammary gland. Milk fat depression is caused by specific intermediates of ruminal biohydrogenation of polyunsaturated fatty acids and is a clear example of nutritional regulation of metabolism. Advances in lipid analysis and chemistry allowed identification of the bioactive conjugated linoleic acid isomers, but nutrigenomic approaches were key to identification of mechanism. Specifically, microarray analysis identified candidate systems and transgenic approaches have allowed demonstration of the functional mechanism. Nutrient intake also entrains the daily rhythm of metabolism through regulation of a transcriptionally regulated biological clock. Although the exact nutrient is not clear, nutritional entrainment of the mammary gland clock has been demonstrated. Understanding the mechanisms of bioactive nutrients has allowed development of targeted nutritional strategies and has great future potential as an experimental approach.

Key Words: nutrigenomics, milk fat depression, gene expression

0777 Nutrigenomics in dairy cows. *M. Bionaz^{*1} and J. J. Loor², ¹Oregon State University, Corvallis, ²University of Illinois, Urbana.*

Nutrigenomics is defined as the study of the genome-wide influences of nutrition altering the expression and/or structure of an individual's genetic makeup. Nutrigenomics can be performed in a reductionist way, with the intent to dissect the nutritional effect on a limited part of the genome (e.g., expression of few genes) or using a systems biology approach, where a holistic view of the nutritional effect on the genome is studied. Nutrigenomics in dairy cows is a relatively new area of research. Among all nutritional factors able to affect cell biology by changing gene expression, dietary energy, fatty acids, and amino acids have the strongest potential. The level of dietary energy has a powerful and broad transcriptomics effect. This was evidenced by data generated in liver and adipose tissue, especially in peripartur dairy cows. Profound nutrigenomics effects of amino acids are emerging, particularly during the process of milk protein synthesis. The most powerful nutrigenomics dietary components are fatty acids, particularly long-chain fatty acids (LCFA). In relation to dairy production, the effect of trans10,cis12-conjugated linoleic acid on depressing milk fat synthesis via effects on few well-studied enzymes was among the first and likely the best-known nutrigenomics example tied to LCFA. The LCFA can affect expression of genes primarily because of their capacity to modulate activity of specific transcriptional factors. Among those the most sensitive to LCFA and best studied are the peroxisome proliferator-activated receptors (PPARs). Emerging data support a role of PPARs in ru-

minant physiology and metabolism, including the regulation of milk fat synthesis. In addition, at least in vitro, there is a strong agonistic effect of LCFA, particularly the saturated fatty acids, in activating PPARs in ruminants. The capacity of LCFA to modulate PPARs (and likely other transcriptional factors such as LXR) offers the possibility to fine-tune the biology of dairy animals, including milk synthesis. The emerging data on PPARs in ruminants allowed proposing a dynamic model where activation of PPARs in several major tissues at distinct physiological stages could improve the adaptation of dairy cows to lactation. We are at the frontier of the nutrigenomics era in ruminants and initial data strongly indicate that this scientific branch can play a critical role in future strategies to feed dairy cattle. Outputs from nutrigenomics research can help improve efficiency of high-producing dairy cows and modifying milk quality for an ever-growing number of consumers demanding "healthy" food.

Key Words: nutrigenomics, dairy cow, transcription factors

0778 Systems biology and the role of nutrition in coordinating adaptations to lactation. *J. J. Loor^{*1} and M. Bionaz², ¹University of Illinois, Urbana, ²Oregon State University, Corvallis.*

The advent of genome- and metabolome-enabled technologies (e.g., microarrays, RNA-sequencing) constituted a setback to the use of reductionism in livestock research. Those tools along with bioinformatics were essential for the advent of modern systems biology. Systems biology is a field of study widely-used in model organisms (e.g., rodents, yeast) to enhance understanding of the complex biological interactions occurring within cells and tissues at the gene, protein, and metabolite level. Application of systems biology concepts is ideal for the study of interactions between nutrition and physiological state with tissue and cell metabolism and function during key life stages of mammalian organisms, including the transition from pregnancy to lactation (i.e., the peripartur period). Within that framework, the use of a single time point to study NutriPhysioGenomics is reductive and insufficient to capture the dynamism of biological adaptations; therefore, implementation of time-course experiments must be undertaken. Modern bioinformatics tools complement the ever-increasing ability to generate large molecular and metabolite datasets. The Dynamic Impact Approach (DIA) was conceived to help interpret in a more biologically relevant manner the longitudinal physiological adaptations to lactation occurring simultaneously in several tissues such as liver, adipose, and mammary. This tool along with gene and transcriptional factor (TF) network analyses using software suites, such as the popular Ingenuity Pathway Analysis, are ideally suited for understanding high-throughput datasets. Results utilizing our own and publicly available datasets demonstrate that the DIA is robust for physiological systems analysis of complex transcriptome datasets within a tissue or among tissues. Simultaneous visualization of the complex inter-tissue adapta-

tions to physiological state and nutrition can be discerned. An example of this approach using liver, mammary, and adipose tissue during late-pregnancy and early lactation is presented. Furthermore, we present examples of new knowledge generated through the application of functional analyses and gene network tools on transcriptome and metabolome datasets encompassing nutritional management of dairy cattle, e.g., plane of dietary energy prepartum or the supplementation of amino acids or long-chain fatty acids. Overall, we demonstrate that the integrative approach across and within tissues provides a more holistic understanding of the complex dynamic physiological adaptations during lactation. The longitudinal analyses of functional and TF networks within adipose and liver in response to nutrition may prove useful for fine-tuning nutritional management of dairy cattle. An important goal during this process is to uncover key molecular players involved in the tissue's adaptations to physiological state or nutrition.

Key Words: bioinformatics, nutritional science, omics

0779 Nutrient partitioning during intramammary inflammation: A key to severity of mastitis and risk of subsequent disease? K. M. Moyes*, *Dep. of Animal and Avian Sciences, University of Maryland, College Park.*

In early lactation, susceptibility to disease is greatest, impacting cow health, productivity, and leading to economic losses. Mastitis is the most economically costly disease to the dairy industry and is most frequent at this time. Glucose and amino acids (especially glutamine) are the primary fuels used by leukocytes in other species and are essential substrates for optimal leukocyte function, but have not been elucidated in bovine leukocytes. Yet, because these substrates are in high demand to support milk synthesis in early lactation, their supply to leukocytes may be compromised. Production-related metabolic diseases during early lactation, such as ketosis and hepatic lipidosis, can also adversely affect health and productivity. Risk of subsequent disease for cows during mastitis is unknown. During an inflammatory response, increases in circulating non-esterified fatty acids and glucose during an IMI in dairy cows have been reported. Previous work indicates that hepatic expression of key genes associated with gluconeogenesis (e.g., PCK1 and G6PC), ketogenesis (e.g., HMGCS2) and fatty acid metabolism (e.g., SREBF1 and PPARA) are downregulated after intramammary infection (IMI). These results suggest a potential link between mastitis and the risk of subsequent metabolic disease for dairy cows during lactation. This presentation will discuss the complex relationships between metabolism and immune function, and how these immunometabolic interactions relate to susceptibility to mastitis and increase the risk of subsequent disease during early lactation. New strategies to prevent or control mastitis development and reduce the risk of subsequent disease during early lactation will also be discussed.

Key Words: cow, mastitis, metabolism

0780 Nutritional effects on immunology and inflammation in dairy cattle. E. Trevisi*, P. Grossi, and A. Minuti, *Università Cattolica del Sacro Cuore, Piacenza, Italy.*

Optimal health is of paramount importance for an acceptable life of farm animals, mainly during the pivotal phases of their life cycle, such as parturition and weaning. Nutrition is one of the most important players of the health status and can influence onset of clinical diseases or mild malaise (subclinical diseases). A large portion of the host resistance to infection involves the immune system and, mainly at the gastro-intestinal level, represents a crucial site of the body for the relationship among nutrients, microbes and host. Balanced diets guarantee that nutrient requirements are met and simultaneously can: 1) counteract the survival of infectious pathogens in the gastro-intestinal tract (as occurs with diets too high in fermentable carbohydrates), 2) prevent damage of the gut epithelium, 3) improve the host resistance to the pathogens, and 4) reduce tissue damage due to metabolic disorders associated with deficiencies (e.g., ketosis, liver lipidosis) and excesses (e.g., milk fever, obesity) of nutrients. A wide variety of nutritional compounds (e.g., macro and micronutrients, secondary metabolites of plants) are involved in aspects of immuno-regulation, but mechanisms are only partly known. The physiological conditions of the animals also play a relevant role in the regulatory effects of the nutrients on immune and metabolic systems. In dairy cows, the transition period represents the most vulnerable physiological life stage, in which the nutrition can influence the immune and inflammatory responses. The tremendous physiologic changes taking place during this period make the diagnosis of the nutritional-management causes challenging. Nevertheless, the immune-metabolic profiling appears as a valuable tool in the management of health of transition dairy cows, particularly for direct diagnosis of sub-clinical diseases (metabolic and infectious). Recently, growing evidence suggests that inflammation around calving is responsible for reduced performance and is associated with decreased production, efficiency and fertility. In particular, composite indices based on multiple variables associated with inflammation (e.g., Liver Functionality Index) are promising for use as an aid in the diagnosis and correction of management and nutritional problems on dairy farms. Nutritional improvements in the periparturient period not only reduce the frequency of inflammatory events, but also minimize their intensity and duration. In particular, some nutrients and compounds (e.g., omega-3 fatty acids, Conjugated Linoleic Acid, methionine, plant extracts) have demonstrated to improve the immune function and the inflammatory response around calving, underscoring a need for further studies of the interactions between nutrition, immunity and inflammatory response.

Key Words: nutrition, immunology, transition cow