IMMUNITY IN DAIRY CATTLE: WHAT'S A HEALTHY COW?

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The maintenance of health for a dairy cow requires the interaction of multiple physiological systems during dynamic shifts in tissue and organ function. Stable immune function during these shifts provides the animal the foundation for health and optimal performance. Health and immune function can be impacted by physiological strain induced from many factors including environment (heat), pathogen challenge and nutritional imbalance. The reaction in the animal is either induction or repression of immune function, both of which can cause inflammatory cascades that can compromise health and productivity. The dairy cow possesses several unique characteristics that make it an ideal livestock species for analysis of the regulation of immune function. Dairy cows have distinct developmental, management and production cycles that last weeks to months and biological samples can be collected repeatedly during these cycles. In addition, dairy cows are exposed to metabolic, environmental and nutritional challenges induced by calving, lactation and housing. Balance of these challenges to maintain health is key to productivity. Measurements that provide a real-time index of health or possibly a predictive index of health would be of great value for all levels of dairy production. The ability to strive for optimal dairy cow production and health requires a repeatable, nondirected analytical approach to identify pathways and markers of known importance in cow immune function as well as shifts in the relative abundance of these markers. This approach may provide an analytical definition of a "healthy cow". Progress is being made in this direction, but a thorough understanding of the inputs needed for the optimal productive and healthy cow is ongoing.

The maintenance of animal health was unlikely a major consideration when the domestication of cattle originated 8,000 to 10,000 years ago (Bollongino et al., 2012). However, the robust nature of aurochs and the ability of these animals to thrive in conditions that were not optimal for human survival was a major driver of domestication. The individuals participating in this key step in the development of modern agriculture initiated a sequence of events that has continued for thousands of years. This achievement demonstrates two important aspects of cattle. First, the plasticity of the animal to acclimate to various conditions. Second, the long-term interest of humans to develop value added products with specific characteristics.

SELECTION OF PRODUCTION TRAITS

The ability to facilitate the development of organisms for economically important traits through genetic selection is a hallmark of modern agriculture. The modern dairy industry has been shaped with the use of identification of desirable genetic traits and utilization of artificial insemination to facilitate selection and propagation of the traits. With production goals in mind, fewer than 10 of the 800 breeds of cattle are used today for large scale milk production. Even within this small group of dairy focused breeds, differences for traits important for the dairy industry have been used to advantage by breed associations for marketing or formulas for profitability. These differences may seem minor to outside observers but represent unique qualities that can shift profitability in relatively short timeframes (Liu et al., 2010). Similarly, the physical appearance of modern dairy cattle has changed little over the past several hundred years. The major changes that resulted in the high production of the modern dairy cow are therefore, largely internal and biological, based on how the physiological systems can tolerate the demands to accomplish maintenance and production through homeostatic regulation.

The shift to high dairy cow productivity is an excellent example how the merger of multiple technologies resulted in major progress in productivity (Akers, 2000). At the farm level, optimized cow housing and disease control, technology advances in milking equipment and computerization of record keeping and for accurate and precise ration formulization improve general management. Quantitative genetics and genomics are used for selection before cows complete their production lifespan, taking advantage of real-time collection of milking data from computerized farm systems for accelerated selection and data sharing (Powell and Norman, 2006; Windig et al., 2006). The use of reproductive technology for artificial insemination and embryo transfer for the rapid expansion of animals with desirable genetics has provided the means to support efficient expansion of herds selected for milk production. Further advancement of cow productivity is expected with continued use of new technology and knowledge (Chesnais et al., 2016). The challenge with emphasis on production, in this case milk, is to avoid negative consequences to other physiological mechanisms that are important for the animal to maintain homeostasis (Rauw et al., 1998).

As stated earlier, while physically similar, the production level of the modern dairy cow is unrecognizable today from even 50-100 years ago. The internal changes have been linked to improved feed efficiency and less energy going to physiological maintenance (VandeHaar et al., 2016). This is a remarkable change that suggests the question: what is lost? Unfavorable genetic correlations have been reported between milk production and reproductive function, metabolic disease during transition, mastitis, displaced abomasum, dystocia and mobility (Rauw et al., 1998; Oltenacu and Broom, 2010; Adamec et al., 2006). The most apparent aspect of these unfavorable side effects of selection for increased production is the negative economic impact for producers (Parker Gaddis et al., 2014). The link between increased milk performance and negative impact on other physiological systems is generally linked to impaired metabolic balance due to the increased need for energy for milk production following calving. Based on this concept, the ability to nutritionally manage and select cows to reduce negative energy balance to prevent increased disease may be possible (Gervais et al., 2017).

The clear and understandable decision is to select cows for milk production. There are consequences to this decision including possible increases in disease or limitations on physiological systems that will negatively impact cow health and ultimately profitability. A producer is faced with the question of how can we maintain productivity and cow health to maximize production? Can we select or balance the selection of traits that optimize production, feed efficiency and cow health so that profitability can still be achieved?

Measurement of milk production is straightforward. Although more complicated than milk production, feed efficiency is measurable and selection for these traits is an active area of research (Pryce et al., 2014; VandeHaar et al., 2016; Seabury et al., 2017). The measurement of cow health is another level of complexity beyond milk production and feed efficiency. When discussing cow health, the first question may be: what should be measured? Then other questions follow – when in the life or production cycle of a cow should health be measured? How frequently should health be measured? And, what does the measurement mean?

COW HEALTH ASSESSMENT

The establishment of dairy cow health starts when it is extremely difficult to collect a sample. Maternal fetal interactions *in utero* due to the environmental conditions and nutritional maintenance are known to impact calf health, development and production potential for the offspring as an adult (Guo et al., 2106; Batistel et al., 2017). Following birth, effective management of the nutrition and environment for calves is critical for development and growth for a productive lifespan (Bach, 2012; Langel et al., 2015). While these are interesting and worthwhile topics, the focus of this paper is to discuss how we can evaluate the health of adult cows.

A simple index for health measurement for humans include body mass index, biological age, waist measurement, blood pressure and heart rate. Unfortunately for cows, these measurements, although useful in general, do not provide enough information for the complex physiological challenges that a growing calf, heifer, dry and lactating cow are experiencing. However, many measurements that are a routine part of the daily management of cows such as feed intake, milk production and movement are a straightforward indication of health status and can be obtained from records (LeBlanc, 2010). These records and producer-generated health records may be an unrealized resource for genetic selection (Parker Gaddis et al., 2014). However, the accuracy and completeness of the records may be a limitation to this approach. The next level of analysis of health status is more invasive than routine observation or records review. This step is the beginning of moving from simple visual and record observation to a potential Schrodinger's Cat model of cow health status and evaluation (Kovac, 2016). More specifically, the cow is healthy until you open the cow box and begin measuring blood components or milk or other biological samples. At that point, the amount of information gained can be almost endless and using the information to gain knowledge becomes challenging.

There are, of course, many measurements that are helpful to evaluate cow health, especially during specific phases of the production cycle. Blood calcium is extremely useful for determining the likelihood of milk fever following calving (Leno et al, 2017). Blood non-esterified fatty acids (NEFA) and beta-hydroxybutyrate (BHB or BHBA) are useful and straightforward assays to determine if a cow is experiencing ketosis and thus increased likelihood for metabolic disease or undernutrition (LeBlanc, 2010; Agenäs et al., 2006). Similarly, the capacity of components of blood to carry oxygen, the blood cell content and amounts and type of proteins in the blood are indicative of a basic health status. The number of blood cells and the ratios of certain blood cells are used by veterinarians regularly to evaluate the overall health status of a cow. These measurements are valuable when extreme shifts occur and are used to determine treatments. These values also provide a foundation for comparison for research projects focused on manipulation of animal health to gain knowledge for potential treatments or preventative strategies. Now the question becomes are these measurements enough?

The most fundamental physiological activity is metabolism to maintain energy resources for tissue and organ function. The extreme metabolic demands of a cow during its life cycle are well known, but the energy needs at the post-calving interval and the connection of metabolic disease and immunosuppression do not require a great intellectual leap to understand why cows are susceptible to health issues. To understand how a cow stays healthy, the balance of production and health need to be understood through the connection of metabolism and immune system function. The immune system is a complex tissue, organ and cellular organization that requires coordination to prevent inappropriate activation. This coordination is primarily through the release of molecules such as cytokines that activate or suppress immune system function. The activation is key to prevent pathogen infection that can suppress health, but the cost can be significant through energy use, fever, inflammation and tissue damage. When considering the metabolic drain of immune activation during a health challenge, the physiological systems must make a resource allocation decision and tolerate the change. This resource allocation shift away from other systems to immune function is likely due to the immediate requirement for response to a health challenge. Indeed, circulating immune cells primarily rely upon glucose and fatty acids for energy (Wolowczuk et al., 2008). This demand has been investigated at both the animal level and the cell level.

ENERGY DEMANDS OF IMMUNE SYSTEM

The elevation of body temperature above the normal range, also known as fever, is an immune system regulated response to gain an advantage over an infectious agent. The physiological mechanism to induce a fever is primarily mediated by the hypothalamus that includes cells with receptors to detect pyrogens circulating in the blood. Pyrogens can be externally derived such as lipopolysaccharide (LPS) or internally produced molecules including interleukin (IL) 1 alpha and beta (IL-1 α and IL-1β) and tumor necrosis factor alpha (TNF-α) secreted by activated immune cells (Stefferl et al., 1996). The response is energetically demanding including increased skeletal muscle metabolism and peripheral vasoconstriction. Depending on the species, a fever requires a 7-15% increase in caloric energy production to increase the body temperature one degree Celsius (Elia, 1992; Demas et al., 1997). Extending the analysis to include all energetic demands of an experimentally induced infection, it has been determined in birds that infection will increase metabolism 7-29% above pre-infection measurements (Nilsson, 2003; Martin et al., 2003). These increases exert a significant strain on an animal operating at a baseline, but in the case of a lactating cow with the additional requirements of milk production and potential support of a fetus, the immunological and resulting energetic strain would be expected to have a long-term negative health impact. To specifically investigate the energetic impact of an activated immune system a technique was developed to estimate the use of glucose in lactating cows following artificially induced activation of the immune system (Kvidera et al., 2016). The researchers determined that the activated immune system in a lactating cow uses approximately 1kg of glucose (Kvidera et al., 2017). This significant glucose drain will result in a negative impact for production and health.

Detailed investigation of how specific cells of the immune system have increased energetic requirements upon activation adds more to the understanding of why so much energy is required during activation. Generating an effective immune response requires cellular activation of proliferation, generation and secretion of autocrine and paracrine factors and potentially active cell movement, all activities that require enhanced energy. Immune cells, circulating and those residing in tissues, are generally considered to maintain a low basal activity that is regulated by cytokines. While increased energy requirements are universal for activated immune cells, the functional needs of cells differ. For example, lymphocytes must present antigens, secrete immunoglobulins and cytokines, and proliferate (Sordillo, 2016; Hume et al., 1978). This energetic demand is mostly met through glucose while it must be emphasized the major checkpoint for limiting lymphocyte metabolism is the availability of trophic signals, not the availability of glucose (Buttgereit et al., 2000).

Components of the innate immune system include epithelial barriers, non-cellular factors such as complement, endothelial cells and immune cells including neutrophils, macrophages, dendritic cells and natural killer cells. Basal metabolism regulates epithelial cell barriers but upon exposure to pathogens, cells that comprise these regions will initiate interaction with resident immune cells requiring increased energy requirements. The gut epithelium may be important for local regulation of the gut immune system by maintaining the balance of nonpathogenic bacteria to prevent immune system activation. A rapid shift in gut epithelial signaling when the commensal bacteria equilibrium is disrupted may allow passage of pathogenic bacteria through the epithelia barrier to stimulate immune activation while commensal bacteria do not move past the epithelia surface (Wolowczuk et al., 2008). While glucose is the primary energy source for cytokine secretion and antigen presentation, these cells also require lipids for membrane turnover associated with phagocytosis. Likewise, upon activation neutrophils require lipids and energy for phagocytic activity. Despite high turnover and short lifespan, neutrophils are critical for an effective immune system response. Neutrophils are terminally differentiated and thus do not require energy for proliferation but they have few mitochondria and must rely on glucose for most energetic requirements following activation (Maianski et al., 2004). The synthesis of components of the reactive oxygen species (ROS) cascade and secretory activity associated with the release of neutrophil extracellular traps (NETs) are almost exclusively dependent of exogenous glycolysis (Rodriguez-Espinosa et al., 2015).

Based on the importance of glucose and fatty acids for immune cell function, variation in concentrations of these key metabolic molecules affects immune responsiveness. An imbalance of metabolism will disrupt the production of immune system regulatory factors. The connection with metabolic challenges faced by dairy cattle are therefore direct. The physiological and endocrine changes that occur during calving strain the bovine metabolic system. The periparturient period is characterized by negative energy balance and immunosuppression (Burton and Erskine, 2003; Aleri et al., 2016). Can indices of metabolic function be connected with immune system responsiveness? Measurement of NEFA and BHBA are common during the periparturient period to determine the metabolic strain on the animal. In addition, serum NEFA concentrations above the normal range have been linked to suppression of immune cell function (Ster et al., 2012). Thus, analysis of molecules that indicate metabolic status such as glucose, NEFA and BHBA in circulating blood can be useful for evaluation of metabolic status and potentially the activity of the immune system as an approach to gain information of overall cow health. Should metabolic stability of a cow be used a selection criteria of the ability of the cow to maintain a healthy immune system?

DEVELOPMENT OF HEALTH INDEX

The link between immune system function has been established in multiple species including research models and humans (Wolowczuk et al., 2008). However, this regulatory system may not be as closely linked in ruminants and especially a high producing dairy cow. The strong selection for production in dairy cows may generate a physiological system balanced for resistance and tolerance. Could the immune system of ruminants, with a unique digestive system compared to other mammals, be less dependent on extracellular glucose or fatty acids and therefore generate a limited picture of immune system health in dairy cows? Limitations associated with the measurement of only metabolites to evaluate metabolic health during the periparturient period have generated investigation into more complex analyses. Metabolic and immunological strain starts during the dry period and continues into early lactation so expansion of the list of metabolites to measure provides the opportunity to develop an index to not only describe animal health but perhaps predict cows that may be high risk to develop disease. In addition, this approach can provide a more advanced understanding of how organ systems are functioning.

Moyes and colleagues (2013) measured urea nitrogen, albumin, cholesterol, NEFA, glucose, and BHBA to create an index for physiological imbalance. This index was compared to calculated energy balance. It is noteworthy that the physiological imbalance index was more effective than other measurements to predict cows during the prepartum period that had a higher risk to develop disease. Physiological imbalance index and NEFA were better indicators of disease during the first week of lactation than other factors measured (Moyes et al., 2013). This approach suggests that predictors for disease risk can be developed, but the complexity of cow physiology during early lactation provides greater challenges. Trevisi and colleagues (Trevisi et al, 2012; Bertoni and Trevisi, 2013) developed a liver functionality index as a tool to characterize the extent of the inflammatory status and health as a predictor for a difficult or smooth transition from gestation to lactation. The index was developed by measuring albumin, cholesterol and bilirubin. Further studies have demonstrated that cows with greater indices of liver function produced more milk (Zhou et al., 2016). The examples suggest that analyzing multiple metabolites from serum and potentially focusing on specific organ systems, may provide a means to establish a health index for cows.

The connection of immune traits with production, fertility and health would represent a useful approach to combine physiological mechanisms with production. An interesting approach was used to determine if cow immune traits correlated with dairy cow health, reproduction and productivity based on characteristics of immune cells (Banos et al., 2012). Cows from a controlled research herd were sampled over a 10 month period and samples were used to determine if correlations between disease and immune system traits were present. Some interesting data were reported demonstrating that certain immune cells, such as CD335+ natural killer cells were positively correlated with the incidence of mastitis during the week of sampling. Other examples include higher ratios of CD4+:CD8+ cells associated with lower somatic cell counts and a higher percentage of T cells were associated with poorer conversion of feed to milk (Banos et al., 2012). These unique findings suggest that creative investigation can lead to interesting and potentially useful links between immune system traits and production traits. Similarly, a project using this research herd generated additional information regarding production traits and immune cell markers such as relationships between CD4+:CD8+ and live weight (Denholm et al., 2017). Interestingly, they also reported a negative correlation between percentage of eosinophils and milk yield, feed intake, dry matter intake and metabolizable energy intake (Denholm et al., 2017). These reports demonstrate that selection for a combination of immune cell traits and production traits may improve animal health and fitness.

Our current recognition of a healthy cow is based on intake, lactation, metabolic balance, reproductive efficiency and the ability to repeat the production cycle. The dynamic nature of dairy cow life cycle physiology requires a more comprehensive assessment of immune system and animal health due to the numerous challenge a dairy cow will encounter. The investigation of new approaches to measure immune system health and how it is controlled at the physiological and cellular level in dairy cows is an ongoing goal. The current direction is to measure multiple endpoints associated with immune function, metabolism, pyrogens, cell characteristics and organ function to develop indices of health. A single timepoint health index should only be a first step, multiple timepoint assessment and predictive indices need to be a long-term goal. Such a measurement may be useful as a predictor of future health and productivity. This goal may be the most beneficial to connect research with producers. Is “animal health” the first response a producer will state when asked what the primary goal of your operation? Embedded in the question and the goal are a list of factors that can and cannot be controlled. If a measurement or index can be provided, the response “animal health” may become more relevant and provide new directions for nutritional and managements strategies.

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