Featured Article

Immunometabolism in livestock: triggers and physiological role of transcription regulators, nutrients, and microbiota

Juan J. Loor[†,◉] and Ahmed A. Elolimy[‡]

[†]Department of Animal Sciences, Division of Nutritional Sciences, University of Illinois, Urbana, IL 61801, USA
[‡]Department of Animal Production, National Research Centre, Giza 12622, Egypt

Implications

- Alterations in immune and metabolic systems within tissues are important during physiological responses to environmental cues, including over or undernutrition. Some of these pathways are shared across tissues, especially those with key metabolic roles.
- Cellular transcription regulators act as sensors for signals that trigger changes in immunometabolic pathways during pregnancy, lactation, and postnatal growth.
- Physiological triggers of immunometabolism include fatty acids and reactive oxygen species generated within cells. Nutrients with the capacity to generate antioxidants, for example glutathione, help control immunometabolic reactions.
- Although not originally considered a component of immunometabolism, gut microbiota have emerged as important effectors of these pathways.

Key words: gene network, inflammation, microbiome, nutrigenomics, nutrition, ruminant

Introduction

The term "immunometabolism" has been formally used in human medicine since at least 2011 to explicitly recognize the link between obesity and the immune system (Mathis and Shoelson, 2011). It was described as an "emerging frontier" underscoring the interface between the historically distinct disciplines of immunology and metabolism, emphasizing how nutrient- and pathogen-sensing pathways are linked to metabolic

and inflammatory responses that characterize chronic metabolic diseases. Although recognition that inflammation is a key feature of obesity and type 2 diabetes (both characterized by insulin resistance) was known since the mid-1990s, the link between specific nutrients and "metabolic surplus" as causative factors of "metaflammation" (i.e., metabolically triggered inflammation) became evident in the early 2000s. Formalizing this concept was crucial for recognizing that the inflammatory state in metabolic diseases was different than the traditional, short-term adaptive response that is essential for tissue repair invoked by the body to deal with injuries. In livestock species, the availability of reagents to measure systemic concentrations of a number of immunometabolic markers (e.g., acute-phase proteins, cytokines) has allowed a better appreciation of the role and potential impact of these molecules on the physiological adaptation of the animal during growth or lactation. Using a variety of systemic immunometabolic markers, the first direct links between inflammation and insulin resistance in beef and dairy cattle were reported in the early 2000s (Kushibiki et al., 2001). This work was instrumental for the development of research ideas on the molecular regulation of immunometabolism in livestock (Loor, 2010).

Immunometabolism as a field of science rests on the idea that there are "multilevel interactions between the metabolic and immune systems," and that key cells and organs "crosstalk" or "communicate" among them (Mathis and Shoelson, 2011). A theoretical representation of the interface between metabolic and inflammatory pathways is depicted in Figure 1. As originally proposed based on data from humans and model organisms, stress signals originating from the periphery (e.g., long-chain fatty acids, inflammatory cytokines) or within cells (e.g., reactive oxygen species [ROS]) trigger signaling cascades that activate inflammation, cause endoplasmic reticulum (ER) stress (accumulation of misfolded proteins), and inhibit insulin signaling (insulin resistance develops). The central role of mitochondria in this scheme arises from its involvement in fatty acid oxidation, which not only generates ATP, but also a variety of ROS that in turn can activate inflammatory and ER stress cascades. The increase in non-esterified long-chain fatty acid availability at parturition or during stressful conditions is a biological trigger of ER stress, mitochondrial dysfunction, and
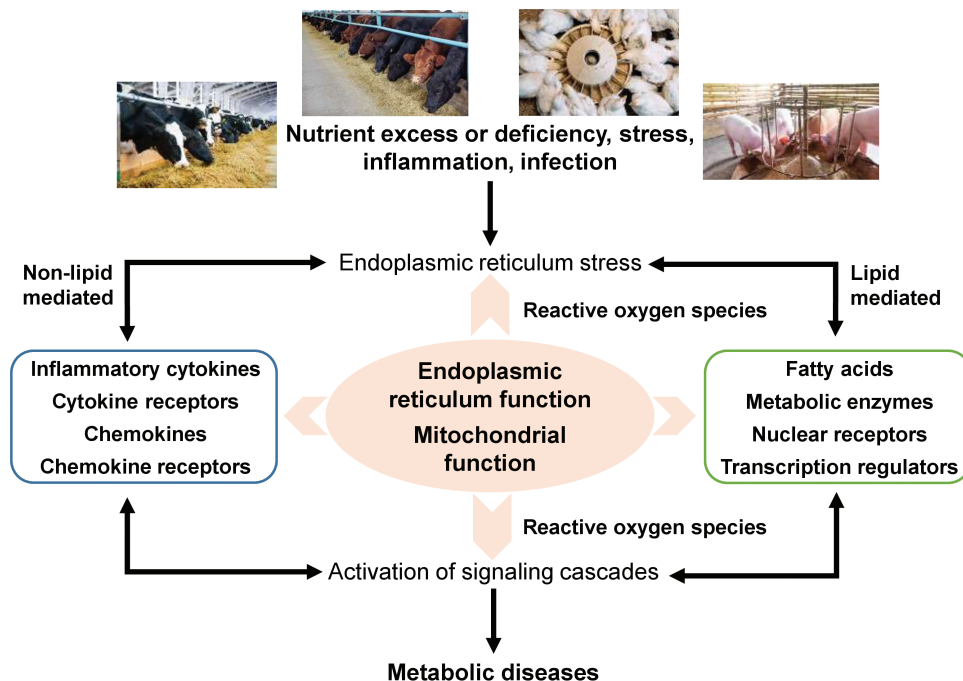
Figure 1. Theoretical model of the immunometabolic interactions in livestock tissues and their links to nutrition, stress, and disease. The original model arose from data generated in humans and model organisms (e.g., rodents), and centered on systemic (e.g., pro-inflammatory cytokines) and tissue-level signals (e.g., mitochondrial function, endoplasmic reticulum stress) that together integrate immunometabolic pathways at the interface of obesity and type 2 diabetes in organs such as adipose and liver. Subsequent research in livestock has confirmed the dynamic interplay among immunometabolic pathways during key stages in the life cycle of the animal (e.g., transition into lactation, fattening, postnatal period).

inflammation in tissues, such as the liver, mammary gland, and cells of the immune system. To counteract these effects, cells are capable of activating transcriptional adaptive mechanisms [e.g., antioxidant response via NFE2-like bZIP transcription factor 2 (NFE2L2 or NRF2)] some of which are responsive to micronutrient supply (e.g., vitamins, trace minerals, amino acids) (Coleman et al., 2021).

Although the focus of immunometabolic research originally revolved around the major metabolic organs (e.g., adipose and liver), the fact that the immune system in the gut represents 70% to 80% of total immune cells in the body (Plaizier et al., 2018) underscores its importance within this framework. In livestock, a healthy gut contributes to proper innate and adaptive immune responses (Plaizier et al., 2018). The establishment of microbiota along the gastrointestinal tract of livestock is influenced by factors, including nutritional status, antibiotic use, and stress; it differs from one gut bioregion to another, e.g., microbial diversity is high in the rumen while in non-ruminants such as swine and poultry, it is highest in the cecum and colon (Yeoman and White, 2014). An often overlooked aspect with regard to the gut microbiota is that during colonization, the commensal microbes produce thousands of biologically active metabolites that are used by the intestinal mucosa and resident immune cells (Taschuk and Griebel, 2012). Dysbiosis, disruption to the microbiota homeostasis caused by an imbalance in the microflora, such as it may occur when animals are fed suboptimal diets (e.g., excessive cereal grain relative to forage in ruminants) also can lead to production of bioactive compounds that can elicit immune responses locally and also peripherally upon entry into the circulation (Plaizier et al., 2018). Therefore, the potential for gut microbiota-derived bioactive compounds to participate in the immunometabolic response cannot be underestimated.

Since the publication of the original papers detailing the immunometabolic concept, there has been steady progress in dissecting tissue-specific networks and mechanisms controlling crosstalk between immune (including the gut) and metabolic systems in livestock (Plaizier et al., 2018). Although progress in this area of research in the context of livestock has been slower, independent groups working with dairy cattle or meat-producing animals recognized the likely links between metabolism and the immune system as key physiological components coordinating adaptations to lactation or growth. This short review focuses on data from livestock in which components of immunometabolism (molecular level), either at the cell or tissue level or from gut–microbe interactions, have been studied.

Immunometabolism in Livestock

Components of immunometabolic gene networks in livestock were first studied in a large-scale using microarray technology in the liver of dairy cows around parturition under normal conditions or during clinical ketosis (Loor, 2010). Prior to that time, it was well established that the transition from late pregnancy to lactation (i.e., the "transition period") encompasses complex interactions among immune, metabolic, and endocrine systems in key tissues (e.g., liver, mammary, adipose, skeletal muscle, immune cells) (Drackley et al., 2005). Although

the best-studied physiological adaptations (in terms of the biochemical pathways involved) during this physiological stage pertain to the liver, adipose, and mammary gland, different aspects of the bovine immune system also change and interact with metabolism. Although cows experience a period of subacute inflammation, a long period of excessive inflammation, in particular, is a dominant feature in several economically important disorders of dairy cows such as metritis and mastitis (Bertoni et al., 2009). In addition to undergoing a period of immune dysfunction, periparturient cows are faced with a tremendous augmentation in the production of ROS and pro-inflammatory cytokines, particularly after parturition (Bertoni et al., 2009). The precise cause driving changes in systemic markers of immunometabolism around parturition is still under debate and will not be discussed here. Rather, we summarize data pertaining to tissue-specific molecular networks in the animal, emphasizing the cellular pathways and specific targets that were proposed to be at the center of immunometabolic adaptations.

Immunometabolic Network Discovery

The application of molecular techniques and "bioinformatics" in livestock has been essential to generate data at the mRNA, protein, and metabolite levels in a large scale. One of the first applications of these combined approaches identified more than 25 transcription regulators (TR) among 4,790 affected genes in the liver of dairy cows fed to requirements, underfed, or overfed energy in the prepartum period (Loor, 2010; Shahzad et al., 2014). This experiment sought to understand in more depth the physiological mechanisms that respond to diets promoting an increase in body fat deposition (i.e., could lead to obesity), which in dairy cows often cause metabolic and immune diseases after calving, especially by affecting liver function in a negative way (Drackley et al., 2005). Pregnant sows overfed energy also gain body fat and undergo high rates of lipolysis at farrowing, both of which are associated with immunometabolic changes suggestive of stress (Che et al., 2019).

Using large-scale gene expression data, a number of immune-responsive TR with important roles in the immunometabolic adaptations of the liver around parturition were first uncovered through bioinformatics analysis in dairy cows (Figure 2). Among those was X-box-binding protein 1 (XBP1) whose transcription is enhanced upon accumulation of unfolded proteins in the ER (Loor, 2010), and was identified as a key hub in the integration of stress and inflammatory responses with insulin action. Additional molecular targets identified included pro-inflammatory TR (e.g., NFKB, STAT) along with a number of target genes encoding interleukins and chemokines. Subsequent research using similar tools revealed alterations in these immunometabolic networks in subcutaneous and visceral adipose depots from periparturient cows and fattening cows (Moisa et al., 2017; Minuti et al., 2020). These networks were expanded to include molecular pathways that are activated by the production of ROS in the ER and mitochondria, e.g., the antioxidant TR NFE2L2 (or NRF2). Although there is overlap across major organs in terms of the immunometabolic networks (Hotamisligil, 2006), their relevance from a physiological standpoint must be considered carefully as, for example, the liver in a species like the mature ruminant (Smith et al.,
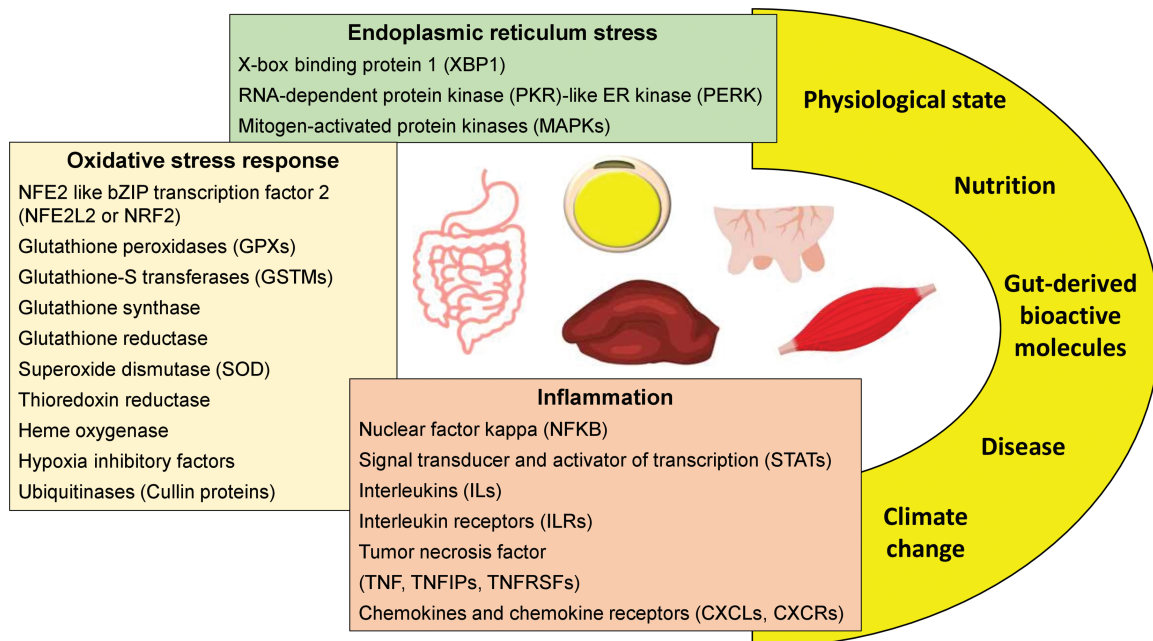

Figure 2. Summary of immunometabolic pathways that have been uncovered experimentally in key organs such as the mammary gland, liver, adipose tissue, muscle, and the gastrointestinal tract. Although inflammation, endoplasmic reticulum stress, and oxidative stress networks expand beyond these pathways, experimental data from non-ruminants and ruminants underscore their importance in the overall control of immunometabolic responses as a function of nutritional management, environmental stress, and during normal growth and development.

1986) is not an insulin-sensitive tissue as it is in swine (Dunshea, 1993) (especially at early stages of lactation). Advances in high-throughput gene expression and more powerful bioinformatics analysis have recently confirmed that immunometabolic networks play an important role in animal growth, with TR, such as XBP1, NFKB, and NFE2L2 in skeletal muscle contributing to feed efficiency phenotypes (de Lima et al., 2020). Therefore, greater emphasis on the potential manipulation of these networks during pregnancy, lactation, and/or growth could, in the medium-to-long term, optimize management at the farm level, e.g., through implementation of nutritional strategies. Examples of such approaches have been recently discussed in a review of the literature focused on the functional outcomes of dietary taurine, L-theanine, L-citrulline, and betaine, including immunometabolic responses, in poultry during heat stress (Uyanga et al., 2022).

The ER and Its Physiological Role in Metabolic Organs

The involvement of the ER on fundamental aspects of tissue function in livestock was highlighted by classical studies of the mammary gland in the 1970s and 1980s (Cant et al., 2018). While early studies cemented the role of ER in protein assembly and secretion into milk, research in the last 10–15 yr using molecular techniques in vivo and in vitro have defined the key components and mechanisms regulating its function under normal (e.g., established lactation) and stressful conditions (e.g., transition into lactation, ketosis, heat stress) in key tissues such as the mammary gland and liver (Invernizzi et al., 2012; Zhang et al., 2020). Although the protein XBP1 was originally identified as the key driver of the ER stress response (i.e., unfolded protein response), the protein inositol-requiring enzyme 1α (IRE1α; a kinase and endoribonuclease) is essential for its activation, i.e., the formation of spliced XBP1 mRNA and subsequent translation (XBP1s) (Fang et al., 2022). Besides IRE1α and XBP1s, the other ER-resident stress sensors include PKR-like ER kinase (PERK) and activating transcription factor-6 (ATF6); however, not all these branches respond to metabolic stressors such as long-chain fatty acids, at least in the bovine liver (Zhang et al., 2020).

Impairment of ER function in ruminants due to metabolic stressors, such as long-chain fatty acids and ketone bodies (e.g., hydroxybutyrate) is driven partly by increases in intracellular Ca^{2+} signaling that together lead to mitochondrial dysfunction, excessive ROS production, and inflammation (Zhang et al., 2020). Under those conditions, insulin sensitivity is dramatically reduced (Fang et al., 2022) and, as a whole, these events confirm the original observations in model organisms linking ER stress and immunometabolism (Mathis and Shoelson, 2011). An ancillary process recently recognized as central for the control of ER stress and its cascade of negative events in cells is autophagy, i.e., the transport of cellular components to the lysosome for degradation (Tesseraud et al., 2021). Metabolic stressors such as fatty acids, similar to their effect on ER function, inhibit autophagy and lead to inflammation and oxidative stress in tissues, with the activity of NFE2L2 being central for enhancing autophagy and reducing these negative effects (Shen et al., 2021; Chang et al., 2022). From a practical standpoint, the beneficial effects of nutrients with anti-oxidant potential (e.g., certain amino acids, plant polyphenols) (Rochfort et al., 2008; Coleman et al., 2020) on ER function in metabolic tissues supports the role of diet as an important tool for regulating immunometabolic responses.

Environmental Regulation of Immunometabolic Networks

Recent examples of how the environment alters immunometabolic networks in livestock include amino acid and energy nutrition of the pregnant cow. Emphasizing the role of nutrition during pregnancy on immunometabolic responses in the offspring is important because of the well-known effect that maternal nutritional status has on conceptus development, embryonic survival, growth, and development (Caton et al., 2020). Furthermore, although genetic variation is an important determinant of feed efficiency, growing interest in optimizing this trait in livestock dictates that approaches besides genetic selection be considered. Available reviews of the literature provide evidence that nutritional factors (e.g., specific nutrients, dietary energy level) and environmental exposure to heat during pregnancy alter immunometabolic programs in offspring tissues (Caton et al., 2020; Ouellet et al., 2020). Therefore, we propose that management programs for the pregnant animal, either early or at late gestation, consider the potential effects of nutrition not only in terms of the cow but also in terms of the developing offspring.

In the first experiment of its kind with lactating dairy cows, it was demonstrated that enhancing post-ruminal supply of the essential amino acid methionine (via rumen-protected supplementation) from parturition until embryo flushing around 70-d postpartum caused marked changes in gene expression without altering phenotypic characteristics of the embryo (Penagaricano et al., 2013) (summarized in Figure 3). Using changes in gene expression from this dataset (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE48147) to determine the degree of alteration in biological pathways, it can be gleaned that a large number of immune-related pathways (especially inflammatory) were downregulated (e.g., chemokines, NFKB, tumor necrosis factor) in the embryos exposed to methionine (Figure 3). This result agrees with the authors' conclusion based on individual genes and gene enrichment analysis (Penagaricano et al., 2013). It is noteworthy that both analyses suggest that the balance between immune and metabolic pathways in the early-developing embryo favors the metabolism of nutrients such as amino acids.

It is unknown if immunometabolic changes early in development translate into unique physiological outcomes in the live animal. However, work with sheep receiving a diet with marginal levels of methyl donors in the periconceptional period demonstrated marked alterations in DNA methylation (i.e., an epigenetic mark) in the fetal liver along with
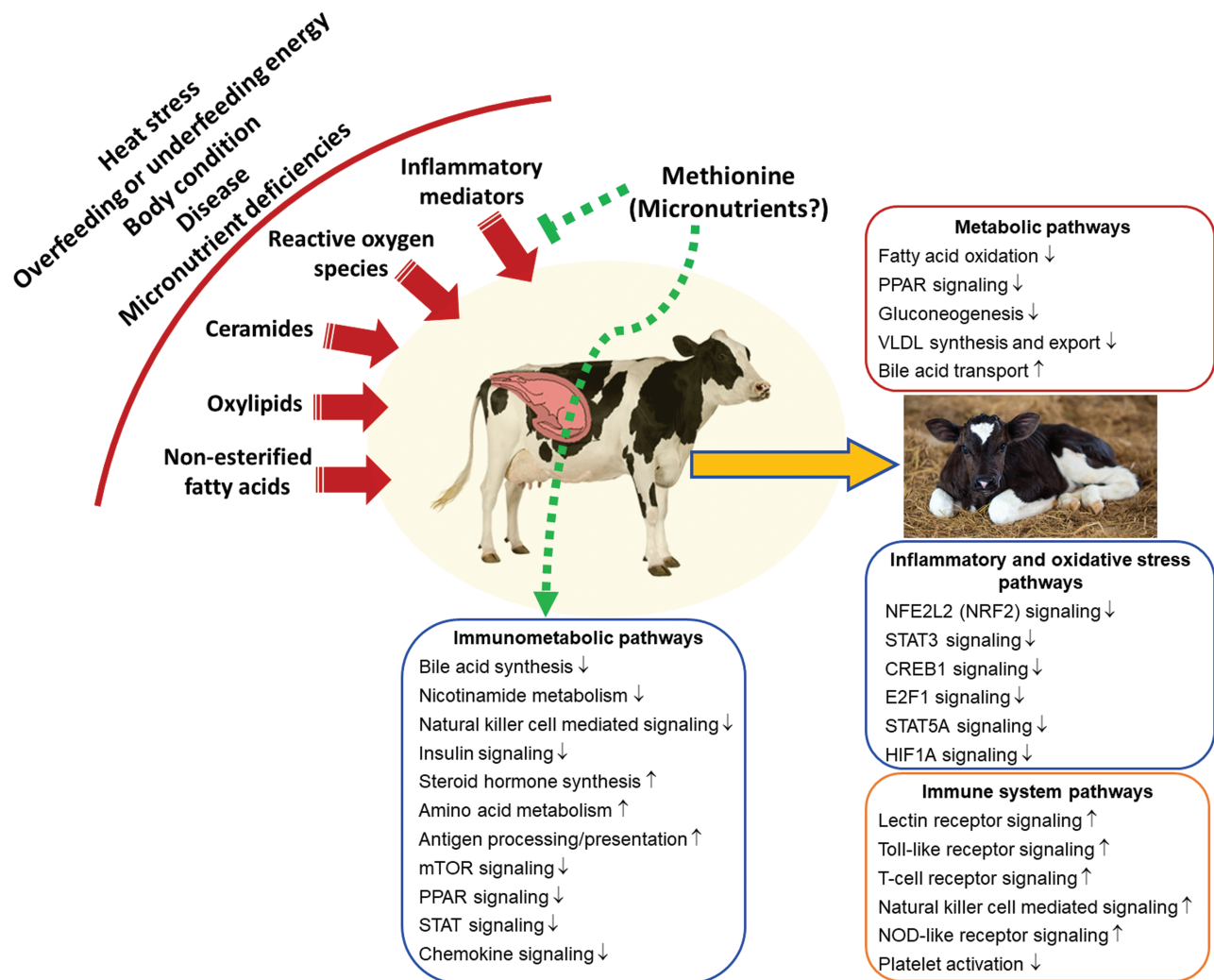
Figure 3. Summary of the major environmental cues and the likely mediators of immunometabolic responses in tissues of the pregnant animal. This model is based on available data for dairy cows, emphasizing molecular and physiological responses demonstrating how post-ruminal supply of methionine in late pregnancy or during early lactation prior to embryo implantation has led to alterations of immunometabolic pathways in the cow (e.g., liver), whole embryo, and neonatal calf (liver). Although emphasis is placed on methionine, experiments with sheep have demonstrated that a lack of other micronutrients (e.g., vitamin B$_{12}$ and folic acid) during the periconceptional period alters immunometabolic responses in the offspring during adulthood. Some of the available research indicates that immunometabolic adaptations in the liver of the young calf exposed to a greater supply of methionine in utero are associated with better performance during the pre-wean and early post-wean periods. Longer-term effects have not, to the best of our knowledge, been assessed.

altered innate immune and glucose-insulin responses of the offspring at 22 mo of age (Sinclair et al., 2007). In a recent study, it was demonstrated that enhanced post-ruminal supply of methionine in late-pregnant dairy cows not only led to greater calf birth weight (Alharthi et al., 2018), but also marked alterations in immunometabolic networks in the calf liver including downregulation of inflammatory and antioxidant signaling pathways along with fatty acid oxidation and gluconeogenesis (Palombo et al., 2021) (Figure 3). It was noteworthy, however, that these calves had an overall upregulation of immune system pathways, which together suggested a more mature capacity to respond to immune challenges (Palombo et al., 2021).

Although some of these responses might appear counterintuitive from a postnatal development standpoint, the calves from cows exposed to a greater supply of methionine had greater rates of growth through the post-weaning period (Alharthi et al., 2018) despite consuming the same amount of milk replacer and starter as the control calves (Elolimy et al., 2019). Whether pathways beyond immunometabolism contributed to these postnatal differences in performance is unknown. However, methionine calves were born with a unique hindgut microbiota profile that persisted through the post-weaning period (Elolimy et al., 2019) along with better innate immune responsiveness (Alharthi et al., 2019). The fact that enhancing maternal methionine supply (via hydroxy analog) during the last ~60 d through ~17 d around parturition had minor effects on immunometabolic networks in beef calf skeletal muscle after vaccination at ~150 d of age (Palmer et al., 2021) suggest that muscle tissue might not be as responsive as the liver. The type of dietary source of methionine (rumen-protected vs. hydroxyl analog) also could play a role, i.e.,

methionine hydroxyl analog is more susceptible to ruminal degradation.

Gut Microbiota and Immunometabolism

The role of commensal gut microbiota on the regulation of the immune system in the neonate and adult animal is an active area of research (Amin and Seifert, 2021) (Table 1). Earlier studies revealed that the absence of gut microbiota in neonatal lambs resulted in premature growth of ileal lymphoid follicles (i.e., Peyer's patches) (Reynolds and Morris, 1984). Furthermore, the absence of gut microbiota in germ-free piglets suppressed immune system development, eventually delaying the antibody response (Trebichavský et al., 1998). Subsequent research identified Toll-like receptors (TLR) as the first line of innate immunity in the gut that protects the body from inflammatory responses (Malmuthuge et al., 2012). Activation of the TLR pathway in the gut of the neonatal animal occurs through the activity of mucosa-attached bacteria (Malmuthuge et al., 2012). Organisms such as *Bifidobacterium* or *Lactobacillus* can alter lymphoid tissue development, dendritic cell maturation, and immune cell development in young animals through their effects on certain microRNAs (miRNA), i.e., small single-stranded non-coding RNA molecules (Liang et al., 2014). Therefore, the gut microbiota play unique roles in facilitating the development of the immune system and the immune response in young animals.

Several studies highlighted that altering microbial composition and microbiota-derived metabolites in the gut contributes to changes in immune function. For instance, Hromádková et al. (2020) reported that an extended colostrum feeding program in neonatal calves resulted in greater abundance of mucosa-associated bacteria (*Lactobacillus* and *Escherichia coli*) and upregulated serotonin and adrenergic receptors genes in the intestine all of which enhanced intestinal growth, induced mesenteric blood flow, improved nutrient absorption, decreased gut permeability, and reduced apoptosis (Connor et al., 2015). The supplementation of *Lactobacillus rhamnosus* in piglets stimulated the development of the early B lineage (largest population of antibody-producing cells) and increased the production of immunoglobulin A (IgA) by the gut mucosa (Jin et al., 2021). Another study indicated that commensal gut *Escherichia coli* recruited T cells to gut epithelium (Haverson et al., 2007).

Microbial metabolites induced enterocytes to generate transforming growth factor beta (TGF-β), which is an essential cytokine for T-reg lymphocyte development and production of anti-inflammatory IL-10 (Kim et al., 2016). Furthermore, gut microbiota can induce enterocytes to generate serum amyloid A (an acute-phase protein also produced by the liver) which stimulates dendritic cells (limit reactivity to gut microbiota) to activate mucosal regulatory cells such as TH17 and T cells (Kim et al., 2016). In addition, microbial metabolites stimulated type 3 innate lymphoid cells to generate IL-22, which can stimulate enterocytes to synthesize defensins such as REGIIIg and REGIIIb (Kim et al., 2016). It is noteworthy that the gut microbiota and microbiota-derived metabolites are key contributors to innate immunity of the gut.

In both ruminant and non-ruminant livestock, a normal physiological event such as the weaning stress results in shifts in the profile of luminal microbiota (Malmuthuge et al., 2013). This period of stress could induce microbiota dysbiosis, i.e., a decrease in beneficial microbes with an increase in harmful microbes (Gomez et al., 2017). The decrease in beneficial microbes suppresses the production of anti-inflammatory cytokines within gut cells and weakens the tight junctions and intestinal epithelium (Gomez et al., 2017). Microbiota dysbiosis resulted in thinner mucosal layers and reduced defensins and secretory immunoglobulin A in the mucosa, allowing opportunistic pathogens to cause disease. Therefore, particularly in the young animal, maintaining gut microbiota homeostasis is vital for normal intestinal development and for ameliorating any potential post-absorptive immunometabolic response as a result of transfer of pathogens or microbial-derived bioactive molecules.

In mature cattle, optimal performance requires feeding of "higher-energy" diets, i.e., diets in which the high content of starch favors the production of the main glucogenic precursor, propionate. Therefore, feeding grain-based diets to lactating dairy cows and finishing beef cattle is common in the field. Although these diets provide extra energy, they also can induce undesirable alterations in the taxonomic composition of ruminal microbiota, including a reduction in richness and diversity of ruminal solid- and liquid-digesta and epithelium-associated microbiota, potentially shifting metabolic functions and inducing dysbiosis. All these events often lead to an increase in opportunistic and pathogenic bacteria within the rumen and can have a negative impact on nutrient utilization, production, and health. Nutritionally, the potential benefit of dietary compounds such as plant polyphenols on the gut microbiota and intestinal development should be emphasized and particularly in non-ruminant species. For instance, feeding dietary polyphenol-rich grape products altered gut morphology (e.g., highest villi height:crypt depth ratio) and the intestinal microbiota flora (*Enterococcus* increased and *Clostridium* decreased in ileal contents) in broiler chicks (Viveros et al., 2011). Those animals are particularly sensitive to stressors that alter immunometabolic status toward a pro-inflammatory state, which causes a marked catabolic state, especially in skeletal muscle (Klasing et al., 1987).

Previous grain-based subacute ruminal acidosis (SARA) challenge studies reported increases in the relative abundance of *Firmicutes* and reductions in *Bacteroidetes*, dominant bacterial phyla in the rumen (Plaizier et al., 2018), leading to decreased ruminal pH and a higher risk of SARA. A decrease in ruminal pH enhances destruction of Gram-negative bacteria and causes release of lipopolysaccharide (LPS) in high concentrations leading to localized inflammation in key organs of the animal. For example, high ruminal LPS production led to induction of MAPK and NF-kB signaling pathways and the production of inflammatory cytokines in the ruminal epithelium, thus, enhancing ruminal inflammation (Abdela, 2016;

Table 1. Examples of the associations between the gut microbiota and the immunometabolic response in livestock

Model	Age or production phase	Treatment	Microbiome sample type	Alterations in microbiome	Immune sample type	Alterations in immune functions	Reference
Neonatal dairy calves	1–28 d of age	Bacillus megaterium supplementation	None	↓ diarrhea	Serum	↓Cholesterol ↓HDL ↑Glutathione ↓Malondialdehyde ↑IgA ↑IgM ↑IgG ↑IL-4 ↓TNF-α	Yao et al., 2020
Neonatal dairy calves	1–49 d of age	Fecal microbiota transplantation from a healthy adult donor mixed in the milk replacer	Feces	↓ Odoribacteraceae ↓ Pasteurellaceae ↓ Actinobacteria	Plasma	↑Haptoglobin ↓IL1-β ↓IL-6	Rosa et al., 2021
Neonatal piglets	2–26 d of age	Dietary β-carotene	Feces	↓ phyla Bacteroidetes ↓ genus Prevotella ↓ genus Blautia ↑ phyla Firmicutes ↑ genera p-75-a5 ↑ genera Parabacteroides	Serum	↓IL-1β, IL-6, and TNF-α; Parabacteroides and Synergistes were negatively correlated with IL-1β, IL-6, and TNF-α; Prevotella and Blautia were positively correlated with IL-1β, IL-6, and TNF-α	Li et al., 2021
Neonatal piglets	1–61 d of age	Enriched housing vs. conventional housing	Feces	↑ VFA-producing bacteria, including Prevotella_2, Christensenellaceae_R_7, and Ruminococcus gauvreauii	Whole blood	↑Hemoglobin ↑T cells ↑Cytotoxic T cells ↑ex vivo secretion of IL1β and TNF-α after LPS stimulation	Wen et al., 2021

Guo et al., 2017). In the liver, LPS causes hepatic inflammation and hepatocyte injury, suppressing liver function (Guo et al., 2017). Furthermore, when high concentrations of LPS reach the uterus it causes endometritis and activates the TLR4 signaling pathway (Bilal et al., 2016). A recent study also reported that rumen-derived LPS activated the inflammatory response in the udder, leading to mastitis (Hu et al., 2022). Available data indicate that rumen-derived LPS increases concentrations of the acute-phase proteins serum amyloid A, haptoglobin, and the inflammatory cytokines IL-1β and TNF-α in the blood, eventually leading to a state of systemic inflammation (Gozho et al., 2005). Similar responses to immune challenges have been reported in poultry (Klasing et al., 1987), underscoring a degree of conservation among livestock species on the immunometabolic response to stressors.

Although an in-depth discussion is beyond the scope of the present review, the traditional high-energy diets fed to pregnant cows in the latter stages of the prepartum period, or during the finishing period in beef cattle not only can lead to overconditioning, but potentially SARA. In both scenarios, the composition of ruminal and post-ruminal microbiota is likely to be altered and may contribute to localized and systemic changes in immunometabolism. The origin of such changes could center on pro-inflammatory cytokines such as TNF-α, which were identified as one of the key components of the original immunometabolic model proposed to explain the link between ER stress and inflammation associated with obesity and type 2 diabetes (Hotamisligil, 2006). This is a hypothesis that should be further examined in future research.
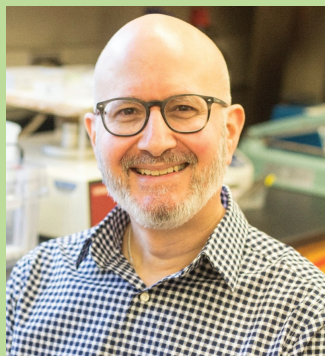
Conclusions

Increased access to and application of molecular tools and bioinformatics methods to generate biologically meaningful data from studies in livestock species has helped expand our understanding of the role of tissue-specific immunometabolic networks. Although the original studies in this area were focused on characterizing the physiological role of these networks during the transition into lactation, a growing body of data indicates they play important roles at various stages of development in various livestock species. The fact that proteins controlling these networks are responsive to the supply of nutrients and the profiles of gut microbes underscores opportunities in the future for manipulating their activity at specific stages of the life cycle. Key issues to be addressed in the future deal with how climate change alters immunometabolism, [some data are available for dairy cows (Ouellet et al., 2020) and poultry (Uyanga et al., 2022)], which are the control points for these networks during normal and abnormal states, and what are the most-effective nutrients that could help manipulate these networks for optimal performance and health.

About the Authors

Juan J. Loor is a Professor of Animal Sciences in the Department of Animal Sciences and the Division of Nutritional Sciences at the University of Illinois, Urbana. He received a BS from the University of California, Davis, and earned an MS and PhD studying lipid nutrition, biohydrogenation, and metabolism in ruminants at Virginia Tech. Since joining the University of Illinois in 2005, his research program has centered on nutritional and physiological genomics during the neonatal period, lactation, and rapid growth in beef and dairy cattle. A central goal of his research program is to uncover physiologic regulatory mechanisms induced by nutritional management through the integration of ruminal microbiome, circulating metabolome, and tissue transcriptome data. **Corresponding author:** jloor@illinois.edu

Ahmed A. Elolimy is a Researcher of Animal Nutrition in the National Research Centre (NRC), Egypt. He received a BS and MS from Cairo University, Egypt, and earned a PhD studying diet-microbiome-host interactions in ruminants from the Department of Animal Sciences, University of Illinois, Urbana. During his postdoctoral fellowship at the University of Arkansas for Medical Sciences, he focused on understanding the impact of milk formula on the gut microbiome, host transcriptome, and immune function in neonates before joining the NRC. His current work centers on nutritional immunology and the microbiome during the stressful stages in the animal's life, including the neonatal period, parturition, and heat stress.

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