Journal of Animal Science, 2020, Vol. 98, No. 3, 1–8

doi:10.1093/jas/skaa035
Advance Access publication February 6, 2020
Received: 1 October 2019 and **Accepted:** 5 February 2020
Companion Animal symposium

COMPANION ANIMAL SYMPOSIUM

NUTRITION AND HEALTH: COMPANION ANIMAL APPLICATIONS: Functional nutrition in livestock and companion animals to modulate the immune response

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Abstract

Advances in the understanding of how the immune system functions in response to diet have altered the way we think about feeding livestock and companion animals on both the short (weeks/months) and long-term (years) timelines; however, depth of research in each of these species varies. Work dedicated to understanding how immune function can be altered with diet has revealed additional functions of required nutrients such as vitamins D and E, omega-3 polyunsaturated fatty acids (**PUFA**), and minerals such as zinc, while feed additives such as phytogenics and probiotics add an additional layer of immunomodulating potential to modern diets. For certain nutrients such as vitamin D or omega-3 PUFA, inclusion above currently recommended levels may optimize immune function and reduce inflammation, while for others such as zinc, additional pharmacological supplementation above requirements may inhibit immune function. Also to consider is the potential to over-immunomodulate, where important functions such as clearance of microbial infections may be reduced when supplementation reduces the inflammatory action of the immune system. Continued work in the area of nutritional immunology will further enhance our understanding of the power of nutrition and diet to improve health in both livestock and companion animals. This review collects examples from several species to highlight the work completed to understand how nutrition can be used to alter immune function, intended or not.

Key words: companion animals, functional nutrition, immunometabolism, livestock, nutritional immunology

Introduction

Advances in human and companion animal immunology in the last 20 yr have allowed further investigation into how host nutrition and immunomodulation are linked to change host health (Grimble, 1995, 2001; Wintergerst et al., 2006, 2007; Maggini et al., 2007, 2018; Newton et al., 2016; Carr and Maggini, 2017; Batatinha et al., 2019). Interest in connecting the fields of nutrition and immunology have been fruitful into understanding how health and disease progress over time and how nutrition may be able to improve immune function (Di Cerbo et al., 2017; Wu et al., 2018a). From a nutrition standpoint in companion animals and livestock, diets are precisely formulated and the feed is consumed to reach the production goals which include growth, maintenance, and reproductive needs. We also

Abbreviations

ALA	alpha-linolenic acid
Bcl6	B cell lymphoma 6
DCs	dendritic cells
DHA	docosahexaenoic acid
EGCG	epigallocatechin gallate
EPA	eicosapentanoic acid
FOXP3	forkhead box P3
IFNg	interferon gamma
IgA	immunoglobulin A
ILC	innate lymphoid cell
IL-10	interleukin-10
LLPC	long-lived plasma cell
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
Mpc2	mitochondrial pyruvate carrier 2
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
PGE2	prostaglandin E2
PUFA	polyunsaturated fatty acid
ROS	reactive oxygen species
RNS	reactive nitrogen species
SCFA	short-chain fatty acid
TCA	tricarboxylic acid
Tfh	T follicular helper
TLR	toll-like receptor
TNF	tumor necrosis factor
Treg	T regulatory cell

know that these needs change over the lifespan of the animal and have, therefore, formulated diets based on production goals, maintenance needs, and age. Furthermore, in livestock production species, the selection for efficient growth and reducing non-necessary immunoreactivity in favor of growth has been emphasized from a resource allocation perspective (Rauw, 2012).

Speaking solely from an immunological standpoint, reagents to investigate companion and livestock immunity lag behind those available for human and mouse models, but have greatly advanced since the early 1990s. A common theme in all areas of nutrition: human and animal is to further understand the link between the selection of feedstuffs and alteration of host health (Keusch, 2003; Monk et al., 2011; Satyaraj, 2011). Examples of foods that largely benefit health include omega-3 fatty acids, direct fed microbials, yeast products, and components of plants such as prebiotics, fiber, phytogenics, and essential oils (Bauer, 2001, 2011; Grimble, 2001; Carr and Maggini, 2017; Di Cerbo et al., 2017; Wu et al., 2018a). Some vitamins and minerals may be also included that have a benefit for health above required recommendations.

In very general terms, the immune system has short- and long-term pathogen response capabilities which are mediated by the innate and adaptive segments of the immune system (Domínguez-Andrés et al., 2019; Dominguez-Andres and Netea, 2019; Netea et al., 2019). The early immune response to pathogen or damage is largely mediated by the innate immune response and the purpose is to mitigate damage and clear the pathogen to prevent further colonization of the host and additional damage (Ganeshan and Chawla, 2014; Gershwin, 2015; Newton et al., 2016; Netea et al., 2019). While emerging data show that the innate immune system may have a memory component, the innate immune system largely does not need prior contact with antigen to perform its duties and responds to both host tissue damage signals and pathogen-associated molecular patterns. To protect the host long term from reinfection with the same antigen and increase the speed of future responses if rechallenged, the adaptive immune system has a memory component and specific pathogen immunity can last months to years, with the capability to remember previous antigens and respond to pathogen invasions. Importantly, when we consider livestock and companion animal nutrition with the potential to impact the immune system, we must consider if the process we intend to target is able to be modified through nutrition. Secondly, the ability to select a target within the innate or adaptive immune system presents different obstacles based on functions desired to alter, as these systems are interconnected. What we are now trying to understand is how we can modulate these two interconnected but different responses through nutrition.

Immunometabolism

Immune system function and metabolism can be precisely tracked based on the preferences in fuel selection of the immune cells in question (Wolowczuk et al., 2008; Buck et al., 2017). Nutritionists consider dietary inputs to meet species and production requirements. When immunologists think about molecular nutrition, they consider how the signaling process might change with a different localized environment (Hotamisligil, 2017). Immune cells shift fuel usage among lipid, amino acids, and glucose. During immune activation, lymphocytic cells preferentially use glycolysis for ATP generation when oxygen is not limiting (i.e., aerobic glycolysis). This switch is termed Warburg metabolism and is a well-understood phenomenon common in cancers (Wolowczuk et al., 2008; Ferreira, 2010; Buck et al., 2017; Lu, 2019; Unterlass and Curtin, 2019). When a naive T cell recognizes an antigen, it undergoes rapid growth, proliferation, and acquisition of specialized effector functions. Aerobic glycolysis is not required for T cell activation but is a hallmark of Warburg metabolism and the switch between quiescent and active states. In immune responses connected to the lymphocyte response, we can, therefore, monitor a shift based on fuel preference of T and B lymphocytes (Ganeshan and Chawla, 2014).

When we specifically consider the gastrointestinal immune system, the first population of immune cells with direct dietary interaction, the organization is such that the intestinal lumen contains secretory immunoglobulin A (**IgA**) antibodies, and the single epithelial cell layer is densely packed with intraepithelial lymphocytes (Hooper et al., 2012). Dendritic cells (**DCs**), macrophages, innate lymphoid cells (**ILCs**), and T cells reside in the lamina propria. Peyer's patches are interspersed along the epithelium, which in addition to supporting sampling of luminal antigens by DCs and M cells, house germinal centers that maturate IgA-secreting B cells with T follicular helper (**Tfh**) cell help (Jung et al., 2010). Peyer's patches are aggregate structures for lymphocytes and central sites for lymphocyte sampling of antigens in the intestinal tract. Sensitized lymphocytes then traffic to mesenteric lymph nodes, to thoracic ducts, and then home back to the gastrointestinal tract. B cells also alter cellular substrate usage upon activation with a switch to glycolysis and depend pyruvate import via mitochondrial pyruvate carrier 2 (**Mpc2**) for longevity as long-lived plasma cells (**LLPCs**; Waters et al., 2018). Increased plasma glucose usage may restrict this nutrient from Tfh cells; however, Tfh cells downregulate glycolysis in response to expression of their lineage defining

transcription factor B cell lymphoma 6 (**Bcl6**). The change in metabolic preference is concurrent with a change in activation state and is functionally specific to immune cell types (Khalsa et al., 2019). Feedback mechanisms through cytokine signaling, such as anti-inflammatory interleukin-10 (**IL**-10), eventually contribute to reduced activation states to prevent continuous activation and cellular exhaustion (Couper et al., 2008; Saraiva and O'Garra, 2010; Khalsa et al., 2019).

Importantly, LLPCs can live in bone marrow for years continuously synthesizing companion animal species with typical lifespans that extend beyond many commercial production livestock (Day, 2007; Maggini et al., 2007). Current B cell models have yet to fully understand how to combine high biosynthetic output and a long life. High production output in livestock species combined with an extended-life model could be advantageous for studying both companion animal and human diseases such as cancers common later in life. It is known that thiamin (vitamin B_1) depletion impairs tricarboxylic acid (**TCA**) cycle activity and initiation of antigen-specific antibody responses (Kunisawa et al., 2015). Naïve B cells and IgA+ plasma cells use non-glycolytic and glycolytic TCA cycles, respectively (Axelrod, 1981; Kunisawa, 2017).

Dietary Modulation of the Immune Response and Gastrointestinal Ecology

To understand species-specific responses and how they potentially can be modulated by diet, it is important to understand some basic immune response differences across companion and livestock species (Day, 2007; Schultz and Magor, 2008; Gershwin, 2015; Guzman and Montoya, 2018). Some responses, such as hypersensitivity reactions, are immune responses that are exaggerated or inappropriate against an antigen or allergen. Hypersensitivity reactions are classified into four categories based on mediators of the reactions: 1) Allergic (Immunoglobulin (Ig) E-mediated, asthma, and allergies), 2) Cytotoxic (**IgG** or **IgM**-mediated, includes blood transfusion reactions); 3) Immune complex deposition (antigen: antibody complexes that induce complement and immune response, such as rheumatoid arthritis); and 4) Delayed (cell-mediated hypersensitivity, such as contact dermatitis). Examples of desirable reactions to modify in companion and livestock species include type 1 (allergic, asthma, and allergies) and type 4 (contact dermatitis). Type 3 (arthritis) may also be desirable but may be harder to study in shorter-lived livestock species.

Although cattle do not develop asthma naturally as a clinical syndrome, they produce IgE to a variety of allergens (Gershwin, 2015). Similarly, IgE is also produced by sheep, goats, swine, and horses. All of these species are capable of undergoing anaphylactic shock. Equines have strong IgE production capabilities in response to nematodes, and respiratory, skin, and food allergies are seen commonly. Equines can experience type 1 hypersensitivity to insect bites (i.e., summer itch) and recurrent airway obstruction (heaves), and may also experience systemic anaphylaxis in response to antigen injection for which the horse already has IgE. Hypersensitivity reactions commonly manifest in the respiratory system via histamine and serotonin.

Skin allergy in canines (atopic dermatitis) is common and has a genetic component. Canines experience type-1 hypersensitivity more commonly as a skin disease than respiratory allergy (Mandigers and German, 2010; Royer et al., 2013). A food allergy mediated by IgE can manifest as gastrointestinal or dermatological, and this is not the same as food intolerance (Gershwin, 2015). Cats are the only domesticated animal to develop asthma spontaneously, and experience airway inflammation and hyperreactivity just as humans do (Trzil and Reinero, 2014). Atopic dermatitis (skin allergy) is also common in cats and also has a genetic component. Anaphylactic shock in cats resembles a horse or pig more than a dog, where organs affected are gastrointestinal and respiratory, and mediated by histamine, leukotriene, and serotonin.

The gastrointestinal tract is a direct interface with the outside world and the foods that are consumed. Also present in the gut is a diverse set of substrates made by the host and commensal bacteria which become available for both host and microbial use (Keusch, 2003; Buck et al., 2017). Commensal bacteria produce metabolites such as short-chain fatty acids (**SCFA**s) from the fermentation of dietary fiber, which influence B cell metabolism and promote IgA secretion (Grizotte-Lake et al., 2018). SCFAs and vitamins support the maintenance of barrier function by promoting the development and survival of T regulatory cells (**Tregs**) and ILCs, while homeostatic signals secreted by gut resident immune cells such as IL-10 may also modulate metabolism and, therefore, control activation state (Schulthess et al., 2019). The SCFA butyrate has had some success in the maintenance or improvement of growth and performance in nonruminant livestock such as broilers (Zhang et al., 2011), but from an immunological and cell differentiation standpoint, butyrate is also a signaling molecule, a potent inhibitor of intestinal stem cell proliferation, and beneficial for immune development and microbial community membership (Zhang et al., 2011; Wu et al., 2018b). Differentiated cells metabolize butyrate to fuel oxidative phosphorylation and limit access to progenitor cells for protection.

To be effective in changing a feature of the immune system using nutrition, that feature must respond to diet. There are several categories for which diet may affect immunity: 1) feed the immune system cells (all nutrients); 2) feed the pathogen (biotin/iron); 3) modify leukocyte response (energy, PUFA, vitamins A, D, and E); 4) protect against immunopathology (PUFA, vitamin E); 5) influence the gastrointestinal microbial ecology (fiber); and 6) stimulate the immune system (lectins, protein antigens; Klasing, 2007). We can even further classify the broad categories of functional nutrients: nonnutritive and required dietary components (Klasing, 2007; Wu et al., 2018a). It is well-understood that nutritional deficiency impairs immune function, and for certain nutrients, inclusion above currently recommended levels may optimize immune function. To broadly categorize the capabilities of feed or feed additives to alter immune function, components can be broken into intervention agents, such as vitamin E, vitamin D, zinc, or omega-3 fatty acids, and functional foods such as probiotics, phytogenics, essential oils, or smaller components of a feedstuff such as epigallocatechin gallate (**EGCG**) in tea.

Intervention Agents

Vitamin E

Vitamin E is a fat-soluble antioxidant that can protect PUFAs in cellular membranes from oxidation, regulate the production of reactive oxygen species (**ROS**) and reactive nitrogen species (**RNS**), and modulate signal transduction. In the literature described here, vitamin E will be used as a general term: referring to those tocopherols and tocotrienols that exhibit the biological activity of α-tocopherol. Vitamin E is immunomodulatory

effects in animal and human models under normal and disease conditions (Lee and Han, 2018).

Immune cells contain particularly high concentrations of vitamin E to protect from oxidative damage related to high metabolic activity and high PUFA content (Pekmezci, 2011; Lee and Han, 2018). Although rare in current diets, vitamin E deficiency is linked to impaired lymphocyte proliferation and function. Evidence is mounting that current recommendations for dietary intake do not support the immune system, especially in the elderly (Pekmezci, 2011; Wu et al., 2018a). Old mice fed 500 vitamin E diet vs. 30 mg/kg had enhanced T cell-mediated immunity, improved lymphocyte proliferation, IL-2 production, and decreased prostaglandin E_2 (**PGE_2**) production (suppresses T cells; Wu et al., 2018a). Human studies using >60-yr-old subjects supplemented with 200 mg/d vitamin E resulted in improved antibody titers to hepatitis B and tetanus. The proposed mechanism of action for enhancement of T cell-mediated function is direct membrane integrity improvement and positively modulating the signaling events in T cells, while also protecting T cell function indirectly by reducing production of T cell-suppressing factors such as PGE_2 from macrophages (Wu et al., 2018a).

Vitamin E supplementation above requirements has also resulted in titer improvements post-vaccination. In a White Leghorn laying hen (44 to 56 wk) vaccination model during tropical summer conditions, vitamin E was supplemented at 25, 125, or 250 mg/kg (white egg layers require 5 IU at 100 g feed intake/d, or 4.5 mg/kg using a synthetic source). Vitamin E supplementation improved Newcastle disease virus titer and lymphocyte proliferation as well as egg production and egg mass. (Panda et al., 2008). Vitamin E supplementation also improved vaccination titers (total immunoglobulins) in broiler chicks in a meta-analysis (Pompeu et al., 2018). In dogs vaccinated against *Taenia hydatigena*, the best immune response was observed in dogs also additionally supplemented with the combination of vitamin E and selenium (Kandil and Abou-Zeina, 2005). Dogs supplemented with vitamin E or vitamin E/selenium had an increased titer and IgG concentration vs. control and unsupplemented groups, with the highest protection observed (83.3%).

Vitamin D

Although critical for bone development, vitamin D receptors and hydroxylases are also present in tissues and cells not involved in mineral and bone metabolism. The overall effect of vitamin D on innate immunity is stimulatory at physiologic concentrations which includes monocyte proliferation and chemotactic and phagocytic activity of macrophages (Wu et al., 2018a). Vitamin D plays a crucial role in enhancing the innate antimicrobial response. Toll-like receptor (**TLR**) binding leads to increased expression of both the 1-α-hydroxylase and the vitamin D receptor. Vitamin D induces endogenous antimicrobial peptide production by monocytes, neutrophils, epithelial cells, and is the overall inhibitory for B and T cells and interferon gamma (**IFNg**) and IL-12 production, two key T cell cytokines. Activation of B and T cells and subsequent proliferation elevates vitamin D receptor expression for feedback inhibition and limits of effector function (Grimble, 2001; Aranow, 2011). At a cellular level, vitamin D modulates $CD4^+$ differentiation into subpopulations, favors Treg and Th2 (humoral immunity and targeting extracellular pathogens), restricts Th1 and Th17, inhibits DC differentiation from precursors and maturation, programs DCs for tolerance, and may help mitigate T cell-driven autoimmunity (Aranow, 2011). These effects result in decreased production of inflammatory cytokines (IL-17, IL-21) with increased production of anti-inflammatory cytokines such as IL-10.

In a proof of concept study, whole blood from three ill dogs was incubated with calcitriol (2×10^{-7} *M*) or ethanol (control) for 24 h and then stimulated with lipopolysaccharide (**LPS**). Tumor necrosis factor (**TNF**)-α, IL-6, and IL-10 were measured using a canine-specific multiplex assay. Calcitriol significantly increased LPS-stimulated whole blood production of IL-10 and decreased TNF-α production without significantly altering IL-6 production, suggesting that calcitriol induced an anti-inflammatory phenotype in vitro (Jaffey et al., 2018).

Zinc

Zinc is a mineral required for key biological processes that affect normal growth, development, repair, metabolism, cell integrity/functionality, and immune tolerance in both innate and adaptive immune systems (Ibs and Rink, 2003). The reaction of the immune system to zinc depends on zinc concentration, where zinc can have both positive and negative effects on immune function. Zinc depletion leads to function compromise in nearly every class of immune cells and also results in thymus involution (Wu et al., 2018a). Thymic involution is a reduction in thymic mass, which reduces function and is typically is related to age; premature involution, therefore, increases the likelihood of disease, as immunosurveillance is reduced (Palmer, 2013). In monocytes, all functions are impaired, whereas, in natural killer cells, cytotoxicity is decreased, and in neutrophil granulocytes, phagocytosis is reduced. Normal functions of T cells are impaired with a skew toward Th1, but autoreactivity and alloreactivity are increased, while B cells undergo apoptosis and reduced antibody response. Inflammatory cytokine and mediator overproduction occurs with a skew toward Th1. Supplementation of zinc reconstitutes immune function, while high doses of zinc evoke negative effects on the immune system.

When zinc is in excess, T and B cell function is suppressed, Treg cells are overloaded, and macrophages are directly activated. In a concentration of 100 mmol/L, zinc suppresses natural killer cell killing and T-cell functions, whereas monocytes are activated directly, and in a concentration of 500 mmol/L, zinc evokes a direct chemotactic activation of neutrophil granulocytes (Ibs and Rink, 2003; Wu et al., 2018a). This balance among adequate, too little, and excess results in varying effects when humans and livestock are supplemented with zinc in an attempt to improve performance and immunity, as zinc requirements change based on species, age, and health status (Nielsen, 2012; Maywald et al., 2017; Wessels et al., 2017; Brugger and Windisch, 2019).

Omega-3 fatty acids

Omega-3 fatty acids are one of the most recognized immunomodulating supplements. When choosing to supplement omega-3 PUFA for an immune-enhancing effect, the source is important. Alpha-linolenic acid (**ALA**) is found in plant sources and is commonly supplemented in the form of flaxseed in animal diets. Eicosapentanoic acid (**EPA**) and docosahexaenoic acid (**DHA**) are found in marine sources such as fish and algae. Nonruminant animals lack the enzymes and efficiency to convert all ALA to bioactive EPA and DHA, so they must be supplemented in order to receive immune benefit (Burdge et al., 2002; Burdge and Wootton, 2002; Lenox, 2015). The potent anti-inflammatory properties of omega-3 PUFA include the ability to inhibit production of inflammatory mediators including eicosanoids (PGE_2, 4-series leukotrienes), pro-inflammatory cytokines (IL-1ß, TNF-α, IL-6), chemokines (IL-8, intercellular adhesion moelcule-1 [**MCP**-1], adhesion

molecules (intercellular adhesion moelcule-1 [**ICAM-1**], VCAM-1 vascular cell adhesion molecule-1 [**VCAM-1**], selectins), platelet-activating factor, and ROS and RNS (Calder, 2007). In addition to inhibiting pro-inflammatory mediators, omega-3 PUFA increase the production of anti-inflammatory cytokines such as IL-10 and are pro-resolution agents by serving as the precursors for several families of pre-resolving mediators, which at least include EPA-derived E-series resolvins, DHA-derived D-series resolvins, and DHA-derived protectins and maresins (Klasing, 2007; Monk et al., 2011; Wu et al., 2018a). Omega-3 PUFA generally suppress T cells by inhibiting Th1 and Th17 differentiation, with little effect on Th2 and Treg populations.

Original work in 1994 focused on pruritus, atopy, and skin inflammation in dogs (Logas, 1994). Each dog received a high-dose capsule with 180 mg EPA and 120 mg DHA/4.55 kg body weight or control (570 mg linoleic acid and 50 mg gamma-linolenic acid/4.55 kg body weight) for 6 wk, and the researchers saw significant improvements in pruritus, self-trauma, and coat damage over time. Additional researchers have reported the benefits of feeding omega-3 PUFA and positive control or atopic dermatitis in dogs (Scott et al., 1997; Singh et al., 2010). In additional conditions found in dogs, Freeman et al. (1998) also reported that dogs with heart failure have low plasma concentrations of EPA, regardless of underlying disease. His research group administered 27 mg EPA · kg^{-1}· d^{-1} and 18 mg DHA · kg^{-1}· d^{-1}, which resulted in reduced PGE_2, decreased IL-1, and improved cachexia vs. placebo. The caveat to omega-3 PUFA supplementation is 2-fold: 1) these immunomodulating changes occur with DHA or EPA supplementation, not ALA (i.e., flaxseed supplies omega-3 PUFA, but not bioactive forms) (Calder, 2007) and 2) the reduction in inflammatory processes leads to increased incidence of bacterial function, as the immune processes that surveil, control, and clear bacterial infections are dampened with continued omega-3 PUFA supplementation (Bauer, 2001; Calder, 2007; Lenox and Bauer, 2013).

Functional Foods

Plant-based compounds: phytogenics and essential oils

Phytogenics represent a group of plant-based natural substances used in animal nutrition. These substances are derived from herbs, spices, plants and their extracts, such as essential oils, and are used to improve animal growth, immunity, and performance due to a myriad of effects which include antimicrobial effects as well as cell-signaling alterations. The use of essential oils and phytogenic compounds in nonruminant animals has become more popular due to restrictions and reductions in antibiotic use (Yang et al., 2015). While the use of these compounds has not been as popular in companion animal nutrition as compared with nonruminant livestock, it is plausible that some of these compounds may make their way into companion animal feed and supplements in the near future.

Supplementation with phytogenics such as cinnamon, oregano, turmeric, or thyme products has been shown to improve the immune response in pigs and poultry (Huang and Lee, 2018). Improvements include improved antibody titer in response to vaccination, higher lymphocyte counts, and enhanced body weight, feed conversion, egg production, and body weight gain (Huang and Lee, 2018). In a common mechanistic pathway, these phytogenics generally acted to alleviate the overall stress response by suppressing nuclear factor kappa-light-chain-enhancer of activated B cells (**NFκB**) and mitogen-activated protein kinase (**MAPK**) signaling pathways and increasing the expression of anti-inflammatory cytokines. As a result, the blood levels of nonspecific immune cells such as heterophils (in chickens; neutrophils in pigs) were lowered, and lymphocyte and antibody production were promoted to defend against invading pathogens (Huang and Lee, 2018; Zhai et al., 2018). Reducing energy expended on the nonspecific immune system also allows to repartition energy for growth and production. Phytochemicals were shown to downregulate NFκB and/or MAPKs signaling pathways in chickens and pigs through a reduction in TLR signaling, but the detailed mechanisms, including expression of upstream molecules involving NFκB and MAPKs signaling as well as the relationship between antioxidant and anti-inflammation, are still under investigation (Huang and Lee, 2018). A separate group reviewed the potential variables that may cause success in the use of phytogenics or essential oils in nonruminant livestock production and reported that factors such as pelleting, energy content of the diet, dietary form, essential oil composition, environment, age of animal, and growth performance level all factored into the success or failure of the phytogenic or essential oil in improving performance and immune function (Zhai et al., 2018).

Green tea components

The most notable and abundant immunomodulatory component of green tea is epigallocatechin-3-gallate (EGCG). EGCG induces IL-10 production and Treg differentiation and reduces neutrophil migration while also slowing DC maturation. EGCG also alters forkhead box P3 (**FOXP3**) signaling, the master regulator in T cell development, and promotes Tregs, which turn the immune system down to reduce inflammation (Grimble, 2001; Wu et al., 2018a). In cancer, excess Tregs prevent the immune system from destroying cancer cells, while in autoimmunity, Tregs are deficient and this allows immune cells to attack the body's own tissues. As we look to the methods of improving livestock and companion animal lifespan and quality of life, we must remember that components that immunoregulate also may have downstream consequences.

Probiotics

Incredible advances in both the fields of microbiology and immunology have shown us how closely linked these two ecosystems are (Maslowski and Mackay, 2011; Hooper et al., 2012). Diet, including fiber content, has a considerable effect on the microbial community, and we also know that composition and products from the microbial community have unexpected effects on immune and inflammatory responses (Makki et al., 2018). SCFAs are known to promote Treg differentiation, while butyrate specifically enhances barrier function, mucus, IgA production, and the promotion of an anaerobic environment. The depletion of anaerobic bacteria, commonly through the use of antibiotics, has been associated with a reduction in butyrate concentrations, thus promoting an aerobic environment, favoring the expansion of aerobes including pathogenic *Salmonella* species (Parada Venegas et al., 2019). In the absence of butyrate, aerobes and facultative anaerobes respond to increased available O_2 and create favorable conditions for pathogens (Maslowski and Mackay, 2011). The supplementation of probiotics specifically has been shown to interact with gut mucosa, M cells, intestinal epithelial cells, Peyer's patch, and DCs, with effects also seen in mucosal respiratory immune system response and reduction of pro-inflammatory cytokines.

The effects of probiotics are known to be strain-dependent in their roles in modulating how the innate immune system interacts with T and B cells, and longer-term and sustained supplementation (months) is required to see an effect (Ganguly, 2013; Baffoni, 2018; Ma et al., 2018; Li et al., 2019).

Summary and Conclusions

The implications of using nutrition and supplements to alter immune function not only may be beneficial but also may create downstream unintended consequences that must be considered when long-term supplementation is indicated. Certainly, not all immunomodulating nutrients and compounds have been discussed in this review. Most of the immunomodulating compounds reviewed here perform a function related to dampening the immune system to offer a growth, immune, or performance benefit (vitamin D, omega-3 PUFA, phytogenics), while some alter interactions with other systems to provide a benefit (probiotics). Supplementation of probiotics or vitamin E at the right concentration and timing may enhance a desirable outcome such as antibody titer in response to a vaccine and can be taken into consideration with both livestock and companion animals to improve health outcomes.

The ability of an added nutritional supplement to alter immune activity depends on the exposure of the immune system to an immunomodulating concentration of each input as well as the desired outcome. In cases where an immunomodulating nutrient needs to be fed above maintenance or reproductive requirements to alter the immune system, nutrient exposure must be sustained to derive a benefit. For example, if the goal is to enhance a vaccine response with vitamin E, a supplement may need to be fed in advance in order for immune cells to incorporate the vitamin, and through the expected vaccine immune response (months). After the removal of therapeutic vitamin E, because it may be stored in fat, effects potentially could persist for a period of time. It is clear that for supplements such as probiotics, continual exposure (i.e., consumed daily as a concentrate, or in each ration) is needed to derive a benefit. The ability to store or access a nutrient (fat vs. water-soluble) beyond maintenance needs also may determine short- and long-term efficacy. Long-term suppression of the immune system could contribute to downstream outcomes such as reduced pathogen clearance or incidence of auto-immunity and certain cancers but may be desirable in the short term to clear pathologic inflammation or hypersensitivity responses.

Acknowledgment

Based on a presentation entitled “Functional nutrition to modulate the immune system”, presented at the 2019 Annual Meeting of the ASAS and CSAS Companion Animal Symposium I: Nutrition and Health: Companion Animal Applications July 9, 2019, in Austin, TX.

Conflict of interest statement

The authors declare no real or perceived conflicts of interest.

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