Emerging Paradigms in Immunonutrition

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Nutritional immunology is the study of the relationship between food and the immune system. It evolved with the study of immune deficiencies caused by malnutrition. However, because of technological advances made over the past few decades, malnutrition is no longer the main cause of lowered immune status in otherwise healthy people/animals. Rather, life stage (neonate or old age) and natural stressors have taken over as the primary cause for immune deficiency. Unlike malnutrition, immune deficiency due to life stage or natural stress cannot be addressed by correcting underlying nutritional problems. Lowered immune status because of life stage or naturally occurring stress is characterized by reduced capacity to process and present foreign antigens to immune cells, resulting in a less efficient or altered immune response that leads to increased susceptibility to infections and an increase in autoimmunity and cancers. Beyond providing essential nutrients, diet can actively influence the immune system. Over 65% of the immune cells in the body are present in the gut, making the gut the "largest immune organ." Receptors present on the immune cells in the gut are the primary targets for immunomodulation via diet. Diet interacts with the immune system at multiple levels, starting with providing basic nutrients, then moving on to providing higher levels of key nutrients such as protein, vitamins, and minerals, and leading to a more focused modulation of the immune system. A framework outlining this interaction, along with relevant examples, will be discussed.

Keywords: nutritional immunology, natural stress, aging, immunosenecence, cytokines, prebiotics, vaccine response, CR, probiotics, colostrums

Both nutrient metabolism and immunity (nutrient-sensing and pathogen-sensing pathways) are essential for survival—the former to sustain and the latter to preserve life. Consequently, nutrient metabolism and immunity have codeveloped organ systems and signaling pathways during evolution.[1] We see many examples of this in nature. In the common fruit fly, *Drosophila melanogaster*, both immune and metabolic response is controlled by the same organ, the "fat body."[2] Although higher animals have evolved different organ systems for immune and metabolic response, the evolutionary relationship is apparent by: 1) the close proximity of immune cells, such as macrophages and Kupferr cells, in tissues actively involved in nutrient metabolism like adipose and liver tissue[3] and 2) the observation that remodeling of adipose tissue often accompanies certain inflammatory disease, such as development of panniculitis during inflammatory bowel disease[4] and the inflammatory stress brought on by obesity.[5] Furthermore, this evolutionary relationship is hardwired at the molecular level in cells involved in both processes. Both adipocytes and macrophages secrete cytokines in response to bacterial products such as lipopolysaccharide (LPS).[6] Preadipocytes can differentiate into macrophages, and transcriptional profiling reveals that they are genetically related.[7,8] Given this close relationship, it is no surprise that chronic nutrient deficiency or excess can negatively impact immune health and consequently overall health. For example, adipose tissue in obesity has been shown to produce higher levels of proinflammatory cytokines such as tumor necrosis factor (TNF) α,[9] resulting in low-grade inflammation that leads to metabolic syndrome and associated diseases such as insulin resistance, type 2 diabetes and arthrosclerosis. The good news is that this relationship can also be used to proactively enhance immune health.

Immunonutrition: History and Renewed Focus

The understanding that food impacts health goes back to antiquity with references in the writings of ancient Egyptians and Indians. Hippocrates, the father of Western medicine, is believed to have recommended that his students evaluate diet to understand disease. However, the earliest scientific evidence implicating the role of nutrition in immune function came from J. F. Menkel in 1810, when he described thymic atrophy in malnourished people in England. These observations, among others, gave birth to nutritional immunology, which continued to evolve as a scientific discipline with the study of nutritional deficiencies caused by malnutrition sometimes referred to as nutritionally acquired immune deficiency syndrome.[10] Since its early beginnings in the 1800s,

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and with new information that came out during the vitamin era of the early 1900s, the emphasis in nutritional immunology was on how nutrient deficiencies impact the immune system. Although malnutrition still remains a global problem, many of the detrimental effects of malnutrition can be addressed by correcting the specific underlying nutritional problem. The current challenge, however, is related to an aging population, increased natural stress, and dietary overindulgence. Unlike immune deficiency caused by malnutrition, age-related immune deficiencies (life stage) and immune deficiency due to natural stress or dietary overindulgence need a more comprehensive strategy and cannot be simply addressed by correcting nutritional problems. Therefore, these problems are difficult to evaluate, understand, and manage. More importantly, as a practicing clinician, one is more likely to see immune deficiencies of the latter kind (immune deficiency not related to malnutrition), hence the paradigm shift in today's research emphasis in nutritional immunology, from malnutrition to addressing impaired immune status because of age, natural stress, and diet.

Why Is It Important to Ensure Immune Health?

The benefits of good immune health go beyond protection from infections. Immune health or a lack thereof has profound metabolic consequences, and new research indicates that it can affect several body systems including brain aging and cognition.[11] At a fundamental level, a healthy immune system affords protection by preventing infectious agent(s) from entering the host and establishing an active infection. This is the critical "barrier" function, otherwise known as the "first line of defense" role of the immune system. When the immune system is compromised, this barrier weakens and pathogens invade, causing disease. This triggers an active immune response to neutralize and eliminate the infections agent involving physiological changes including fever, inflammation, and cellular responses such as generation of T cells and antibodies that can specifically target the pathogen. Although such a full-blown immune response is critical for survival, it nevertheless comes with a price; it is a metabolically costly endeavor that uses precious resources. To put this in perspective, a 1°C increase in body temperature (fever associated with active infection) involves energy expenditure equal to a 70-kg person walking 45 km (9.4×10^6 J).[12] Clearly, repeated immune activation to combat infection can be a significant drain on metabolic resources and will unfavorably compete with energy-demanding processes like reproduction, lactation, and growth, because evolutionarily "protection" is assigned a higher priority than these other processes. Repeated immune activation has other secondary consequences such as increased oxidative stress, which is especially harmful in older animals. A healthy immune system capable of preventing infections, thus has profound positive metabolic implications. Recent research in rodents and people with age-related dementia suggests that poor immune health can negatively impact cognition and brain aging.[11] Clearly, a healthy immune system has implications that go beyond disease prevention.

In this review, I want to 1) discuss causes of immune deficiency in an otherwise healthy animal, 2) explore how food influences the immune system, and 3) propose a framework to understand how nutrition interacts with the immune system.

What Impacts Immune Health?

In the absence of disease, age and natural stress are 2 important factors influencing immune status. The immune response of a neonate or an older animal tends to be less vigorous than that of an adult, making them more susceptible to infection.[13] Aging is also characterized by low-level chronic inflammation that contributes to the declining ability of the immune system to respond and regulate the immune response.[14] Stress and, in particular, chronic stress, has been shown to have a significant negative impact on the immune system irrespective of the age of the subject.[15]

The Effect of Age on the Immune System

Immune Response in Neonates

Neonatal immune responses tend not to be as strong as those in an adult animal.[16] In beagle pups between the ages of 0 to 4 weeks, mitogenic responses (a measure of how immune cells would respond during an immune challenge) were shown to be significantly lower than those in an adult animal.[17] Somberg *et al* found that the *in vitro* lymphocyte proliferation activity (also a measure of the immune response like the one above) of newborn pups was 50% lower than that of the adult.[18]

Although neonates are capable of responding to an immune challenge, their immune responses tend to exhibit a T-helper type 2 (Th2) bias.[13] A T-helper type 1 (Th1) immune response is characterized by proinflammatory cytokines such as interferon (IFN)-γ, interleukin (IL)-6, and TNFα, and hence is more effective in preventing infectious diseases. In contrast, a Th2-biased immune response is predominated by antiinflammatory cytokines such as IL-10, IL-4, and tumor growth factor (TGF) β and is not as effective in dealing with microbial infections, making neonates more susceptible to infections.

There are several cellular and molecular reasons for this Th2 bias. These include

1 As compared with adult cells, neonatal antigen presenting cells (APC) are less efficient in antigen presentation because of their reduced capacity to express crucial costimulatory molecules CD86 and CD40 and upregulate MHC class II molecules.
2 The feto-placental environment tends to be immunosuppressive and Th2 biased because of locally acting cytokines and hormones, and these influence neonatal immune responses.[13]

3 Neonatal B cells, which also function as APC, have altered signaling due to lowered MHC class II molecules as well as lowered accessory signaling molecules. Lack of upregulation of CD40 (accessory signaling molecules) and CD40L (receptor for CD40) tends to dampen B-cell response as well as its ability to class switch immunoglobulin (Ig) production contributing to the Th2 bias.
4 Neonatal Th-1 cells undergo apoptosis because of the unique receptors they express. In a recent study, Lee and coworkers showed that although a primary immune response from neonatal T cells includes a significant Th1 component, the Th1 cells generated have unique characteristics. They tend to have high levels of IL-13Rα1, which heterodimerizes with IL-4Rα. As the immune response progresses, because of the lack of appropriate dendritic cells (DC), the immune response is dominated by IL-4, which binds the IL-13Rα(1)/IL-4Rα complex expressed on the Th1 cells and induces apoptosis, eliminating the Th1 cells, which results in a Th2 bias. As the neonate ages, a significant number of appropriate DCs start accumulating, especially in the spleen. These DCs produce IL-12, and this IL-12 triggers the downregulation IL-13Rα 1 on the Th1 cells, rescuing them from IL-4–induced apoptosis.[19]

Immune Response Changes with Aging

Aging brings changes to both the humoral and cellular immune responses. These include defects in the hematopoietic bone marrow and defects in lymphocyte migration, maturation, and function. Aging also involves involution of the thymus, which contributes to loss of immune function with increasing age.[20]

With age, the immune system loses plasticity, resulting in lowered response. Immune plasticity is the ability of the immune system to remodel itself to respond appropriately to danger signals, which include pathogens, tissue damage, and oxidative stress, and return to a quiescent state once the danger has passed. One of the reasons for this declining immune plasticity is chronic metabolic stress associated with aging.[21] This results in reduced immune response and a lower cellular capacity in DNA repair, leading to a condition described as immunosenescence, which increases the risk of age-related diseases, i.e., cancer and infection.[22,23] Declining immune plasticity leads the cells of the immune system to undergo cell death or necrosis triggered by oxidative stress.[24]

Age (life stage) of the animal has a significant impact on immune status and is one of the important reasons to consider nutritional strategies to address immune system effectiveness.

Naturally Occurring Stress

Naturally occurring stress, both physical and mental, has a significant negative impact on the immune system, irrespective of age. Both major and minor stressful events have been shown to have a profound influence on immune responses in both animal and human studies. One of the hallmarks of chronic stress is the general increase in levels of oxidative stress, and oxidative stress gradually erodes immune plasticity. Research in this area has spawned a new discipline called psychoneuroimmunology—the study of the interaction between the psychological process and the nervous and immune systems.[25] Using vaccine responses as an indicator of immune status,[26-31] researchers have demonstrated that among medical students taking exams, stress levels lowered immune response to vaccine (virus-specific antibody and T-cell responses to hepatitis B vaccine were lower), whereas the degree of social support increased vaccine response.[32] Another good example of chronic stress is the stress associated with caregiving for a spouse with Alzheimer's disease, which was associated with a poorer response to an influenza virus vaccine when compared with well-matched control subjects.[28] Vaccine responses demonstrate clinically relevant alterations in an immunological response to a challenge under well-controlled conditions and therefore can be used as a surrogate for responses to an infectious challenge. Individuals who respond poorly to vaccines tend to have greater susceptibility to the pathogens when compared with those with better vaccine responses. Burns and coworkers, among others, have shown that adults who show poorer responses to vaccines also experience higher rates of clinical illness, as well as longer-lasting infectious episodes.[33,34] Cohen and coworkers showed that human volunteers who were inoculated with 5 different strains of respiratory viruses showed a dose-dependent relationship between stress and clinical symptoms observed after infection.[35] Therefore, from these vaccine studies, it is clear that stress puts individuals at greater risk for more severe illnesses.

At the molecular level, stress delays inflammation by reducing efficiency of CD62L-mediated immune surveillance by phagocytes.[36] Stress decreases IFN-γ secretion by lymphocytes and may decrease antigen presentation efficiency by downregulating MHC class II molecule expression on APCs, and delay or impair immune response.

Hormones play an important role in effect of stress on the immune system. Stress sets into motion those physiological changes that help the organism cope with the stressor—the fight-or-flight response. However, chronic stress results in sustained activation of stress responses, which include activation of the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary axis, resulting in the production of glucocorticoid (GC) hormones and catecholamine. GC receptors are expressed by a variety of immune cells that bind cortisol, interfering with nuclear factor-κB function, which in turn regulates the activity of cytokine-producing immune cells. Sustained release of stress hormones negatively impacts the immune system. Several models have been proposed to explain the mechanism of action of stress hormones on the immune cells.[37] GC impacts expression of cytokines, costimulatory molecules, and adhesion molecules, which influences immune cell migration, differentiation, proliferation, and effector function.[38-40] Adrenergic receptors bind epinephrine and norepinephrine and activate the cAMP re-

sponse element-binding protein, inducing the transcription of genes that encode a variety of immune-response genes including genes for cytokines. Elevated levels of catecholamines produced during stress can modify immune-response genes.[41] Natural stress is another key factor that can negatively impact the immune status of an animal irrespective of its age.

Age and natural stress can clearly undermine the immune status in an otherwise healthy animal. Immunodeficiency, irrespective of its etiology, can severely undermine the health of the animal, triggering debilitating diseases such as infections, malignancies, as well as autoimmune diseases. Hence, there is a critical need to evaluate immune status and address deviations, which if managed effectively, can significantly enhance the quality of life.

How Can Diet Influence the Immune System?

The Gut Is the Largest "Immune Organ"

Besides being the gateway for nutrient intake, the gut is the largest immune organ, containing over 65% of all the immune cells in the body and over 90% of all Ig-producing cells.[42,43] In an adult human, the intestine contains 3-fold greater Ig-producing cells (about 7×10^{10}) as compared with the bone marrow (2.5×10^{10}).[44] It is estimated that a total of ~3 g of secretory IgA is secreted daily into the lumen of an adult human.[45] Thus, a significant part of the immune system can interact with what we eat or feed our pets.

Gut-associated Immune Tissue Plays an Important Role in Development of the Immune System

Research conducted with germ-free animals has documented that stimuli from the environmental antigens, especially microbiota in the gut, are essential for the development of a healthy immune system (JJ Cebra, 1999). Germ-free animals tend to have a very underdeveloped immune system, clearly underscoring the role played by symbiotic microflora and associated environmental antigens. The gut-associated lymphoid tissue (GALT) therefore offers unique opportunity for immunomodulation via diets. The GALT is unique in its ability to be exposed to a diverse array of antigens from foods (roughly 10-15 kg/year/human) and from over 1000 species of commensal microorganisms (10^{12} mL/mL of colon content, making them the most numerous cells in the body) and yet remains quiescent until it encounters a threat, such as a pathogen. This is initiated by molecules called pathogen-associated molecular patterns (PAMPs) expressed by microbial pathogens. PAMPs are highly conserved motifs present in these microorganisms and include LPS from the Gram-negative cell wall, peptidoglycan, lipotechoic acids from the Gram-positive cell wall, the sugar mannose (common in microbial glycolipids and glycoproteins but rare in mammals), bacterial DNA, N-formylmethionine found in bacterial proteins, double-stranded RNA from viruses, and glucans from fungal cell walls. Most dietary immune-modulating strategies involve targeting PAMP receptors of the GALT using appropriate ingredients.

Efficient Antigen Presentation Is Fundamental for Efficient Immune Response

Efficient antigen presentation to T lymphocytes by the APC-like macrophages is a prerequisite for an effective immune response. APCs set the tone of the immune response by the costimulatory molecules they express and the cytokines they secrete. APC function is central to the altered immune response that is characteristic of the neonatal immune system, the immune response of an aging immune system, and the immune response during stress. In all 3 cases, because of the lack of immune-potentiating cytokines such as IL-1 and IL-12, APCs responding to an immune challenge are not able to upregulate MHC class II molecules and costimulatory molecules such as CD86. Lack of these cytokine signals also modifies the immune response, reducing its efficiency and giving it a Th2 bias. The resulting immune response therefore tends to be not as efficient. The approach to address this deficiency hinges on providing the required signaling to the APCs.[46] Receptors on immune cells present in the gut serve this function and are the primary targets of strategies for immunomodulation via diet. These receptors have evolved to respond to molecules in microbial pathogens collectively known as PAMPs (described in paragraph above). Examples include yeast β-glucans,[47] yeast mannans,[48] and nucleic acids.[49] Probiotics interact with the immune system by virtue of their PAMPs' molecules such as LPS.[50] These molecules, also referred to as immune response modifiers (IRMs), primarily initiate a local proinflammatory cytokine secretion that activates local APCs to upregulate MHC class II and costimulatory molecules, enabling them to be present antigen efficiently to T lymphocytes. IRMs provided by diet enhance APC efficiency, and APCs in the gut continually process and present antigens to T lymphocytes in the GALT. Although the GALT is quiescent to the myriad antigenic stimuli it receives via diet, when it encounters a pathogen it is able to initiate a more efficient immune response.

The enhanced immune activity induced by dietary IRMs in the GALT (mucosal immune system) spread to the entire immune system by the trafficking of activated lymphocytes and cytokines and the significant overlap with the nonmucosal immune system.[51]

Nutrition Interacts with the Immune System at Multiple Levels

Nutrition and the immune system interact at multiple levels and, for simplicity, can be considered in a framework of 4 stages. Stages I and II are passive because they involve providing the immune system with essential nutrients. Stages III and IV focus on modifying the immune response using agents such as IRMs that primarily target the PAMP receptors in the

gut and involve more active approaches in enhancing immune status.

Stage I: Complete Nutrition

At the first stage, the focus revolves around dietary energy, protein, vitamins (vitamin A, C, and E), and minerals such as zinc, magnesium, iron, etc.[52] Minerals such as Ca+ and Mg+ drive signaling mechanisms in the immune system and are therefore also important for enhanced immune response. Providing basic nutrition is the very least that we can do for the immune system.

Stage II: Optimizing Macro and Micro Nutrients

The second stage involves optimized key nutrients that are critical for the immune cells. The immune system has a need for certain nutrients, and providing greater amounts of these key nutrients will optimize immune function. A temporary deficiency of a key nutrient can negatively impact the immune system. For example, during strenuous exercise, muscle cells preferentially use glutamine as their energy source and, as a result, there is a reduction of glutamine levels in circulation. Glutamine is also the preferred energy source for immune cells, and because of low levels of glutamine in circulation following strenuous exercise, immune cells cannot function efficiently if challenged, making these athletes vulnerable to infections immediately after vigorous bouts of exercise.[53]

Key ingredients needed for a healthy immune system would include higher levels and higher quality proteins in diet. At a molecular level, proteins make up the structural components and mediate key processes of the immune system. Receptors, cytokines, Ig, complement components and bactericidal proteins are all proteins. A source of high-quality protein in diets is therefore important for a healthy immune system. Vitamins (vitamin A, C, and E) and minerals such as zinc, magnesium, and iron are critical for the immune system. For this reason, dietary products for companion animals often exceed the required minimum for dietary energy, proteins, vitamins, and minerals.

Addressing oxidative stress and subsequent damage to cellular DNA is another example of this strategy. Aging, along with other environmental stressors, tends to increase the levels of oxidative damage to cellular DNA, including immune cells. Cells have the ability to repair damage in response to injury or stress. However, beyond a point, the damage can be irreparable and results in cell death by apoptosis. Oxidative DNA damage due to free radicals produced during cellular metabolism is one of the primary causes of cell death.[54] Increased apoptosis can break immune tolerance to self-antigens resulting in autoimmunity.[55] Immunosenesence is characterized by a decreased response to mitogens and decreased cytokine production, and changes in signal transduction have been associated with aging (reviewed in[52]). Various strategies can help to address senescence, tissue damage, and apoptosis associated with aging, including the following:

1) Caloric Restriction Apart from increasing the lifespan,[56] data from laboratory animals have demonstrated that caloric restriction (CR) reduces immunosenescence.[57] Recent data from a CR study conducted in Labrador retriever dogs clearly show that CR can help retard immunosenescence.[58] A CR diet will help aging animals maintain a healthier immune system.

2) Antioxidants Increased levels of antioxidants such as vitamin C (R Anderson and coworkers, 1990), vitamin E,[52] and carotenoids (β-carotene, α-carotene, lycopene, astaxanthin, etc.) can help prevent damage mediated by free radicals. There are a number of reports documenting the benefits of carotenoids in dogs, particularly in older animals.[59-61]

3) Prebiotics Prebiotics that help maintain normal gut flora also fall into this category. Intestinal microflora play an important role in keeping the immune system primed to prevent colonization by pathogenic microbes. However, under certain conditions, such as after an antibiotic therapy, gastrointestinal infections, stress, or old age, the normal flora in the gastrointestinal tract is perturbed, leading to a change in the bacterial flora due to overgrowth of harmful bacteria (e.g., *Clostrodium difficile*). Prebiotics such as inulin help maintain a healthy commensal population in the gut under stress.[62]

The first 2 stages are passive approaches in "immunonutrition." These are passive because they focus on providing dietary energy, protein, vitamins, minerals, and antioxidants and manage caloric intake to help the immune system function optimally. Stages III and IV are considerably different and involve a more proactive approach at managing the immune system to obtain the desired outcome.

Stage III Active Modulation of the Immune System

In Stage III, the emphasis is on active interaction with the immune system to modulate its function toward a desired goal. Examples would include:

1) Reversing the Th2 Bias and Restoring Th1 Response by Enabling Efficient Antigen Presentation A Th1 (pro-inflammatory) response is important for protection against microbial infections. The Th1 component of the immune system is boosted by stimulating the immune system with probiotic bacteria or PAMP-expressing moieties (e.g., yeast β-glucans). Probiotics (*Enterococcus faceum*, *Lactobacilli* sp., *Bifidobacteria* sp., etc.) in diet have been shown to enhance immune status in dogs.[63] Milk bioactives from bovine colostrum have been shown to have immune-enhancing effects in both human and murine studies, making bovine colostrums an interesting immunomodulating ingredient. Colostrum (and whey protein, which has a very similar composition) contains Igs, cytokines, lactoferrin, and lactoperoxidase, each of which can influence the immune system.[64] Mice that were fed milk bioactives produced significantly higher serum and intestinal

antibodies to several antigens (influenza virus, diphtheria and tetanus toxin, poliomyelitis vaccine, ovalbumin and cholera toxin subunit).[65] In another study, mice fed milk bioactives had enhanced resistance to pneumococcal infection.[66,67] In in vitro studies conducted with human monocytes, Biswas and coworkers[68] report that coculture with bovine colostrum without antigenic stimulus induced a dose-dependent production of IL-12 by CD14+ monocytes, but did not induce IFN-γ production. Interestingly, in the same study, bovine colostrum differentially affected stimuli-induced IFN-γ production; it enhanced IFN-γ in response to weak antigenic stimulation and it inhibited IFN-γ in response to strong antigenic stimulation. As discussed earlier, IL-12 and IFN-γ are cytokines involved in the Th1 polarization required for a successful immune response toward intracellular pathogens, such as bacteria and viruses. In a clinical study conducted in a highly trained cyclist, low-dose bovine colostral protein concentrate supplementation favorably modulated immune parameters during normal training and after an acute period of intense exercise, which contributed to lowering the incidence of upper respiratory illness.[69] In a research study conducted with adult dogs,[70] we evaluated the immune-enhancing effect of bovine colostrum. Our results demonstrate that adding bovine colostrum significantly enhanced their immune status as measured by their response to canine distemper vaccine as well as increased level of GALT activity measured by IgA production. Colostrum-supplemented diets also enhance immune status in cats as evidenced by increased rabies vaccine response and increased GALT activity also measured by IgA production.[71] Stimulating the immune cells in the gut likely leads to a cascade of immune cell activation, which results in the secretion of cytokines that reach the rest of the immune cells via circulation and results in overall activation of the immune system and an increase in the production of IgA in the gut.

2) Better Management of Inflammation Will Prevent Further Damage Chronic inflammation is central to the pathophysiology of a number of diseases, including cardiovascular diseases and neurological diseases (Alzheimer's, impaired cognition).[72] Physiologically, the effects of inflammation are mediated by prostaglandins and leukotries, all end products of the arachadonic acid metabolism. A diet rich in docosahexaenoic acid and omega-3 fatty acids can control the damaging effects of inflammation because of the reduced levels of active prostaglandins and leukotries, and can be an effective strategy in addressing the effects of chronic inflammation. Reduced inflammation not only improves quality of life by preventing a number of cardiovascular and neurological diseases but also helps prevent autoimmunity by reducing exposure of the immune system to self-antigens.

Stage IV Personalized Nutrition: Predictive, Preventive, and Personalized Nutrition

Interaction between diet, environment, and genome ultimately defines health status and can be critical in influencing chronic disease.[73-76] Over the last few decades, the science of pharmacogenomics, which deals with the genetic basis underlying disease susceptibility and variable drug response in individuals, has brought about a paradigm shift in the pharmaceutical industry by moving it from a "one drug fits all" approach toward personalized therapy. This process has been greatly accelerated by advances in the -omics fields: single nucleotide polymorphism analysis, transcriptomics (complementary DNA analysis), proteomics, and metabolomics. A good example of genetic variability affecting disease is breast cancer therapy with the drug trastuzumab (Herceptin, a humanized monoclonal antibody against the HER2 receptor developed by Genentech Inc.) linked to HER2 overexpression. Individuals expressing low levels of HER2 receptor respond poorly to Herceptin.[77,78] Another example is the influence of genetic variability on cytochorome P450 monooxygenase system enzymes (P450 family of enzymes are important for the metabolism of most drugs) and drug toxicity in individual patients.[79]

The concept of "personalized medicine" is now being explored in nutrition. Although personalized nutrition is still in its infancy, it is practiced in principle as in dietary management of diabetes or maintaining a healthy lipid profile to manage risk of cardiovascular disease. For a practical personalized diet strategy, there are 2 basic requirements: a clear understanding of the disease pathogenesis and the availability of cheap and reliable disease biomarkers to identify either susceptibility or diagnose disease. Biomarkers are an objectively measured characteristic that is an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention. The ultimate goal here is to modify physiology through personalized dietary regimen before the animal enters into the disease continuum, preventing disease or at least delaying the onset of disease significantly and thereby enhancing quality of life.

Induction of a local Th2 bias in animals with inflammatory bowel disease using dietary means is an example of a targeted approach to immunomodulation. Probiotic microbes have been characterized based on the cytokines' responses they induce. Certain bacteria induce secretion of antiinflammatory cytokines such as IL-10, TGF-β, and IL-13 (D Ma and coworkers, 2004). These probiotic agents give us the opportunity to explore probiotic-fortified diets that will help animals with inflammatory bowel diseases. Similarly, TGF-β–rich ingredients such as colostrum and whey proteins are being increasingly used to effectively address localized inflammatory conditions in the gut, especially with diets for inflammatory bowel diseases.

In summary, as research advances in understanding complex physiological networks in health and disease, the role played by the immune system and its interaction with diet take a whole new meaning. As our understanding of the relationship between nutrition and the immune system matures, a variety of diet-based approaches to address immune needs will become available— both for us and our pets. The food we eat and feed our pets can clearly deliver several other

benefits beyond basic nutrition and therein lies the promise of immunonutrition.

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