An immunologist’s perspective on nutrition, immunity, and infectious diseases: Introduction and overview

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Primary Audience: Poultry Nutritionists, Immunologists, Veterinarians, Researchers

SUMMARY

The immune system is a multifaceted arrangement of membranes (skin, epithelial, and mucus), cells, and molecules whose function is to eradicate invading pathogens or cancer cells from a host. Working together, the various components of the immune system perform a balancing act of being lethal enough to kill pathogens or cancer cells yet specific so as not to cause extensive damage to “self” tissues of the host. A functional immune system is a requirement of a healthy life in modern animal production. Yet infectious diseases still represent a serious drain on the economics (reduced production, cost of therapeutics, and vaccines) and welfare of animal agriculture. The interaction involving nutrition and immunity and how the host deals with infectious agents is a strategic determinant in animal health. Almost all nutrients in the diet play a fundamental role in sustaining an optimal immune response, such that deficient and excessive intakes can have negative consequences on immune status and susceptibility to a variety of pathogens. Dietary components can regulate physiological functions of the body; interacting with the immune response is one of the most important functions of nutrients. The pertinent question to be asked and answered in the current era of poultry production is whether the level of nutrients that maximizes production in commercial diets is sufficient to maintain competence of immune status and disease resistance. This question, and how to answer it, is the basis of this overview. Clearly, a better understanding of the interactions between the immune signaling pathways and productivity signaling could provide the basis for the formulation of diets that optimize disease resistance. By understanding the mechanisms of nutritional effects on the immune system, we can study the specific interactions that occur between diet and infections. This mechanism-based framework allows for experiments to be interpreted based on immune function during an infection. Thus, these experiments would provide a “real world” assessment of nutritional modulation of immune protection separating immune changes that have little impact on resistance from those that are truly important. Therefore, a coordinated account of the temporal changes in metabolism and associated gene expression and production of downstream immune molecules during an immune response and how nutrition changes these responses should be the focus of future studies. These studies could be answered using new “-omics” technologies to describe both the local immune environments and the host-pathogen interface.

Key words: nutrition, avian immunity, infectious disease, nutrigenomics

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DESCRIPTION OF PROBLEM

This paper is not a review of nutritional impact on the avian immune system. There are several recent reviews that do a much more thorough job than can be approached here [1–5]. However, we will use Klasing’s unique perspective on this topic as presented at the Gordon Memorial Lecture on “Nutrition and the Immune System” to the World Poultry Science Association (United Kingdom branch) as the basis for this overview of the topic [3].

The US poultry industry is the most productive in the world, with 15 million metric tons of broiler meat produced in 2004. The industry is fully integrated and supports the intensive production of 8 billion birds annually. The production of a large volume of meat that meets consumer demands requires birds to be grown intensively at high population densities. In part, because of these intensive rearing conditions, infectious diseases remain a threat to the poultry industry. Infectious diseases represent a serious drain on the economics (reduced production, cost of therapeutics and vaccines) and welfare of animal agriculture. The outcome of a host-pathogen encounter is determined by virulence factors of the pathogen and defense factors of the host.

From an immunologist’s point of view, the amount of information on poultry nutrition is vast when compared with the field of avian immunology, which is essentially in its infancy. For example, many required nutrients have been identified, the concentrations of these essential nutrients in feedstuffs and their availability to the bird are known, and minimal concentrations of many nutrients required for maximum production have all been defined. However, when this information is applied to the interactions of nutrition (diet) and immune status, the outcome is less definitive. To be sure, it has been shown that almost all nutrients in the diet play a fundamental role in sustaining an optimal immune response, such that deficient and excessive intakes can have negative consequences on immune status and susceptibility to a variety of pathogens. However, based on the current literature, the pertinent question to be asked and answered in the current era of poultry production is whether the concentration of nutrients that maximizes production in commercial diets is sufficient to maintain competence of immune status and disease resistance. This question and how to answer it will be the basis of this overview. We make no attempt to provide an ultimate answer to the question, but instead provide an outline for future studies that should provide the foundation for the answer to the question. Furthermore, we should all keep in mind that in discussing the interaction of nutrition (diet) on infection and immunity, there is a need to consider the agenda of the bird, determined by its genotype through metabolic and physiologic mechanisms, in developing and maintaining an optimal immune system during an infection.

OVERVIEW OF AVIAN IMMUNE RESPONSE

The immune system is a multifaceted arrangement of membranes (skin, epithelial, mucus), cells, and molecules whose function is to purge a host of invading pathogens or cancer cells. Working together, the various components of the immune system perform a careful balance of being lethal enough to kill pathogens or cancer cells yet specific so as not cause extensive damage to healthy “self” tissues of the host. A functional immune system is a requirement of a “healthy” life in modern animal production.

The foremost function of an immune response is to identify and eliminate infection. The immune system of vertebrates is made up of 2 functional elements, the innate and the acquired, which contrast in their mechanisms of pathogen recognition [6]. The innate system uses germ-line encoded receptors, known as pattern recognition receptors (PRR), that recognize the evolutionarily conserved molecular components {i.e., pathogen-associated molecular patterns (PAMP) of infectious microbes [7–10]}. The acquired response uses highly specific antigen receptors on T and B lymphocytes that are generated by random processes by gene rearrangement [7, 11]. Therefore, the antigen receptors of the acquired immune system can be produced for any given antigen.

Innate Immune Response

The host immune response to pathogens in the earliest stages of infection is a critical deter-
minant of disease resistance and susceptibility. These early responses are dedicated to the containment of the pathogens, holding infections to a level that can be resolved by the ensuing development of acquired immune mechanisms. The innate immune system is a rapidly induced, phylogenetically conserved response of all multicellular organisms [6] that depends on PRR recognition of PAMP on or in major groups of microbes. The PAMP are critical for pathogen replication, survival, or both and are unique to large groups of microorganisms and not host cells, thus providing the host with an efficient, nonself means of detecting invading pathogens. Several well-known examples described are lipopolysaccharides of all gram-negative bacteria, lipoteichoic acids of gram-positive bacteria, double-stranded RNA of RNA viruses, mannans of yeast cell walls, unmethylated CpG motifs of bacterial DNA and not eukaryotic DNA, lipoproteins and peptidoglycans of all bacteria, and the glycolipids of mycobacteria [6–8].

Recognition of PAMP induces various extracellular activation cascades and intracellular signaling pathways, leading to the inflammatory response, recruitment of phagocytic cells for clearance of the pathogens, and mobilization of professional antigen-presenting cells. The PRR are present in 2 separate compartments of the host: cell membranes and cell cytoplasm. The PRR on cell membranes have assorted functional activities, including promotion of phagocytosis, presentation of PAMP to other PRR, and the initiation of major intracellular signaling pathways. Cytoplasmic PRR detect intracellular viruses and bacteria, resulting in the production of type I interferons and activating inflammasomes. Both families of PRR are essential to impart global antimicrobial responses to the host. Each family of PRR is differentially expressed to optimize their ability to respond to a variety of pathogens activating specific intracellular signaling pathways that lead to the release of cytokine profiles specific for particular PAMP.

Recognition of PAMP by PRR, either alone or in heterodimerization with other PRR [Toll-like receptors (TLR), nucleotide-binding oligomerization domain proteins, retinoic acid-inducible gene-I, and C-type lectins], induces intracellular signals responsible for the activation of genes that encode for proinflammatory cytokines, antiapoptotic factors, and antimicrobial peptides [12–14]. Although a certain degree of redundancy exists between signals induced by various PRR, in general, no single PRR is likely to be the sole mediator of activation of the innate immune response. Therefore, a variety of pathogens, each containing different PAMP, can interact with a certain combination of PRR on or in a host cell. The variety of PRR complexes triggers specific intracellular signal transduction pathways that will induce specific gene expression profiles, particularly cytokine/chemokine expression, best suited for the invasive pathogen [15–20]. Furthermore, the induction of cytokine mRNA transcripts is regulated by molecular bridges known as transcription factors. The activation of transcription factors, such as NF-κB, activation protein-1, and interferon regulatory factors 3, 5, and 7, are required step(s) in intracellular signaling that result in changes in gene expression.

Over the last few years, it has become readily apparent that an essential function of the innate immune system is to instruct the lymphocytes to develop a particular effector response to a specific pathogen [6, 11]. Because PAMP are produced exclusively by microbes and not by the host, recognition by host PRR signals the presence of pathogens. The PAMP recognition activates effector mechanisms of innate host defenses, including phagocytosis, the synthesis of antimicrobial peptides, and the induction of respiratory burst and nitric oxide synthase. Furthermore, PAMP induce the expression and production of proinflammatory cytokines and chemokines. These endogenous signals orchestrate the recruitment of leukocytes to the site of infection and regulate the activation of the suitable effector mechanisms by controlling differentiation of T lymphocytes into effector cells of a particular type. Last, and most important, recognition of PAMP by PRR induces the expression of costimulatory molecules by antigen-presenting cells (i.e., natural adjuvant activity) and leads to the development of highly antigen-specific memory cells [6, 8, 21]. The ability of the lymphocytes to differentiate into effector cells is dependent on, and controlled by, signals produced by the cells of the innate system [6, 22]. Thus, it can be seen that adjuvants are primarily PAMP that induce the innate immune
response to produce the required costimulatory molecules that result in protection.

In chickens, heterophils, the avian polymorphonuclear leukocyte equivalent to the mammalian neutrophil, and macrophages ingest and kill a variety of microbial pathogens. Functionally, both cell types exhibit an assortment of cytoskeletal and biochemical activities that include adhesion, chemotaxis, phagocytosis, and the microbicidal activities of degranulation, respiratory burst, or both that can be easily assayed in vitro [23–25]. We have been investigating whether the avian heterophils and macrophages have a more direct contribution to host defenses than their traditional role as professional phagocytes. We have shown that types of phagocytes can be induced to produce proteins that function to regulate inflammatory and immune responses including TLR, nitric oxide, and cationic antimicrobial peptides [26, 27]. Both types of phagocytic cells are also capable of rapid changes in proinflammatory cytokine and inflammatory chemokine gene expression following receptor-mediated phagocytosis [24–26]. Because heterophils and macrophages represent the first cell types encountering and interacting with an inflammatory or etiologic agent, the ability to synthesize and release an array of cytokines provides evidence for their role in both the immunoregulation and pathophysiology of disease.

There are 8 known TLR in chickens (TLR 2, type 1 and type 2, TLR3, 4, 5, 7, 8, 15, and 16, formally 1/6/10) [26–33]. We have found that heterophils constitutively express all 8 known chicken TLR [26]. However, chicken monocytes constitutively express all but TLR5 and TLR8 [34], whereas macrophages constitutively express all but TLR3, 7, and 8 [27–33]. Stimulating heterophils and monocytes with specific TLR agonists stimulates oxidative burst, nitric oxide production, and degranulation [35–38] and induces upregulation of proinflammatory cytokines and inflammatory chemokines [26, 34].

**Acquired Immunity**

The acquired immune response is an inducible response found only in vertebrates. The acquired host defenses, mediated by T (thymus-derived) and B (bursa-derived) lymphocytes, are infinitely adaptable to antigenic response because of the somatic rearrangement of immunoglobulin and T-cell receptor genes to create clones of lymphocytes that express distinct antigen receptors. The receptors on lymphocytes are generated by somatic mechanisms during the ontogeny of each individual and thus generate a diverse repertoire of antigen receptors with random specificities on the lymphocytes. After the elimination of an infection, the antigen-specific clones remain expanded as memory lymphocytes that provide a more rapid response to second exposure to the same antigen. Recognition of an antigen by T or B lymphocytes requires the antigen to be presented bound to cell surface proteins called major histocompatibility complex class I or II and costimulatory molecules [38, 39]. It is important to note that the ability of the acquired response to differentiate self from nonself antigens is not absolute.

Acquired immunity differs from the innate responses by possessing specificity in recognition of foreign invaders (antigens) and the development of memory (i.e., re-exposure to an antigen results in a more rapid response than was elicited during the primary exposure). Acquired immunity is mediated by 2 different types of responses depending on the type of lymphocyte that primarily responds to the antigen: humoral (B lymphocyte) or cell-mediated (T lymphocyte) [39]. Humoral immunity is characterized by the production of antibodies by the B lymphocytes in response to extracellular antigen recognition, whereas cell-mediated immunity is characterized by the recognition of infected or transformed host cells by T lymphocytes. Two types of phenotypically different T lymphocytes perform different effector functions to control the host response: T cytotoxic lymphocytes lyse viral-infected or neoplastically transformed host cells, whereas T-helper cells activate B lymphocytes to produce antibodies, inhibit pathogen proliferation in host cells through the production of effector cytokines such as interferon-γ, and direct further cell-mediated immunity through the production of interleukin-2 [38, 39].

**NUTRITION-INFECTION-IMMUNITY INTERACTIONS**

**Nutrition**

The interaction involving nutrition and immunity and how the host deals with infectious
agents is a strategic determinant in animal health. Traditionally, the nutrition-immune-infection interaction has concentrated on the role of nutrients in upregulating host defenses, whereas the effect of infectious agents has been on host nutritional requirements. Klasing [3] has suggested that to interpret the available and future literature as well as to establish whether changes in diet are beneficial or detrimental, a first-principles approach to experimental design should be adopted. These principles can be categorized as mechanisms by which diet can affect immunity and the response to infections. Simply put, experiments would be designed by evaluating the effect of a diet on 1 of 5 specific immune mechanisms. By understanding the mechanisms of nutritional effects on the immune system, we can study the specific interactions that occur between diet and infections. This mechanism-based framework allows for experiments to be interpreted based on immune function during an infection. Thus, these experiments would provide a real-world assessment of nutritional modulation of immune protection, separating immune changes that have little impact on resistance from those that are truly important. Thus, detailing specific mechanisms of how a diet can affect immunity, one can then evaluate how these mechanisms relate to various nutrients and pathogens. For example, knowing how a diet or nutritional supplements induce temporal changes in host metabolism and the associated function of immune cells and expression of immune response genes during different stages of an immune response could result in the formulation of affordable diets that optimize disease resistance to a variety of pathogenic organisms. Each mechanism provides an applicable hypothesis that can be tested, answered, and these science-based results provided to commercial interests for the development of least-cost diets:

- Substrates for cells of the immune system = what is the priority of immune cells for critical nutrients vs. nonimmune cells? Examples: amino acids as substrates for cytokine production by leukocytes, protein production by liver cells.
- Supplying critical nutrients to pathogens = what nutrients are important for pathogens as well as immune cell function? Examples: iron, biotin.
- Modulating signaling in leukocytes = what nutrients up- or downregulate immune cell function? Examples: vitamin D, polyunsaturated fatty acids for eicosonoid production.
- Protecting against immunopathology = what nutrients can be used to prevent or manage inflammation, or both? Examples: antioxidants such as vitamins E and C for repair of local oxygen radical damage by phagocytes.
- Influencing intestinal dynamics = what nutrients can stabilize microflora that equals optimal growth and health? Example: dietary fiber provides growth substrates for microflora.

**Immunity**

Until recently, one of the main problems in avian immunology with application of the first-principles approach to nutrition-immunity interactions is the lack of understanding and characterization of the specific cellular and molecular mechanisms of the immune response, in particular innate immunity. However, with the clarification of more cellular and molecular avian innate immune pathways, from pathogen recognition by specific cells to the generation of effector peptides and production of inflammatory and regulatory cytokines, the connection between nutrition and immunity can be further delineated. Some recent fundamental discoveries in avian immunology are outlined in Table 1. Thus, the ability to evaluate the effect of diet on specific immune mechanisms can now be evaluated at the cellular and molecular level. We can study the effect of nutritional status on the functioning immune system in practical applications. These include the use of immune parameters to assess the nutritional status of flocks, to evaluate the efficacy of nutritional therapy, and to formulate dietary recommendations to achieve the immune responses needed to prevent specific infectious diseases at the national, regional, or local level. The availability of the chicken genome sequence provides the opportunity to resolve questions concerning the molecular components of the avian immune system. Key developments in molecular, genetic, and cellular biological techniques provide us with new approaches to
use the genome to investigate the nutritional effects on functional genomics (the study of how and why a given gene behaves in a certain way under specific conditions), pathogenomics (the study of how genes behave when pathogens interact with their host) of the avian innate response to pathogens, and also to develop and apply the specialized field of nutrigenomics (the study of the influence of nutrition on gene and protein expression) to poultry production.

**CONCLUSIONS AND APPLICATIONS**

1. Almost all nutrients in the diet play a fundamental role in sustaining an optimal immune response, such that deficient and excessive intakes can have negative consequences on immune status and susceptibility to a variety of pathogens.

2. Dietary food components can regulate physiological functions of the body, and interaction with the immune response is one such important function of nutrients.

3. Although an optimal immune response depends on various circumstances in the host (phenotypic quality, exposure to multiple stressors, infection status, nutrient intake), the immune system has a priority in the partitioning of nutrients at critical times during infections.

4. Simply adding one nutrient to prevent infection by a single organism is obsolete and expensive, and potentially increases the susceptibility of the birds to another pathogen.

5. The immune system is regulated by factors other than simply the degree of antigenic stimulation and immediate nutrient supply, as evidenced by the fact that if a strong immune response were resource-cheap, then all hosts would be expected to respond vigorously to an infection.

6. Clearly, a better understanding of the interactions between the immune signaling pathways and productivity signaling, for example, food intake, could provide the basis for the formulation of diets that optimize disease resistance.

7. Although nutrients can modulate immune function, nutrient status and intake must also be considered in immune response studies during infection. Variations in nutrient uptake undoubtedly contribute to variations in immune responsiveness to pathogens between individual birds and possibly between groups of birds.

**REFERENCES AND NOTES**


