Immunometabolic considerations with regard to the domestic chicken, *Gallus gallus*

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Implications

- The term "immunometabolism" is a recently coined expression that has its origins in the foundations of and synergy between homeostasis, a prioritized partitioning of nutrients to organs, internal body surveillance, and regulatory endocrine, immune, and microbe/metabolite feedback loops.
- The modern production broiler chicken is a model for immunometabolism geared toward accelerated reaction and performance in parallel with and necessary for the greatly enhanced genetic programming for growth and tissue/protein accretion.
- Continued discovery of host–microbe–metabolite interactions will better define critical control points in immunometabolism that can be exploited to improve both natural production efficiency as well as welfare optimization opportunities.

Key words: gut microbiome, immunometabolism, nutrient partitioning, nutrient sensing

Introduction

The first real literature usage of the term "immunometabolism" aligning immune status with metabolism can be tracked back to about 2011 (Mathis and Shoelson, 2011). However, the principles underlying this association were, in fact, articulated as far back as the late 1800s with clinical observations regarding disease and infection impacting metabolic issues and vice versa. For the most part, all physiological processes are, in some manner, energy and metabolism dependent. Also, all animal life that has evolved on earth has done so because of the developed capacities to defend against perturbations. As such, it is natural that this defensive, what we now call immune, capability evolved coordinately with metabolic capabilities (Hotamisligil, 2017). Discovering the signals coordinating between these two capabilities led to the present use of the term immunometabolism. A focus on immunometabolism in the chicken, *Gallus gallus*, suggests that it is a rather unique research model for immunometabolic relationships, is essence, a biology genetically geared toward high rates of growth and whole-body protein accretion as well as one of the highest feed efficiencies to be found in production animals but also challenged to maintain the high efficiency in the face of immune challenges that otherwise would divert nutrients from growth to survival measures. Factors relevant to chicken immunometabolism warrant elaboration.

Evolution of the Principles Underlying Immunometabolic Crosstalk

Across the immunometabolic response spectrum, one underlying concept has been consistent as an endpoint. This concept was put forward back in 1944 by Sir John Hammond in a short, though vital, paper describing a model to explain the priority with which different tissues in the body get "access" to nutrients to carry out the prescribed biological processes as a function of age, or development, or physiological/functional need. He termed this the "priority of nutrient partitioning" (https://journals.sagepub.com/doi/abs/10.1177/001789694700500405). At the time, he related these priorities back to purpose of the fundamental organ systems and their relationship as a hierarchy based on metabolic rate and with further considerations of reproduction and species survival capabilities: thus brain and central nervous system > viscera > muscle > fat, in general, with the highest priority yielding to change in the female in concert with pregnancy and placental demand, the fetus, and subsequent lactation. In that first model, regulatory mechanisms mediating the nutrient distributions were largely unknown and missing. More recently, our laboratory filled in some of the information gaps in that model (Elsasser et al., 2012) adding the "endocrine–immune gradient" (endocrine/hormone and immune/cytokine), a crosstalk mechanism regulating the extent to which nutrients could be "assigned and reassigned" to tissues as need demanded. In the young growing animal, during stress, the crosstalk between these endocrine and immune components serves to rapidly and proportionately

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(in respect to the intensity of the stress) shift metabolism from anabolic to anti-anabolic to catabolic, and the impacts on a given tissue bed would vary with the capability of that tissue to assimilate or give up nutrients for survival purposes. The immune component should be, in fact, viewed as variable in its priority status; in states of relatively good health the energy needs of the system are low but increase (activated state) significantly with sensed perturbation with a redirected higher priority of nutrient. Metabolically, for example, infection calls for robust activation of immune cells and amplification of defense mechanisms or hypothalamic readjustment of thermoregulation to generate fever (energetics studies suggest that basal metabolism increases 10% for every 1° rise in body fever temperature); all occurring perhaps at a time when voluntary feed intake and nutrient load is decreased.

Modeling Immunometabolism in the Growing Broiler Chicken

To provide a more complete model, Figure 1 was generated as a representation of immunometabolism in the broiler. The key to understanding this model is that the regulation of immunometabolism can be represented by the extensive communication that exists between the animal's endocrine and immune systems in addition to the contributions of the gut microbial populations, the microbiome (figure bottom: "Endocrine–Immune–Microbiome Gradient"). The major organ/tissue systems considered in broad categories are the neural immune, visceral organs, muscle, and adipose. For simplicity, a "basal" growth and accretion state for broilers is considered that wherein the optimal rates of tissue accretion occur in conjunction with the highest feed efficiency for a given diet and age; stresses on physiological systems, proinflammatory and pathogenic signals in particular, activate the immune system with commensurate changes (decreases) in growth. Visceral organs, the intestine in particular, are highly metabolically active accounting for as much as 20% of body O_2 consumption though only a fraction of the total bodyweight. With the high priority for the gut to transform feed into metabolites and get these nutrients into the body for distribution, assimilation, and energy supply, these tissues are assigned (as a result of differential tissue accretion experiments) a relatively high priority to obtain their own nutrients whereas adipose tissue accretion has a rather low priority since fat is deposited largely in states of nutrient/energy excess. In times of pathology, growth takes a lower physiological priority to survival as imparted on the animal body by the immune surveillance system and defense responses. As such, immune tissue components rapidly

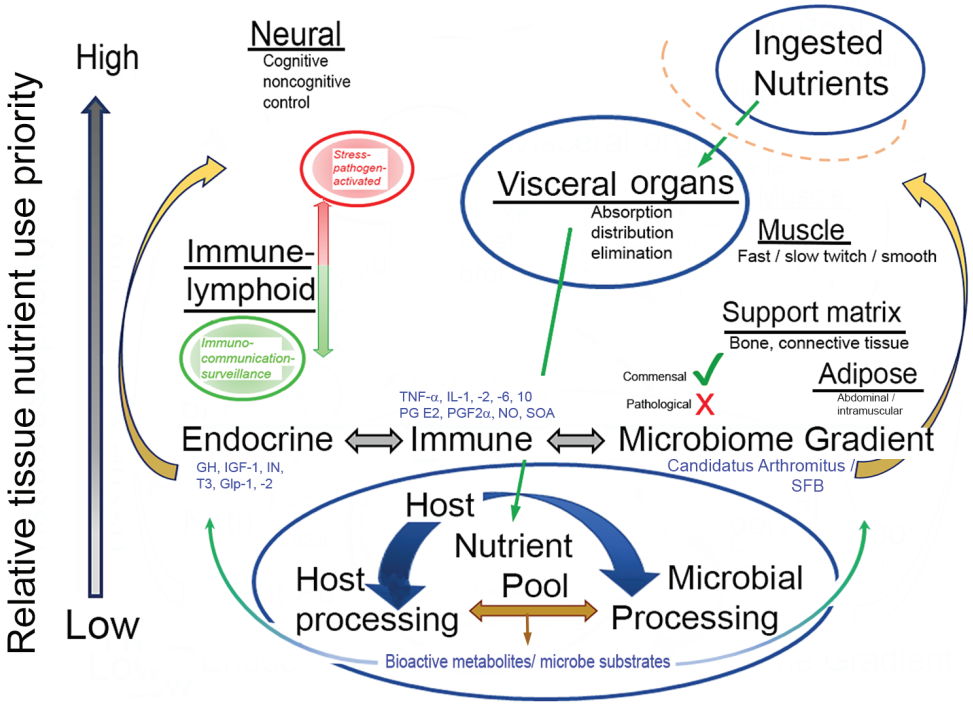


Figure 1. Crosstalk between the endocrine and immune systems with input from microbial and bioactive metabolite milieus constitute the immunometabolic axis and sets the priority for tissues to access nutrients in times of good health and periods of stress. Different tissues have different priorities depending on the (a) availability of diet nutrients (top right) and (b) the relative "physiological importance" of a tissue in the course of survival and reproductive capability (underlined tissues/organs). Note that neural tissues are the top priority and function with degrees of independence from the regulatory gradient elements. The immune system (left red and green balloons) varies in its priority changing from a state of low nutrient demand during health and general surveillance and increasing in proportion to the severity of detected health/stress threats. Host and microbial processing of digesta (bottom) shapes the metabolite milieu yielding bioactive metabolites that feedback on the endocrine, immune, and microbial systems: Elaboration of bacterial components like Candidatus Arthromitus directly modify immune function. Effectors in the various systems include Endocrine: GH (growth hormone), IGF-1 (insulin-like growth factor and the associated binding proteins), insulin (IN), T_3 (triiodothyronine), Glp (glucagon-like peptides)-1, -2. Immune: TNF-α (tumor necrosis factor-α), IL (interleukin)-1, -2, -6, -10, PG (prostaglandin) E_2, $F_2α$, NO (nitric oxide), SOA (superoxide anion).

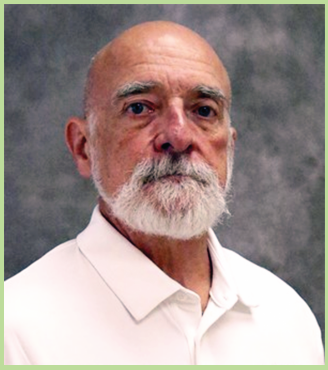
gain priority from a relatively low surveillance state to an activated robust metabolic response, muscle accretion of protein may be decreased, and fat may be mobilized to provide energy substrates.

Presently, nutrient signaling as a part of immunometabolism is not just a matter of feed composition but rather the complex matrix of the digesta as it is processed in its flow down the intestinal tract yielding bioactive metabolites that can provide signaling to all aspects of the immunometabolic regulatory gradient. Most recently, immunometabolic regulation mechanisms (sensing and signaling metabolite outputs associated with nutrient sensors like the "mechanistic target of rapamycin" receptor) were associated with specific microbe–host enzyme-derived metabolism, that is, kinome array analysis (Bortoluzzi et al., 2021). New to the nutrient priority/partitioning model, the role of the host–gut microbiome bidirectional communication shapes the metabolite milieu as a function of where in the intestinal tract the various digestive enzymes, host or microbial, exist. Changes in the gut microbiome occur as a result of diet changes as well as host-derived "signals" that in conjunction with the metabolite milieu and oxygen status of a given gut segment create microenvironments optimal for different bacteria to proliferate and thrive. If the microbial community is balanced and in concert with the host's needs, the microbial state is referred to as eubiosis; disruptions to this host–metabolite–microbe balance is termed dysbiosis. Dysbiosis, sensed within the gut immune cell/enterocyte architecture, and the ensuing immunometabolic response occur as somewhat mutually graded responses where, most often, the degree to which dysbiosis "turmoil" exists aligns closely with gut inflammation and the intensity of the immune activation presenting changes in both microbe–host metabolite processing and proportional decreases in growth.

Stresses ranging from pathogenic microbe emergence to social to behavioral or environmental have significant consequences on the broiler in regard to voluntary intake; with reduced stress-associated intake, there develops a less than optimal presentation of nutrients to the gut to support an optimal microbiome, a stabile quiescent immune system, and proscribed genetic potential for growth. In the immunoendocrine crosstalk component of the model, many times the elaboration of proinflammatory cytokines or prostaglandins decrease secretion levels of anabolic growth-facilitating hormones or block signal transduction pathways through which the anabolic hormones act—nutrient-sparing actions.

Finally, new observations on microbiome composition indicate another important aspect of immunometabolism—the ability for specific bacteria to modify microbial environments by inducing immune responses. A further example of immunometabolic crosstalk can be observed in the ileum as a result of diet–digesta component regulation. Recent data clearly show that specific metabolites and differing bacterial populations modify the abundance of the epithelial cell-attached Candidatus Arthromitus, a segmented filamentous bacteria that modulate adaptive and innate immunity via TH-17 immune cell pathway (Hedblom et al., 2018) and trigger host cells to secrete factors that disfavor microbes that correlate with dysbiosis, inflammation, pathogenesis, and disease.

About the Author



Ted Elsasser is an endocrinologist working in the field of interactions between the innate immune system and endocrine regulation of growth and tissue accretion. His larger background includes areas of microbiology, protein chemistry and molecular modeling, animal nutrition, and mechanisms underlying inflammation at the cellular and molecular level. Animal models for integrative inflammation biology include beef cattle, dairy cattle, swine and poultry. **Corresponding author:** teddoge@gmail.com

Conclusion

Immunometabolism as a subdiscipline of physiology is evolving. Significant to the chicken, immunometabolic processes toward homeostasis and preserving the intense drive for growth are robust and rapid, incorporating significant coordination between regulatory compartments consisting of endocrine, immune, metabolomic, and microbial systems.

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