

Role of diet-microbiota interactions in precision nutrition of the chicken: facts, gaps, and new concepts

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ABSTRACT In the intestine, host-derived factors are genetically hardwired and difficult to modulate. However, the intestinal microbiome is more plastic and can be readily modulated by dietary factors. Further, it is becoming more apparent that the microbiome can potentially impact poultry physiology by participating in digestion, the absorption of nutrients, shaping of the mucosal immune response, energy homeostasis, and the synthesis or modulation of several potential bioactive metabolites. These activities are dependent on the quantity and quality of the microbiota alongside its metabolic potential, which are dictated in large part by diet. Thus, diet-induced microbiota alterations may be harnessed to induce changes in host physiology, including disease development and progression. In this regard, the

gut microbiome is malleable and renders the gut microbiome a candidate ‘organ’ for the possibility of precision nutrition to induce precision microbiomics—the use of the gut microbiome as a biomarker to predict responsiveness to specific dietary constituents to generate precision diets and interventions for optimal poultry performance and health. However, it is vital to identify the causal relationships and mechanisms by which dietary components and additives affect the gut microbiome which then ultimately influence avian physiology. Further, an improved understanding of the spatial and functional relationships between the different sections of the avian gut and their regional microbiota will provide a better understanding of the role of the diet in regulating the intestinal microbiome.

Key words: gut microbiome, biomarkers, metabolites, intestinal physiology, biotics

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INTRODUCTION

Modern broiler operations have undergone dramatic changes in production practices with genetic selection for high growth rates, improved management techniques, and a greater understanding of, and ability to meet nutritional requirements have all led to increased performance standards. However, there is the question that of whether poultry performance will soon reach its biological ceiling due to genetic and/or physiological limits. Thus, “gut health” has entered the collective consciousness of the animal production industries as a connotation for overall animal health (Kogut and Arsenault, 2016). For this review, gut health is defined as the ability of the gut to perform normal physiological functions, maintain homeostasis, and withstand infectious and non-infectious stressors. Although there are multiple components that explain a healthy gut, the signaling hubs known as the “intestinal ménage a trois” may be the three most critical: the diet, the intestinal microbiota, and the host mucosal immune system (Kogut, 2019).

Understanding the interactions between systems of the diet-microbiota-host axis should provide science-proven mechanisms that link the gaps between the animal feed, gut microbial ecology, and regulating physiological functions of the chicken. For example, current findings suggest broad feedback responses between the microbiome, the diet, and the host immunity (Oakley et al., 2014; Stanley et al., 2014; Kogut et al., 2017) where the gut immune system alters the richness of the bacterial microbiota, modifying the metabolism of the dietary components by the microbiota, which then alters the immune response (Oakley et al., 2014; Stanley et al., 2014; Kogut et al., 2017). Further, there are undoubtedly synergistic effects of the microbiota and dietary factors on the immune response. Defining these dynamic interactions, albeit difficult, will set the stage for precision poultry nutrition and science-driven alternatives to antibiotics for poultry health and improved performance without altering current poultry genetics.

FACTS

The gut is a multifaceted ecosystem that links host elements, including the intestinal epithelium, with its neuroendocrine connections, the mucosal immune system, with the commensal microbiota (Stanley et al., 2014; Kogut et al.,

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2017; Kogut, 2019). The avian commensal microbiota consists of trillions of microorganisms, predominately bacteria, in a dynamic ecosystem that have a fundamental symbiotic functional association with the host and, thus; are strategic managers of host physiology involved in regulating bird health (Oakley et al., 2014; Stanley et al., 2014). Further, the microbiome directs host intestinal metabolism and immunity and drives a metabolome that affects energy balance and body weight in the avian host (Nicholson et al., 2012; Carrasco et al., 2019). In turn, the mucosal immune system shapes the microbiome while host nutritional status influences elements of host defenses and makeup of commensal microbial community (Lavelle et al., 2010; Nicholson et al., 2012). The microbial community in the chicken gut is a multilayered, dynamic system with a homeostasis state and a certain capacity of structural resilience (Liu et al., 2018; Shang et al., 2018), although species composition and metabolic functions of the gut microbial community can be readily changeable by diet, ingestion of antibiotics, infection by pathogens and other host- and environmental-dependent events (Yoeman et al., 2012; Pan and Yu, 2014; Shang et al., 2018; Yadav and Jha, 2019; Mahmood and Guo, 2020).

Diet interacts with the intestinal microbiota to directly promote or inhibit their growth and change the gut luminal microenvironment, and indirectly modify host metabolism and immune system. The capability of gut microbiota to extract energy from specific dietary components (nondigestible carbohydrates) confers a more competitive advantage to selected members of the gut microbial community at the expense of less-adept members. However, dietary components might also disrupt protective functions of the intestinal barrier in ways that could affect the microbiome-host interface and prompt gut microbiota imbalance, contributing to inflammatory processes, and conferring downstream effects on the host physiological functions.

The complexity of the nutritional interactions within an animal is made substantially greater by the gut microbiota that receives their nutrition from the host and, in turn contributes essential nutrients and play a role in host physiological systems, including immune defense (Chow and Mazmanian, 2010). Increasing evidence shows that the nutritional value of food is influenced by the structure and operation of the gut microbial community, and that food, in turn, shapes the microbiota and its vast collection of microbial genes within the gut microbiome (Kohl, 2012; Oakley et al., 2014; Pan and Yu, 2014; Shang et al., 2018).

Diet performs a critical function in shaping and regulating the gut microbiota with the microbiome crucially implicated in the bioconversion of feed components to changes in host physiology, metabolism, and immunity. Dietary modifications can induce a significant shift in microbial composition within 24 h (David et al., 2014) that can be beneficial or detrimental to the host physiology, contingent on the abundance and diversity of the resulting microbial composition and the production of resulting metabolites (Montalban-Argues et al., 2015). The diet supplies necessary nutrients to meet the basic nutritional requirements

for animal maintenance and growth; whereas, some dietary components exert beneficial effects beyond basic nutrition, leading to the concept of functional foods (Roberfroid, 2000): “food or feed that has added benefits that can improve both the health and growth promoting performance of animals which ingest them” (Montalban-Argues et al., 2015). The metabolic activity of the gut microbiota on bioactive food components can modify the host exposure to these components and their potential health effects. Additionally, some functional food components influence the growth and/or metabolic activity of the gut microbiota and, thereby, its composition and functions (Gibson et al., 2005). Accordingly, the intestinal microbiota can be both a target for nutritional intervention to improving health and a factor that impacts the biological activity of other food compounds.

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. The interactions between poultry diet, dietary nutrients, and dietary factors on the bird’s immune system has long been known (Humphrey and Klasing, 2004; Kidd, 2004; Klasing, 2007; D’Mato and Humphrey, 2010; Korver, 2012). However, the role of the microbiota in mediating some of these immune functions was not considered in any of these citations and has not yet been fully deciphered in poultry. Klasing’s (1998) seminal paper acknowledges nutritional effects on the host response to infections and discussed the “physical and chemical aspects of the diet can modify the populations of microorganisms in the gastrointestinal tract”. Over twenty years later, the interplay between the gut microbiota and host nutritional processes that mediate these immunophysiological functions in poultry still remains to be fully elucidated (Kogut, 2021). It has also become apparent that the intestinal immune system can also detect the metabolic state of the microbiota by recognition of microbial metabolites via their pattern recognition receptors (PRRs) (Levy et al., 2016; Blacher et al., 2017). The microbiota, using several biochemical pathways, metabolizes both diet- and host-derived metabolites that then influence various components of the intestinal immune system. For example, the microbiota converts nondigestible fibers to short chain fatty acids (SCFA; acetate, propionate, butyrate) that have several anti-inflammatory activities on chicken immune cells both in vitro and in vivo (Zhou et al., 2014; Zou et al., 2019; Gupta et al., 2020).

GAPS

Understanding That the Nutritional Value of Feed Affects Host Phenotype but is Dependent Upon the Gut Microbiota

The basic dietary premise of broiler production worldwide is that diets provided to the birds at the various stages of growth are iso-energetic, iso-nitrogenous, and formulated to meet or exceed the bird’s requirements with a basic host phenotype depending upon the breed

used (body weight gain, feed conversion ratio, etc.). The specifics of nutrient requirements in diets for broiler chickens, based on the animal's stage of growth or production and genetic capacity with different diets for various physiological stages, are known and are the basis for feed formulation. Nevertheless, nutritionists for broiler production companies routinely formulate diets based on a least-cost basis that considers ingredient cost, the nutrient composition, and the animal's nutrient requirements. The point being made here is not to criticize how a bird's diet is formulated, but to spotlight that the lack of consideration of the role of the microbiota plays in these decisions. We have all heard that we are actually 'feeding the microbiota and not the animal', and though this may be true 'in general' there are very little data that are used when formulating feed. One specific example, during homeostasis it is well known that in chickens, a healthy gut microbiota enhances the nutritional value of the diet through the production of complementary enzymes to ferment non-starch polysaccharides to produce SCFAs. Butyrate or butyric acid is the primary energy source of colonic epithelia and has been shown to be essential to homeostasis of colonocytes and the development of gut villus morphology (Yoeman et al., 2012; Mahmood and Guo, 2020), improve growth performance and carcass quality characteristics, increase intestinal barrier integrity, and reduce *Salmonella* colonization in chickens (Panda et al., 2009; Guilloteau et al., 2010; Onrust et al., 2015). Unfortunately, most of the published studies describing the effect of diet on physiological functions, specifically the immune system, the role of the gut microbiota interaction with dietary components has been ignored. In fact, most of the studies have concluded a *direct* effect of a nutrient (protein, fatty acids, carbohydrates) on the immune system without determining the direct effect on the gut microbiome, leading to an indirect effect on immunity (Kidd, 2004; Babu and Raybourne, 2008; Wils-Plotz and Klasing, 2017). Studies are required that can dissect the effects of the microbiota on dietary components and the resulting effects on host physiological phenotypes are required so that true least-cost feed formulations can be developed that use the microbiota to improve poultry health and performance.

Microbial Population and Ecology

Increasing evidence shows that the nutritional value of food is influenced by the structure and operation of the gut microbial community, and that food, in turn, shapes the microbiota and its vast collection of microbial genes (collectively the gut microbiome (Stanley et al., 2014; Shang et al., 2018)). Therefore, to define the nutritional value of foods and nutritional effects on host physiological functions, we need to know more about gut microbial communities. A better understanding of microbial ecology and how nutritional interventions impact microbiota is required. Understanding these impacts will provide more definitive opportunities to use

the microbiome as a predictive biomarker to evaluate its sensitivity to dietary components which may modulate the microbiota and improve avian health and performance.

Further, within the intestine, microbes exist in the lumen, which facilitate primary and secondary metabolism, and on mucosal surfaces, where they interact with host immune cell populations. Dietary components and metabolites stimulate these biochemical interactions among different microbial species (direct substrate-derived low molecular weight metabolites, quorum sensing, contact-dependent signaling) and between microbes and host cells. Understanding the chemical interplay between the intestinal microbial populations is of utmost importance to identify management and feeding strategies to optimize intestinal health.

Spatial and Functional Relationships

The composition of bacterial communities found in the different regions of the chicken intestine might be judged as distinct ecosystems (Yoeman et al., 2012; Stanley et al., 2014; Huang et al., 2018; Shang et al., 2018). However, as described by Sklan and colleagues (1978), these communities are connected, able to sow microbes and influence the microbiota throughout in the gastrointestinal tract. However, the functional activities of the sections of the intestine are quite different (Huang et al., 2018; Rychlik, 2020; Yuan et al., 2020; Kang et al., 2021). The microbial functions in the hindgut have been well-documented, but in the foregut, to date, these functions of the microbiota and their relationship with gut function have received scant attention in the research literature which limits the understanding of the interplay between the gut microbiome and cellular functions. Virtually all studies with pre- and probiotics have been directed toward the ileal-cecal region and their respective microbial communities (Kogut, 2019).

NEW CONCEPTS

Establishing a Cause-Effect Relationship Between Diet, the Microbiota, and Host Physiology

As described previously, the avian gut microbiota along with their genes and gene products (the microbiome), perform several functions that heavily impact host physiology. Not only does the gut microbiome play a critical role in modulating host immune defense (Kogut et al., 2017; Broom and Kogut, 2018), brain function (Villageliu and Lyte, 2018; Lyte et al., 2021), host metabolism regulation (Stanley et al., 2014; Lyte et al., 2021; Zhang et al., 2021), but also other physiological processes and characteristics thought to depend solely on the genetic program of the bird; gut-liver axis (Bao et al., 2021), gut-bone axis (Wideman et al., 2012; Tomaszewska et al., 2015; Airubaye et al., 2020), and gut-muscle axis

(Zhang et al., 2021). A greater understanding of the key signaling pathways of the cross-species homeostatic regulation between the gut microbiota and its host implicated in these axes are a prerequisite for optimizing therapeutic dietary strategies to manipulate the gut microbiota.

Most of the studies looking at diet and dietary effects on poultry microbiota have failed to establish a cause–effect relationships between physiological functions, including immunity, bird performance, and changes in the gut microbiota. These collective correlative studies have failed to prove the mechanisms of action in use of diet and nutrition that aim to target the gut microbiota for maintaining homeostasis in a healthy animal and therapeutic effectiveness in disease prevention. It is imperative that a cause–effect relationship be established before the true therapeutic potential of microbiota-targeted precision nutrition can be established.

Evidence-Based Studies Delineating the Relationship Between Diet, the Microbiota and Its Associated Metabolome

Evidence from humans and murine models has clearly established the causal role of the gut microbiota in modulating several physiological functions including nutrition, metabolism, and immunity (Fischbach, 2018; Round and Palm, 2018). Unfortunately, few of these microbes have been confirmed in chickens. Understanding the origin, production, and actions of metabolites will lead to a better understanding of host and bacterial processes aiding in therapeutic design. However, because host-derived factors are hardwired to the genome and difficult to modulate, diet-induced microbiota alterations have a more direct impact host physiology by providing crucial benefits in the form of immune system development, prevention of infections, nutrient acquisition, and the synthesizing or modulating several bioactive compounds.

Using – Omic Technologies to Concurrently Describe the Host Intestinal AND Microbiota Metabolic Activities to Diet and Feed Supplements (Transcriptomics, Proteomics, and Metabolomics)

The microbiota is understandably engaged in numerous metabolic interactions with each other and multiple avian host metabolic pathways which regulate a series of host-microbiota metabolic, immune and signaling axes that physiologically link to several systemic organ systems, for example the production of SCFA (Polansky et al., 2016; Sun et al., 2021). However, a more comprehensive understanding of the gut microbiota influences on poultry nutrition will have to come through systems biology analyses of the metabolic and immunological interactions of the bird intestine to the gut microbiota.

Understanding Mucosal Microbiology and Spatial Organization Throughout the Entirety of the Intestine

The gut microbiota is an environmental factor that largely impacts on host physiology and disease susceptibility. Yet spatial distribution of microbiota is highly diverse, and little is known about local host-microbiota interactions along the length of the intestinal tract in poultry. To date, most microbiota studies in poultry have relied on analyzing microbiota composition via 16S rRNA gene sequencing of either ileocecal samples or fecal material (Borda-Molina et al., 2018; Shang et al., 2018) with few studies on the physiological impacts on the avian host. However, the luminal microbiota (epithelium-associated microbes) are significantly different in terms of composition (Oakey et al., 2014; Borda-Molina et al., 2018). Further, the dissemination of the microbiota fluctuates along the tissue-lumen axis where nutrient availability from the diet, oxygen gradient, and protective immune responses from the host epithelium (secretory IgA, mucus, antimicrobial peptides) vary dramatically from region to region (Redweik et al., 2020). Because of the biogeography of the microbiota and its differential effects on host physiology, identifying the local interactions between the microbiota and host tissue along the length of the intestine are now required (Sigerstetter et al., 2017; Metzler-Zebeli et al., 2018, 2019). Lastly, in mammals, the existence of a crypts- and inner mucus-associated microbiota has recently gained a lot of attention but has never been identified in poultry (Pedron et al., 2012; Daniel et al., 2021). Only by understanding this spatial organization of the avian gut microbiota will we be able to fully be able to use diet and feed supplements to improve bird gut health and improve overall performance without changing the genetic make-up of the modern commercial broiler.

PERSPECTIVES

Existing investigations in poultry have afforded a basic understanding of the impact of diet and feed supplements on the composition and activity of the gut microbiota in the hindgut, but not in the foregut, with a few exceptions (Wen et al., 2019; Kang et al., 2021; Schekkers et al., 2021). However, currently, a detailed translational approach in applying diet as a tool to improve bird performance and health remains limited. Contemporary advances in sequencing techniques for characterizing the gut microbial communities have hastened some understanding how diet modulates gut microbiota and its effect on poultry performance and health (Stanley et al., 2014; Wen et al., 2019). However, further advances are required to understanding microbiota population composition and functionality of gut microbiota. Unlike humans, the host genome of poultry has limited, if any, effect on the structure of the gut microbiome (Wen et al., 2019; Schekkers et al., 2021).

This should enable us to better comprehend the contribution role of diet in shaping gut microbiota.

The future of precision nutrition effects on the microbiome in poultry for the improvement of bird performance, prevention of enteric infectious diseases, or increased physiological functions requires a standardization of microbiome research methods to reduce the assorted research outcomes that have been published thus far due to the complexities of the diet-microbiome-host axes. Procedures and analytical methods used to measure poultry microbiome will need to be more reproducible and consistently applied across studies and populations to obtain accurate diet and dietary intake assessments and to minimize technical variation in metagenomic data than have been implemented to date.

New investigations should include the identification of specific microbiota signatures (specific species, genes or enterotypes [Kang et al., 2021]) and their associated metabolic properties and will generate large and comprehensive data sets that will require the development and use of new computational tools and analytical technologies including big data, multiomics, and machine learning in which information on feed composition or feed additive components, microbiota signature(s), and the bird physiological responses can be used to predict the impact of each factor on any desired outcomes.

DISCLOSURES

The authors declare no conflict of interest with this manuscript.

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