Immune responses to improving welfare

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ABSTRACT The relationship between animal welfare and the immune status of an animal has a complex nature. Indeed, the intuitive notion that "increased vigilance of the immune system is by definition better" because it is expected to better keep the animal healthy, does not hold up under scrutiny. This is mostly due to the fact that the immune system consists of 2 distinct branches, the innate and the adaptive immune system. While they are intimately intertwined and synergistic in the living organism, they are profoundly different in their costs, both in terms of performance and wellbeing. In contrast to the adaptive immune system, the action of the innate immune system has a high metabolic cost as well as undesirable behavioral consequences. When a pathogen breaches the first line of defense (often a mucosal barrier), that organism's molecular signature is recognized by resident macrophages. The macrophages respond by releasing a cocktail of pro-inflammatory cytokines (including interleukin-1 and -6) that signal the brain via multiple pathways (humoral as well as neural) of the ongoing peripheral innate immune response. The behavioral response to the release of proinflammatory cytokines, known as "sickness behavior," includes nearly all the behavioral aspects that are symptomatic for clinical depression in humans. Hence, undesired innate immune activity, such as chronic inflammation, needs to be avoided by the industry. From an immunological standpoint, one of the most pressing poultry industry needs is the refinement of our current veterinary vaccine arsenal. The response to a vaccine, especially to a live attenuated vaccine, is often a combination of innate and adaptive immune activities, and the desired immunogenicity comes at the price of high reactogenicity. The morbidity, albeit limited and transient, caused by live vaccines against respiratory diseases and coccidiosis are good examples. Thankfully, the advent of various post-genomics technologies, such as DNA vaccines and vectored subunit vaccines, offer reason for optimism that substantial progress can be made towards the vaccine refinement goal in the near future.

Key words: poultry, welfare, immunity

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INTRODUCTION

When trying to answer the question to which extent immune responses can contribute to welfare and be incorporated in new and improved management practices, it is important to make the distinction between innate and adaptive immune responses. Although in the living animal these 2 "branches" of the immune system collaborate in a concerted manner, the dichotomy between innate and adaptive (acquired) immunity is a highly useful intellectual framework when addressing the relationship between immune activity and welfare in farm animals. While both immune system branches are vital for the health and survival of any animal, their repercussions on welfare differ vastly. In a metaphorical way, it may be helpful to think of the innate system as a first aid kit that is always at hand but rather primitive in nature, as opposed to the acquired immune system, which is a highly sophisticated system that is unfortunately much harder to reach in a timely manner, much like a fully equipped modern hospital. Another metaphor that can be used to illustrate the fundamental differences between the 2 immune system branches is a military one. The innate immune system is more like a grenade: readily available and relatively effective, but causing a lot of collateral damage, as opposed to the acquired immune system, which has, much like a sniper, the capacity to "surgically" and effectively neutralize an enemy with negligible collateral damage. In reality, however, both immune branches are intimately interwoven and constantly interacting with one another.

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Innate Immune System

Like the term "in-nate" indicates, this is a collection of mechanisms that we are "born with." Unfortunately, those tools and their efficacy are still the exact same when the host dies: No adaptations against infections, i.e., no immunological memory has been acquired. The innate immune system consists of a number of defensive barriers that are available from birth until death and that can be mobilized quickly, within minutes or hours. Those include physical barriers (like the mucosa of the gut), phagocytic cells (especially heterophils in birds), physiological mechanisms (such as fever), and a vast number of molecules such as the complement system, antimicrobial peptides, and others. Unlike the adaptive system, the innate immune system does not acquire a large repertoire of pathogen-specific receptors during the life of the animal. The innate immune system relies on dozens of pattern recognition receptors (**PRRs**) that have a fairly broad specificity for one or more microbe-associated molecular patterns (**MAMPs**) (Kumar et al., 2011). In light of the intimate relationship between wellbeing and performance, it is not surprising that decades of broiler selection, either directly or unintentionally, have minimized sensitivity to inflammagens such as bacterial lipopolysaccharides (**LPS**) (Leshchinsky and Klasing, 2001). As a consequence, broilers are behaviorally much less vulnerable than laying hens to the ill effects of MAMPs.

Adaptive Immune System

The adaptive immune system differs from the innate immune system in almost all of the characteristics described above. It is not yet developed at birth but takes shape during the early phase of ontogeny, estimated to take about the first 2 wk of life in a chicken. The adaptive immune system relies on an estimated 10^8 to 10^{10} lymphocyte receptors (antibodies and T-cell receptors), which confer extremely high specificity to this branch of the immune system (Boehm, 2011). However, a primary adaptive immune response is slow: It takes about 10 d to take effect and a secondary immune response takes about 4 to 7 d. This delay in the adaptive immune response is caused by the sequence of antigen presentation followed by clonal expansion of specific B- and T-lymphocytes, and ultimately the secretion of antibodies and other effector molecules. While highly specific in nature and extremely effective, this is a complicated process that takes a lot of time. During this response lag, the innate immune system has to fend off any invading pathogens.

Finally, when considering the cost in terms of energy and collateral damage, the 2 branches of the immune system could not be more different. An adaptive immune response, consisting mostly of the proliferation of carefully selected lymphocytes comes at a very low nutritional cost (Iseri and Klasing, 2013, 2014) and causes virtually no damage other than to the target (much like a sniper). The innate immune system is effective but causes considerable collateral damage (rather like a grenade). Indeed, fever and inflammatory reactions consume considerable resources, depleting carbohydrate stores and catabolizing proteins (Iseri and Klasing, 2013, 2014). These sequelae make inflammation a highly undesirable phenomenon from a production standpoint. This type of innate immune reaction is mediated and coordinated by proinflammatory cytokines, a group of immune proteins predominated by IL -1 and -6 (Klasing, 1991, 1998).

The release of proinflammatory cytokines causes a syndrome known as "sickness behavior" (Shattuck and Muehlenbein, 2015) making innate immune reactions like inflammation also undesirable from a welfare perspective. Proinflammatory cytokines are signaling the brain via 2 different mechanisms that an urgent immune reaction is ongoing. When released into the circulation, cytokines enter the brain at the level of paraventricular organs where they cross the blood brain barrier and cause the local release of prostaglandins, initiating the febrile response. The cytokines also induce the local cytokine expression in the brain itself (Wang et al., 2003). In addition to this humoral communication route, there is also a neural mechanism informing the brain of peripheral immune activity. Proinflammatory cytokines bind to receptors on afferent branches of the vagus nerve, influencing the brain centers that are responsible for a range of activities including appetite, mood, emotion, thermoregulation, and sleep (Cryan and Dinan, 2012; Sankowski et al., 2015).

As a consequence, a bird displaying sickness behavior is febrile, lethargic, and anorectic and loses weight. Less obvious symptoms of sickness behavior include increased slow-wave sleep, reduced social behavior, reduced exploratory behavior, and reduced ability to experience pleasure (anhedonia). Therefore, it is not an exaggeration to equate this syndrome with depression in humans (Dantzer et al., 2008). This scenario needs to be avoided because of the interrelatedness of productive performance and wellness.

The practical consequence of these premises lies in the area of vaccination. The perfect vaccine induces a maximal adaptive immune response while displaying minimal reactogenicity, which is a set of undesired side effects, often referred to as the "vaccine reaction." Vaccines that are notorious for their reactogenicity include the live-attenuated vaccines whose use persists because killed disease agents (bacteria or viruses) are not sufficiently immunogenic to confer effective disease protection. However, the ability of live-attenuated vaccines to cause morbidity, inflammation, and necrosis is the cause of temporary weight loss (Lee et al., 2011), as well as sickness behavior. This is especially obvious in the case of vaccines against coccidiosis and certain respiratory diseases, such as infectious bronchitis and laryngotracheitis. Substitution of subunit vaccines or DNA vaccines for live-attenuated vaccines would have

the added benefit of avoiding live-pathogen induced sickness behavior as well as reduce the risk of attenuated pathogens reverting to virulence (Bande et al., 2015). Although alternatives to live-attenuated vaccination exist, more work is required to develop vaccines with optimal immunogenicity (protection) and minimal reactogenicity (Kaiser, 2010). Remarkably, passive immunization against chicken IL-10 (Sand et al., 2016) is capable of mitigating the growth rate depression that typically follows vaccination with live-attenuated *Eimeria spp.* in broiler chickens (Lee et al., 2011). This is a new development in the area of vaccine refinement that may usher in a new practice in fine-tuning existing vaccines.

Another concern is any pathology in which low level chronic inflammation may occur during production, both in broilers or layers. Although broilers are relatively insensitive to sickness behavior due to their genetic background, inflammation of the gut due to subclinical coccidiosis, necrotic enteritis, or any other impact that results in poor microbiological gut health remains a major welfare problem. By contrast, in laying hens, skeletal and foot health (both negatively impacted by chronic inflammation) are the more obvious areas of concern, especially in ageing birds (Webster, 2004).

CONCLUSION

Maintaining bird health and vigor is critical for optimizing the animal's welfare as well as productivity. As changes in bird genetics occur and new technology develops, maintenance of the immune system will continue to be a significant challenge requiring continual investigation.

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REFERENCES

Bande, F., S. S. Arshad, M. H. Bejo, H. Moeini, and A. R. Omar. 2015. Progress and challenges toward the development of vaccines against avian infectious bronchitis. J. Immunol. Res. 2015:424860. doi: 10.1155/2015/424860.

Boehm, T. 2011. Design principles of adaptive immune systems. Nat. Rev. Immunol. 11:307–317.

Cryan, J. F., and T. G. Dinan. 2012. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 13:701–712.

Dantzer, R., J. C. O'Connor, G. G. Freund, R. W. Johnson,, and K. W. Kelley. 2008. From inflammation to sickness and depression: When the immune system subjugates the brain. Nat. Rev. Neurosci. 9:46–56.

Iseri, V. J., and K. C. Klasing. 2013. Dynamics of the systemic components of the chicken (*Gallus gallus domesticus*) immune system following activation by *Escherichia coli*; implications for the costs of immunity. Dev. Comp. Immunol. 40:248–57.

Iseri, V. J., and K. C. Klasing. 2014. Changes in the amount of lysine in protective proteins and immune cells after a systemic response to dead *Escherichia coli*: implications for the nutritional costs of immunity. Integr. Comp. Biol. 54:922–930.

Kaiser, P. 2010. Advances in avian immunology–prospects for disease control: A review. Avian Pathol. 39:309–324.

Klasing, K. C. 1991. Avian inflammatory response: Mediation by macrophages. Poult. Sci. 70:1176–1186.

Klasing, K. C. 1998. Avian macrophages: Regulators of local and systemic immune responses. Poult. Sci. 77:983–989.

Kumar, H., T. Kawai, and S. Akira. 2011. Pathogen recognition by the innate immune system. Int. Rev. Immunol. 30:16–34.

Lee, J. T., N. H. Eckert, K. A. Ameiss, S. M. Stevens, P. N. Anderson, S. M. Anderson, A. Barri, A. P. McElroy, H. D. Danforth, and D. J. Caldwell. 2011. The effect of dietary protein level on performance characteristics of coccidiosis vaccinated and non-vaccinated broilers following mixed-species *Eimeria* challenge. Poult. Sci. 90:1916–1925.

Leshchinsky, T. V., and K. C. Klasing. 2001. Divergence of the inflammatory response in two types of chickens. Dev. Comp. Immunol. 25:629–638.

Sand, J. M., M. K. Arendt, A. Repasy, G. Deniz, and M. E. Cook. 2016. Oral antibody to interleukin-10 reduces growth rate depression due to *Eimeria spp.* infection in broiler chickens. Poult Sci. 439–446.

Sankowski, R., S. Mader, and S. I. Valdés-Ferrer. 2015. Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration. Front. Cell. Neurosci. 9:28. doi: 10.3389/fncel.2015.00028.

Shattuck, E. C., and M. P. Muehlenbein. 2015. Human sickness behavior: Ultimate and proximate explanations. Am. J. Phys. Anthropol. 157:1–18.

Wang, R., J. R. Millam, and K. C. Klasing. 2003. Distribution of interleukin-1 receptor in chicken and quail brain. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 136:663–671.

Webster, A. B. 2004. Welfare implications of avian osteoporosis. Poult. Sci. 83:184–92.