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Immunomodulation - what are we trying to achieve?

Immunomodulation, as the term suggests, attempts to influence immune function, often through nutrition or feed additives. Successful immunomodulation requires a fundamental understanding of the immune system. Simplistically, in vertebrates, the immune system consists of the (rapid-responding, non-specific, no memory) innate and (initially slower-responding, specific, with memory) acquired components. These parts are often thought of separately but there is a great deal of interplay between them, particularly as innate cells present antigen to acquired cells. Innate immunity provides the initial line of defence against microbes and includes epithelial barriers, and phagocytic and antigen-presenting cells that sense highly conserved microbial molecules (microbe-associated molecular patterns; MAMPs) via the expression of pattern recognition receptors (PRRs). Acquired immunity provides both targeted and rapid humoral (antibody) and cell-mediated responses to previously encountered antigens, which are orchestrated by B and T lymphocytes (cells) that can generate a diverse array of antigen receptors. B lymphocytes mediate humoral responses that are particularly effective against extracellular microbes, but can also help block viruses and other pathogens from entering host cells. T (cytotoxic; CD8+) lymphocytes are primarily involved in cell-mediated responses against intracellular pathogens (by monitoring intracellular-derived peptides bound to specialised host cell surface (MHC) molecules) and thus initiate destruction of host cells identified as infected or damaged. Other T (helper (h); CD4+) lymphocytes direct the immune response by stimulating cytotoxic T cells, B cells and other immune-related cells through the secretion of chemical messengers (e.g. cytokines and chemokines). There are various subsets of activated CD4-expressing T cells, including Th1, Th2, Th17 and T regulatory (reg) cells. Generally, Th1 responses are directed against intracellular bacteria, viruses and protozoa, Th2 against extracellular pathogens, including helminths, Th17 against certain extracellular pathogens, including most fungi, while T regs promote tolerogenic, inflammation limiting and tissue repair responses (Filyk and Osborne, 2016).

An optimum immune system is both effective and efficient, and limits host damage. To achieve this, the immune system must employ various checks and balances for its regulation. There are numerous dynamic pathways and interactions between immune cells that determine the response generated. For example, promoting the expansion of a particular Th

subset can inhibit, promote, and/or balance other subsets - Th1 and Th2 cells antagonize each other, while Tregs limit the activation of Th1, Th2 and Th17 cells (Filyk and Osborne, 2016).

Immunomodulation may be particularly useful in, for example, young (immature immune system), immunosuppressed (e.g. due to various stressors) or vaccinated animals to elevate immune function. To date, however, and keeping the preceding section in mind regarding balance, there are very few, if any, nutrients that can increase the entire immune system when provided above requirement (and below toxicity) (Klasing, personal communication). For example, in several species, excess fish oil or n-3 fatty acids have been frequently shown to upregulate the Th2, to the detriment of the Th1, response, resulting in greater antibody responses and protection against extracellular pathogens but reduced cell-mediated and inflammatory responses, and thus increased susceptibility to intracellular pathogens (Selvaraj, 2012). In contrast, increasing dietary nutrient concentrations, when below requirement, does, typically, enhance all components of immunity (Klasing, 2007). These observations highlight the current challenge with nutrition-related immunomodulation; i.e. providing nutrient(s) above requirement may enhance host protection against some pathogens but reduce protection against others.

Conclusion

The adequate provision of nutrients is the foundation of optimal immune responses, with sufficient 'overages' to accommodate inevitable immune system stimulation occurring in commercial animal production. Specific immune cells and responses utilise nutrients differently but estimates indicate that an activated immune system can use up to 10% of dietary nutrients (Klasing, 2007). From this basis, we can then consider which elements of the immune system we wish to influence, knowing that increasing one component may suppress another, and thus immunomodulation should be based on a thorough understanding of a particular production unit's challenges. For example, boosting immunity against extracellular microbes can increase susceptibility to intracellular pathogens. With this in mind, interest in anti-inflammatory strategies (e.g. seeking to (relatively) enhance the 'anti-inflammatory' cytokines IL-10 and TGF-β), particularly in relation to intestinal inflammation, has increased but risks compromising essential immune responses and protection against some commercially ubiquitous pathogens. Modest intestinal inflammation is considered important as it likely reflects a state of immunological 'readiness' and limiting the immunogenicity of feed (e.g. through raw material selection and/or use of enzymes) might be most beneficial here. Moreover, targeting IL-10 secretion has been suggested for improving vaccine efficacy (Wu et al., 2016) and has improved growth performance in *Eimeria* challenged chickens (Sand et al., 2016). Immunomodulation might be particularly useful in young animals. Young animals have immature acquired immunity and are thus very reliant on the innate response, which could be a target for interventions. In addition, young animals are typically vaccinated and immunomodulation could improve efficacy. There is still a lot to learn about the immune system and its suitable modulation but, attempted appropriately, immunomodulation does offer some exciting possibilities to animal production.

References

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