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Q&A REVIEW

Feeding the Immunity Defenders; The Evolving Field of Nutritional Immunology

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Presenter: Dr. Barry Bradford

1. As noted in your talk, the complexity and interaction of nutrients as signal molecules is profound. It seems, to study the impact of nutrients on immune function requires a challenge approach to the system which implies a complex and possibly disproportionate impact across many cellular functions. Which would be more beneficial to understanding and improving animal performance; return to normal function after challenge (ability to return to normal function, and the time that takes and degree to which it can be achieved) or resilience to the insult in the first place and how specific nutrients might aid in achieving this? This is a really interesting question, and there is probably no right answer. It brings to mind the concept that the immune system has to draw a line somewhere to separate those challenges that it will tolerate vs. those it will respond to. It is clear that nutrients can shift that line (omega-3's, at a minimum). Is it good to make the immune system take a more tolerant stance? It depends. If animals are in environments that rarely require a robust immune response to survive (think pre-COVID Americans), then calming the immune system, limiting auto-inflammatory and allergic types of responses are probably a net benefit. On the other hand, we know that suppressing inflammation (and promoting tolerance) makes rodents much more susceptible to infectious disease. For example, there is good data on omega-3's increasing death rate from TB infection in mice. Because of these trade-offs, my philosophy is more focused on resilience. Ideally, I would like an animal to have a "normal" setpoint differentiating tolerance from response, but to be able to respond very robustly while also resolving that response quickly afterwards. There is less evidence regarding the ability of nutrients to enable this kind of response, other than meeting requirements for essential nutrients involved in immunity (Se, vitamins). But that is where I would like to sniff around.

2. Corticosteroids and dexamethasone. When would you use these? I hesitate to respond to this at all, as I have little experience with these compounds and do not have clinical/veterinary training. As a very broad generality, I tend to think of this as treatments for more acute inflammation/shock scenarios.

3. Could you comment, if in less productive cows such as beef or double purpose cows, are having similar responses in the immune system? We don't have much information on this. Feedlot cattle, which are known to have altered immune status after weaning/transportation stress, have been studied quite a bit, but there has been very little work on beef dams. We do know from work in New Zealand that early lactation grazing dairy cows (with a different genetic background) generally show the same shifts in immunity as TMR-based dairy cows.

4. Does immune activation prepartum affect or prime in some manner the immune functionality of the fetus? Can this be a "positive"? Should we be considering nutrient signaling to the fetus to "program" a more robust immune response after birth? If so, what nutrients? Great question, but I really don't know. One issue is that immune "memory" is transferred very differently in different species, so work in mice may have little or no relevance to cattle for this question. We do have some evidence that vaccinating cows prepartum influences antibodies in colostrum, so that is at least one mechanism linking prepartum immune function and immune development of the calf. There is also recent evidence that in utero exposure to colostrum altered neonatal response to endotoxin exposure, pointing to a programming effect on the calf's immune system. Beyond that, we don't know a whole lot other than from huge manipulations like cutting energy and protein to the dam by 30%+ (beef and sheep research).

5. Is there any reason to think the "energy requirement" is overestimated in some studies based on the metabolism of glucose? If the innate cells are using glycolysis, that lactate goes back to the liver and is made into glucose again so the same mol of glucose is not being completely oxidized so its heat of combustion may not be an accurate way to estimate the energy used from it? Yes, agreed, although with indirect calorimetry, it's not the recycling per se that is the problem, but the anaerobic glycolysis vs. aerobic respiration. Unfortunately, very few places remain where direct calorimetry can take place for cattle. A more complex stable isotope approach could be used to determine fates of glucose and lactate independently in combination with indirect calorimetry to determine a corrected energy utilization rate. Alternatively, I believe that covering a larger window of time, after lactate levels have re-equilibrated, would end up giving a more accurate assessment of energy burn; eventually, carbon dioxide would be exhaled when the accumulated lactate is fully oxidized.

6. I have a daughter with ME (CFS). Is there hope that this technology and knowledge can be mirrored in humans? Again, this is beyond my "pay grade". Suffice it to say that whatever level of this work is going on in cattle, there is at least 1,000x as much research in this space with a focus on humans (though much occurs in mice first).

7. In transition cows, Ca requirements are also increased to support immune response? This is certainly an important feature of Ca, but I don't think this contributes quantitatively to Ca requirements in a meaningful way. The only net loss of Ca from immune use would be within cells that exit the body (i.e. neutrophils into milk, the gut, etc.). Some of that does occur and it increases during lactation, I believe (milk), but I suspect it's only a few percent of the total Ca required.

8. In your work to date is there any one area of focus that holds a key to better health and performance? For example focus on innate vs. adaptive response factors or impact of energetics on health or some other area? I don't have a great answer for this right now. We have vaccines (adaptive) that very clearly decrease disease burden, and it's tough for me to say with confidence that we have innate tools that are proven to decrease disease burden. But that may come – we are just starting to do large enough studies to really ask about whether "nutraceuticals" can decrease disease incidence. I hope that in the coming 5 years we can start to see this more clearly, but even then, the most important focus may well vary from farm to farm, depending on the relative pressures at each place.

9. Is there a marker in blood that can be used on farm to access immune challenge/status in transition cows? There is no one marker that consistently tells us whether a cow is under any immune challenge or has "good immune status". The dual test developed by Bonnie Mallard and colleagues in Canada is not a bad model of assessing immune status on-farm. They use two tests to get at both antibody-mediated and cell-mediated immunity, which also incorporates some innate immune contribution, and this has been used successfully as a phenotype to generate genetic predictions. In terms of assessing whether cows are undergoing on immune challenge, acute phase proteins have been the most useful. There are many, but haptoglobin has been used the most in dairy cattle research. A few diagnostic labs offer this test, and I think we may finally be at a point where monitoring herd average haptoglobin in transition cows may be useful (i.e. sample 20 transition cows once/month).

10. Key signaling nutrients like choline appear to require transporter proteins into cells. What do we know about what controls the expression of these proteins and can we influence this nutritionally? There is no reason to believe these are not regulated, and we recently found that choline treatment enhanced expression of the choline transporter in bovine immune cells. It is a little surprising for a nutrient to promote expression of its own transporter, but that is what we found. See: Garcia, M., L.K. Mamedova, B. Barton, and B.J. Bradford. 2018. Choline Regulates the Function of Bovine Immune Cells and Alters the mRNA Abundance of Enzymes and Receptors Involved in Its Metabolism in vitro. Front. Immunol. 9:1–14. doi:10.3389/fimmu.2018.02448.

11. Methionine is involved in the cycle of choline, if I remember correctly. Is there any data that shows an improvement in immune response when feeding RP-Met and RP-Choline? Yes. There are quite a number of studies now looking at these questions in transition cows, showing improvements in neutrophil function with RP-Met. The evidence for choline is slightly different, with less mechanistic immune function data published but stronger clinical data – for example, strong evidence of reduced mastitis incidence in choline-fed cows. I don't think there is an easy explanation for reduced mastitis in response to choline other than some improvement in immunity.

12. There appears to be a "need" for some "controlled" level of inflammation at parturition for the dairy cow in order to restore "normal" function. The role of fat mobilization seems critical to this. How should we think of this? Is some weight loss essential or is the amount of lipolysis needed for immune performance more subtle and not necessarily observable from a body condition standpoint? I'm not sure that the local, immediate inflammatory response helping to drive calving is really dependent on adipose lipolysis. There are lipids required to contribute to those processes, but they are mostly going to come from membrane lipids within leukocytes. Longer-term, whole-body inflammation is probably more influenced by elevated NEFA, but this may not be positive. In fact, some scientists think this response may contribute to the lack of resolution of inflammation after ~ day 4 of lactation. Some weight loss may still be necessary for endocrine and/or energy balance reasons, but I'm not yet convinced that it's necessarily beneficial for immunity/inflammatory status.

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