The impact of feeding effects on the dairy cow's immune system

The immune system is a biological defence system comprised of different structures, cell types and processes that act to protect the host animal from pathogens. Pathogens include micro-organisms, viruses and parasites. The immune system is also primed to identify and destroy tumour cells. As such, the immune cells must be able to differentiate between healthy host tissues and cells and those of a pathogen or tumour.

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The immune system is a complex, tiered arrangement that facilitates the detection of pathogens. The initial line of defence is usually in the form of a physical barrier, such as the epithelium. Cuts or abrasions to the skin can allow the entry of pathogens into the body that subsequently stimulates the next step in the defence process: the innate immune response. This dominant response is immediate but non-specific, meaning that it reacts in the same way, whatever the pathogen. Inflammation, white blood cells and other molecules aid in halting pathogens from proliferating.

In certain vertebrates, another part of the immune system exists: the adaptive, or acquired, immune response. This is more complex than the innate system, as it involves recognition of specific, individual pathogens. Recognition occurs via pathogen cell surface antigens and allows for the generation of responses that are tailored to specific pathogens or pathogen-infected cells. Antibodies are produced as part of this response, and activation of the adaptive immune response forms the basis of vaccination.

This system also possesses immunological memory, whereby memory cells from a previous infection remain in circulation. This means that if the same pathogen is encountered for a second time, the response is more rapid and of greater magnitude.

The failure of any stage of defence leaves the animal at greater risk of succumbing to infection and/or disease. Effective host defence requires that both innate and acquired protective factors be highly interactive and coordinated to provide optimal resistance to disease.

Factors affecting immune function

The periparturient period is by far the most physiologically demanding time in the production cycle. It is well-established that immune function during the periparturient period is compromised, and research has looked at targeting factors that contribute to this immunosuppression, often with an emphasis on mastitis.

Numerous factors influence immune function, including genetics, hormones, oxidative stress and nutrition. There appears to be substantial genetic variability in resistance to certain diseases, and selection for animals showing lower disease susceptibility during periods of immunocompromise may significantly improve overall herd health.

Hormones, such as corticosteroids, can have direct effects on immune function via a reduction in numbers of certain white blood cells. Reduced levels of thyroid hormones can have negative effects on the body's innate (non-specific) response, and elevated and suppressed levels of oestrogen and progesterone, respectively, affect both innate and adaptive responses.

Oxidative stress occurs when the balance between oxidants, such as reactive oxygen species (ROS) and the body's antioxidant system, shifts toward the former. The abundance of ROS, including hydroxyl radicals and peroxides, increases when there is an increased demand for oxygen. These ROS are potent mediators of cell and tissue damage, putting additional strain on the immune system.

Nutritional effects

One of the most influential factors regarding immune function is nutrition, and much data exists to demonstrate the adverse effect of malnutrition on immune function in mammals.

As mentioned, the transition period represents the greatest physiological stress to a dairy cow, and physiological stress also has a negative impact on the body's ability to fight disease. Physiological stress is the adaptation of the body's functions to try to cope with the current situation (calving).

Certain processes occur, leading up to and during calving, that allow the animal to cope with what is happening. Hence, optimal nutrition is vital to avoid exacerbating the situation. Both deficiencies and excesses of various nutrients can result in impaired immune function, so careful attention must be paid to transition cow diets.

Energy balance is a key attribute to successful dairy production, and negative energy balance (NEB) is an omnipresent issue during the immediate post-partum period. Animals with a NEB tend to have elevated levels of circulating non-esterified fatty acids (NEFA). These compounds are associated with an increase in inflammatory conditions, though the exact mechanism is unclear.

Negative energy balance results in mobilisation of adipose tissue to provide additional energy, as nearly all the glucose available is directed to the mammary gland. This creates a shift in the profile of circulating fatty acids (FA), which has knock-on effects for compounds generated from these FA. Douglas et al. (2007) highlight the reduction in cell membrane concentrations of the polyunsaturated FA (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

PUFA are also the precursors for many compounds, such as eicosanoids, prostaglandins, leukotrienes and thromboxanes, which are all involved in the immune response. Eicosanoids show varying degrees of inflammatory stimulation, and, thus, alterations in FA profiles due to NEB will influence the inflammatory response. Promoting a positive, or less negative, energy balance is therefore vital during the transition period.

This requires a healthy and efficient rumen, which can be encouraged by feeding a balanced ration using good quality ingredients. As foetus size increases, dry matter intake decreases, meaning adjustments in the energy density of the

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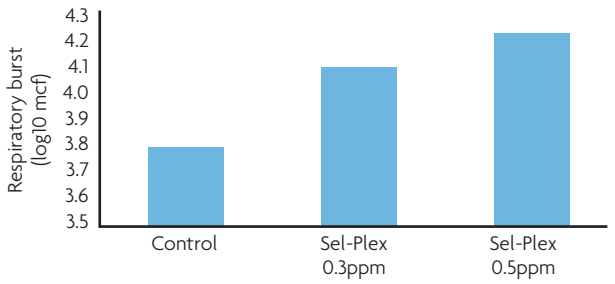

Fig. 1. Effect of dietary supplemental Se source and level on respiratory burst of neutrophils (adapted from Ibeagha et al., 2009).

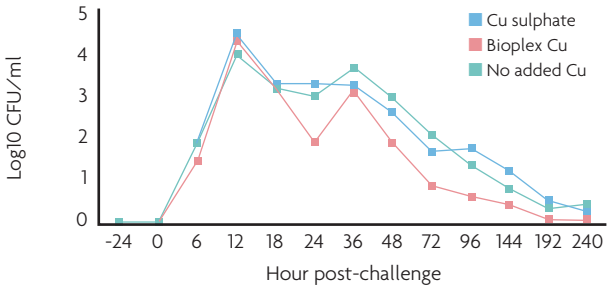

Fig. 2. Effect of copper source on E. coli in milk (log10 CFU/ml) following E. coli challenge (adapted from Scaletti et al., 2012).

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ration may be required. Whilst the basic rules of feeding apply, there are additives and ingredients available that can facilitate good rumen function.

Dietary inclusion of a yeast culture, such as Yea-Sacc, has been shown to reduce negative energy balance during the transition period. Increases in plasma insulin levels have also been seen. High insulin levels have been linked to reduced days to first service and calving to conception.

Oxidative stress

Oxidative stress has also been cited as a negative influence on immune function. Aerobic biological processes require oxygen and, thus, generate ROS. These damaging entities are kept in check by a cascade of antioxidant defence processes.

The production of ROS is elevated in times of physiological stress, such as transition, due to increased oxygen utilisation as well as lipid peroxidation. The risk of oxidative stress is also increased during the immune response, as the process of phagocytosis generates free radicals. Hence, ensuring rations support antioxidant status during the transition period is critical.

There has been much research on antioxidants in dairy cattle, including vitamins E, A and D, as well as selenium (Se). Vitamin E is a membrane-bound antioxidant that works together with Se to scavenge free radicals and peroxides. Vitamin E (Toc - OH) acts as a free radical (LOO•) scavenger (breaks the oxidation chain):

$$\text{Toc - OH} + \text{LOO}\bullet \rightarrow \text{Toc - O}\bullet + \text{LOOH}$$

The reaction results in the production of the phenoxyl radical Toc - O•, which is more stable and less reactive compared to the lipid radical LOO• and is eventually reduced back to vitamin E. As well as an antioxidant, vitamin E also has specific effects on macrophages.

Vitamin E requirements are related to the complex inter-relationship between vitamin E, Se deficiency and quantities of UFA in the diet. Indeed, many of the studies showing supplementation of vitamin E reducing the incidence of mastitis were carried out in Se-deficient herds.

Se-containing enzymes also scavenge ROS and have a vitamin E-sparing effect. Levels of selenoenzymes are known to decrease during the periparturient period but rapidly increase again in early lactation. This decrease may partly contribute to the immunosuppression seen in periparturient cows. Glutathione peroxidase is a selenium-containing enzyme that oxidises glutathione in the presence of peroxides:

$$2\text{GSH} + \text{H}_2\text{O}_2 \rightarrow \text{GSSG} + 2\text{H}_2\text{O}$$

Where GSH = reduced glutathione and GSSG = oxidised glutathione. Se inadequacy is also linked with adverse immune function effects, such as impaired antibody production and reduced phagocytotic capacity. Adequate Se status has a positive effect on the animal's ability to resist infection as well as fertility parameters.

One of the ways Se exerts its effects on the immune system is via interleukin-2 (IL-2), which is involved in T-cell proliferation and differentiation. IL-2 is directly related to Se levels; hence, poor Se status is reflected in an inability to mount a good T-cell response, whether to a pathogen itself or to a vaccine.

Optimising mineral status

Optimising Se status in cows is essential for supporting immune function, and not only the amount, but the form, of Se supplied is important. It is well-established that organic forms of minerals generally have higher bioavailability and retention in the body compared to their inorganic counterparts. This retention in body tissues allows the animal to build a reserve of the mineral to use in times of increased physiological stress (transition).

As Se cannot be chelated, Se-enriched yeast (Se-yeast), such as Sel-Plex, is often used to deliver Se in an organic form. Using Se-yeast has been shown to improve the respiratory burst of neutrophils compared to inorganic sodium selenite, while at the same time reducing the number of neutrophils that experienced cell death as a result (Fig. 1).

Positive effects have been noted with feeding an organic form of other minerals, such as zinc and copper. Zinc deficiency can result in immune abnormalities and, subsequently, greater vulnerability to infections. A decrease in lymphocyte proliferation, as well as reduced phagocytotic activity, has been demonstrated following zinc deficiency.

Interestingly, disruption of immune function has also been noted following an excess of zinc, which highlights the possible role of zinc in immune regulation. Zinc is also crucial for maintaining the integrity of the primary barrier, the skin. Cells involved in the innate response require zinc for normal function and development.

Copper is also crucial for immune function. It affects the IL-2 responsible for T-cell proliferation in the adaptive response. Neutrophil proliferation is also affected by copper deficiency. Hence, copper deficient animals often show immunosuppression.

Fig. 2 shows the effect of supplementing copper as sulphate or as an organic chelate on the excretion of E. coli in milk following a challenge. Organic copper was better at reducing levels of E. coli in milk compared to inorganic copper. This indicates that supplementation with organic copper tended to improve the clinical status of cows after live E. coli intramammary challenge.

Essentially, the immune system must be promoted at all times throughout the lactation cycle, but particular attention should be paid during times of physiological stress (parturition).

Feeding to enhance immunity is vital and should focus on maintaining a less negative energy balance as well as building tissue reserves of key minerals, which is most effectively done by feeding them in the organic form. ■

References are available from the author on request