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Review

Immune system, inflammation and nutrition in dairy cattle

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Abstract. Good health is essential for good performance and the welfare of dairy cows, and nutrition is an important component of good health. Health is influenced by the interaction between the innate adaptive components of the immune system and other factors, such as the local and systemic inflammatory response, which can sometimes be more harmful than useful. Therefore, for dairy cows, particularly those in the periparturient period, it is important to avoid, or reduce as much as possible, any kind of infectious, parasitic or metabolic disease and the associated inflammation. Such inflammation can impair cow performance by lowering milk yield, dry matter intake, fertility and energy efficiency, and can reduce liver function. Good nutrition is essential in maintaining a functional immune system, while also avoiding other causes of inflammation, such as tissue damage, and digestive and metabolic syndrome-related disorders. Provision of appropriate nutrients, such as antioxidants, omega-3 polyunsaturated fatty acids, conjugated linoleic acid and vitamin D can have anti-inflammatory effects. In the future, ways to reduce inflammation while maintaining a good immune defence must be developed and the susceptibility of the cow to diseases and inflammation evaluated. Ideally, we would be able to selectively breed for cows with a lower susceptibility to both diseases and inflammation.

Additional keywords: dairy cow, health, transition period.

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Introduction

The periparturient period is widely recognised as a critical time for the health and productivity of dairy cows (Drackley 1999); for example, the incidence of several metabolic and infectious diseases, such as milk fever, metritis, acidosis, mastitis and lameness, is elevated during this period (Drackley 1999). The negative genetic relationship between milk yield and health could be one reason for the high incidence of health disorders during this period; however, the metabolic stress resulting from high milk yield coupled with a restricted capacity to reach the necessary nutrient intake is also a likely contributor (Pond and Newsholme 1999).

Recently, there has been increased interest in the interactions among the immune system, inflammation and nutrition. Nutrition influences the activity of the immune system and the inflammatory response through its effect on health, but health status also influences dry matter intake and the utilisation of nutrients, which can further exacerbate health problems. Taken together, the health status of the cow and her nutritional state can greatly affect dairy cow performance and efficiency.

Immune system: its function and the influence of nutrition

The immune system is an interactive network of lymphoid organs, cells and humoral factors, such as cytokines, organised to recognise, resist and eliminate contaminants that penetrate the body membranes. The immune system can be divided into two components, namely, innate and adaptive, on the basis of the speed and specificity of the reactions, although the two parts are highly integrated (Daha 2011). Innate immunity encompasses the physical, chemical and cellular elements of the immune system that provide immediate non-specific defence to the host through the actions of neutrophils, monocytes, macrophages, complement, cytokines and acute-phase proteins; ~95% of infectious challenges are resolved by innate immune responses (Daha 2011). Cells of the innate system recognise pathogen-associated molecular patterns and damage-associated molecular patterns through specific pattern-recognition receptors (PRRs) and produce mediators (cytokines) that induce inflammation and attract more immune cells into the damaged area (Medzhitov 2008).

According to Calder and Jackson (2000), malnutrition is caused not only by inadequate dietary intake but also by disease, which increases nutrient requirements while often decreasing voluntary intake. In fact, the two factors (i.e. ill health and malnutrition) can reinforce one another. A further complication is that, during the transition from gestation to lactation, dairy cows undergo physiological modifications that include some impairment of the immune system. Meglia *et al*. (2005) found that neutrophil phagocytosis and oxidative burst activity decrease dramatically in the month before parturition and Catalani *et al*. (2010) observed a higher endotoxin tolerance-like condition in early lactating dairy cows. Nevertheless, Sander *et al*.

(2011) and Graugnard *et al.* (2012) suggested that this suppression is less important than previously assumed. Important inflammatory response (Bertoni *et al.* 2008) and oxidative stress (Sordillo and Aitken 2009) can be also observed in the peripartum, but these phenomena have not received as much attention as has the immune system.

Inflammation mechanisms and relationships

Inflammation is the innate immune response to infection or injury, the latter generally referred to as sterile inflammation. Its function is to combat dangers of all types, not simply to recognise non-self from self (Piccinini and Midwood 2010). These are the best known causes of inflammation, but there is a growing interest in 'systemic chronic inflammation', which characterises certain conditions that will be discussed later and which, at least in humans, can contribute to the development of a wide variety of diseases, such as type-2 diabetes, cardiovascular diseases (Medzhitov 2008), cancer and neurodegenerative diseases. The innate immune system engages 'invaders' by a highly conserved set of PRRs. These receptors are the key to initiate inflammation and can be induced exogenously, by microbial or non-microbial inducers, or endogenously, by signals from stressed, damaged or otherwise malfunctioning tissues (Medzhitov 2008). Endogenous inducers may also include some crystals, such as monosodium urate, which causes gout, oxidised lipoproteins, which cause atherosclerosis, and advanced glycation end products, which are accumulated under hyperglycemic and pro-oxidative conditions that typify type-2 diabetes.

All of these inducers act on macrophages resident in tissue, on mast-cells and on specific tissue cells (Luster *et al.* 2005) to trigger the production of inflammatory mediators. These mediators include vasoactive amines and peptides, complement fragments, lipid mediators such as prostaglandins, thromboxanes, leukotrienes and lipoxins, pro-inflammatory cytokines such as TNFα, IL-1 and IL-6, chemokines, proteolytic enzymes, and also the purinergic signalling component as suggested by Seo *et al.* (2014). All together, the inflammatory mediators affect the vasculature and the recruitment of leukocytes and induce the acute-phase response, which may appear as changes to plasma protein concentrations, increased vascular permeability, but also as changes in metabolism. This coordinated set of responses helps repair damaged tissue.

The effects of these inflammatory mediators can be both local and systemic. The local response is characterised by redness, heat, swelling and pain, while the systemic response results in symptoms of fever, endocrine and brain effects. The most important systemic effects of inflammation are mediated by pro-inflammatory cytokines (PICs) and some eicosanoids, which act on peripheral and central targets (Kelley *et al.* 1994). Peripherally, PICs induce catabolic metabolism, increasing adipose tissue lipolysis and muscle proteolysis, and increase blood glucose probably due to increased cortisol release and insulin resistance. At the level of the liver, PICs increase the synthesis of some proteins and reduce the synthesis of others; these proteins are known as acute-phase proteins (APP). PICs also reduce the rate of gastric emptying, induce pain in the joints and affect activation of the pituitary–adrenal system, resulting in a rise in body temperature, lethargy and sickness, lower body-care activity, decreased locomotion and social exploration, and reduced interest in food and eating. These effects can help stop pathogens and favour repair of tissue damage. Nevertheless, depending on the seriousness of inflammation, the negative effects can be also very important for quality of life, due to their detrimental effect at a physical and mental level (Dantzer *et al.* 2008).

In humans, low-grade systemic inflammation, which is also called metaflammation, referring to its metabolic trigger, is associated with obesity and chronic diseases. The trigger is a surplus of nutrients and excessive metabolic activity (Hotamisligil 2006). This status is probably exacerbated by stressful conditions in the adipose tissue when adipocytes are hypertrophic and when there is hypoxia. When this happens local macrophages are activated and pre-adipocytes are converted to macrophage-like cells (Conroy *et al.* 2011).

The degree of inflammation is affected by the following three factors:

(1) the type of trigger: infection and injury, particularly if severe, produce the highest response, and tissue malfunction causes the lowest response;
(2) the severity of triggers: mild stressful conditions, whether infectious or non-infectious, can be handled by tissue-resident macrophages and mast cells, rather than a systemic response;
(3) the success of the inflammatory response: when the initial noxious stimulus has been removed, the animal usually returns to its basal homeostatic set point and the inflammatory event is resolved. This is not always the case and abnormal conditions can be sustained by the endogenous danger signals (damage-associated molecular patterns), which induce a pro-inflammatory cascade by activating toll-like receptors (Piccinini and Midwood 2010; see Fig. 1).

These three factors are very important because inflammation, particularly chronic inflammation, produces undesirable collateral effects in the host. According to Sorci and Faivre (2009), even if a good inflammatory response is essential to reduce the sensitivity to infections and to increase the prospect of survival, the inflammatory response may be viewed as a double-edged sword, protecting the host, but being potentially very harmful. This raises the question of whether we can modify inflammation without negatively compromising the whole defence mechanisms.

Because activation of toll-like receptors is the first step in the damage chain reaction (Fig. 1; Piccinini and Midwood 2010), we could perhaps reduce the local availability of toll-like receptors; however, this would increase susceptibility to pathogens (Si *et al.* 2014) and also to the bacteria responsible for symptoms of acidosis in ruminants (Chen *et al.* 2012). Nevertheless, this may not be the case when we consider low-grade systemic inflammation (metaflammation), because the potential risks are lower.

Effects of inflammation on welfare and efficiency of dairy cows

When a dairy cow becomes sick, its welfare deteriorates and its performance decreases; this appears to be particularly so when the malaise occurs during the periparturient period

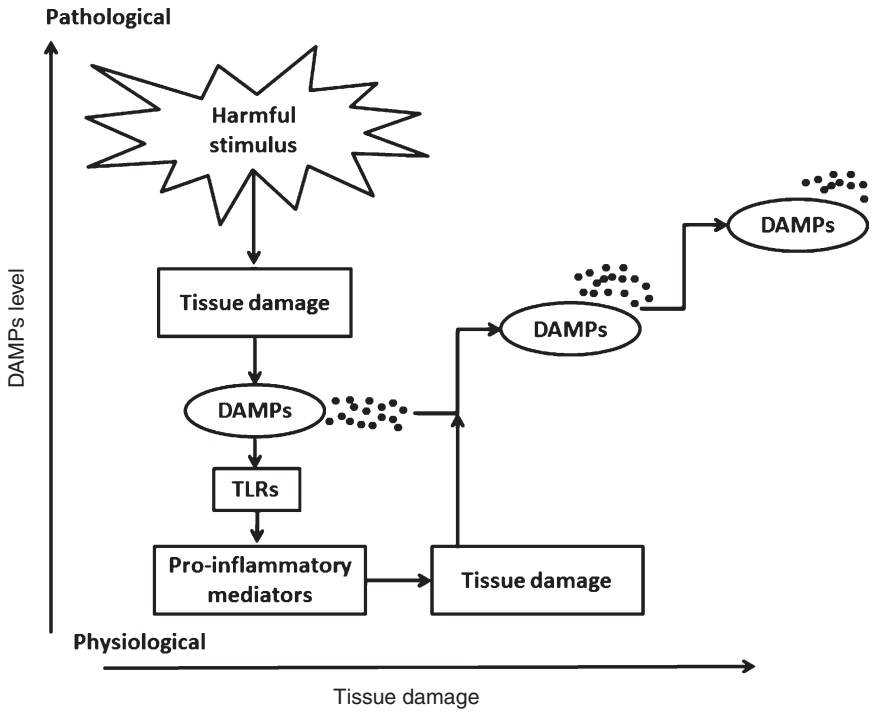

Fig. 1. The 'damage-chain reaction'. Harmful stimuli, including pathogens, injury, heat, auto-antigens, tumourous and necrotic cells, cause tissue damage. Endogenous danger signals are generated and induce a pro-inflammatory cascade by activating toll-like receptors (TLRs). Inflammation causes further tissue damage that magnifies the pro-inflammatory cascade (modified from Piccinini and Midwood 2010).

(Drackley 1999). Even subclinical disease can affect welfare; however, the effects are not evident. For example, Bertoni *et al*. (2008) undertook a retrospective study in which early lactation cows were separated into those with either high or low inflammatory responses at calving, regardless of their clinical symptoms. Their study demonstrated that inflammation in the transition period:

- can occur in many cows without clinical symptoms (58% of cows);
- was associated with a more severe negative energy balance than in unaffected herd mates, with a greater loss of body condition score and greater blood β-OH butyrate concentrations, despite lower milk production; and
- was associated with poorer reproductive performance, with cows requiring more insemination per pregnancy and having more open days.

So, systemic inflammation can occur at a subclinical level and can be serious enough to reduce dairy-farm efficiency in several ways. Energy efficiency was lowered by 15% in dairy cows with subclinical inflammatory conditions (Trevisi *et al*. 2010). This can be explained by the energy cost of mounting an inflammatory response, together with increased thermogenesis. These studies also drew attention to the high frequency of subclinical and clinical inflammation (assessed as acute-phase protein changes) in dairy farms ranked as having low animal welfare (Calamari *et al*. 2008).

The effects of systemic inflammation on liver function, primarily through elevated PICs, are particularly important. It promotes the synthesis and quick release into blood of positive APP, such as haptoglobin, serum amyloid A, C-reactive protein and ceruloplasmin (Powanda 1980). But, at the same time, it reduces blood concentrations of negative APP, such as albumins, some lipoproteins, retinol-binding protein and paraoxonase. The consequences of these changes in liver and whole body metabolism have recently been reviewed (Loor *et al*. 2013). A few examples illustrate the impact of inflammation on liver function. Among the usual liver proteins are the apolipoproteins, a reduction in which can favour the accumulation of triglycerides in the liver (Bertoni *et al*. 2008). There are also 'carriers' of vitamin and hormones, a lack of which threatens the availability of vitamin A and E, and perhaps D, or of hormones, such as cortisol, when the level of cortisol-binding protein is low (Trevisi *et al*. 2013). However, as a corollary to this, a proper evaluation of blood proteins of liver origin, in particular the negative acute-phase proteins, provides a useful way of monitoring systemic inflammatory response during the periparturient period (Bertoni and Trevisi 2013).

Nutrition of cows to reduce inflammatory responses

Nutrition is involved in inflammatory phenomena and may be a direct contributor through metabolic diseases or tissue damage caused by nutrient deficiencies or excesses as well as toxins such as mycotoxins. It may also impair the immune system indirectly, heightening the risk of infectious or parasite diseases. Nutrition can also transform the animal from a pro- to an anti-inflammatory phenotype, resulting in a lower inflammatory response to the same stimuli (Calder 2008).

When looking for ways to reduce inflammatory conditions in dairy cows, it is important to remember that there are many inflammatory conditions experienced during the periparturient period (Loor *et al*. 2013; Van Knegsel *et al*. 2014). These conditions include metabolic and infectious diseases, stressful events, such as unfavourable social interaction, trauma at calving time, energy excess or deficit, and digestive upsets (Drackley 1999). In contrast to lactation, the dry period is characterised by low requirements and high dry matter intake relative to requirements. As a consequence, an excess of energy, protein and minerals can occur during this period and it has been suggested that this can cause negative effects (Douglas *et al*. 2006). Janovick *et al*. (2011) suggested that, in ruminants as well as in humans, prolonged excess of energy could trigger a metabolic syndrome-like condition with associated inflammation. Results reported in a recent series of papers from the University of Illinois indicated that a high-energy diet in cows can cause fat to accumulate at a different rate in visceral adipose tissue than in subcutaneous adipose tissue, such that BCS is not a sensitive measure of overall nutritional condition of the cows (Drackley *et al*. 2014). Interestingly, the surplus energy did not induce an overt inflammatory response in subcutaneous adipose tissue (Ji *et al*. 2014*a*), but did in the visceral adipose tissue (Ji *et al*. 2014*b*). This may explain a phenomenon that has been observed previously, namely that cows fed a high-energy diet in the last part of pregnancy are more susceptible to infectious and/or inflammatory diseases (Janovick and Drackley 2010).

When considering risks associated with dietary factors that lead to acidosis, the transition period is important because early lactation cows are abruptly changed to a high-energy diet in an effort to minimise negative energy balance (Plaizier *et al*. 2012). Bertoni *et al*. (1989) suggested that conditions comparable to those in the rumen can also occur in the large intestine; this has since been confirmed in monogastric (Piè *et al*. 2007) and ruminant (Liu *et al*. 2014) species. The major problems associated with both ruminal and hindgut acidosis are attributed to the absorption of bacterial lipopolysaccharide through the ruminal epithelium or intestine mucosa; this results in an inflammatory response (Ametaj *et al*. 2005). However, some lipopolysaccharide is always present, both in the rumen (Nagaraja *et al*. 1978) and the intestine, without associated health problems in the host. Moreover, subclinical acidosis is not always followed by systemic symptoms (Trevisi *et al*. 2014). Therefore, the possibility that the integrity of both the ruminal epithelium and intestinal mucosa can be lost due to an underlying inflammatory response should be considered. For example, tight junctions (TJ) could be damaged, allowing microbial translocation and leading to more serious disorders. According to Plaizier *et al*. (2012), the barrier properties of TJ can be affected by several physiological stresses caused by antigens, microorganisms, PICs, cold or heat, dietary modification, early stage of lactation, psychological stress and prolonged exercise (Lambert 2009). We are not aware of specific data on the effects of such stresses in dairy cows at calving, but prolonged physical activity is common in dystocia, and heat and psychological stresses are also possible in summer or in conditions of overcrowding. These, and temporary reductions in feed intake, all have the potential to reduce the blood flow to the gut and cause hypoxia and associated TJ damage.

Animals with induced membrane-barrier leakage have been studied recently. When healthy sheep were injected with indomethacin – an anti-inflammatory and antipiretic drug with strong side effects at a gastro-intestinal level – sudden changes in blood proteins, typical of an acute-phase response, were evident. Concentrations of haptoglobin and ceruloplasmin rose, while those of albumin, cholesterol, vitamin A and paraoxonase fell. Interestingly, the lactulose test that was used to evaluate the integrity of the gut indicated that the absorption of lactulose was roughly correlated with the seriousness of the acute-phase response (Minuti *et al*. 2013). The induction of acute rumen acidosis by wheat flour in rams caused effects similar to those found in the indomethacin experiment, but rectal temperature also rose to 40.5°C. The kinetics of the appearance of lactulose in blood, however, suggested that it was absorbed before intestine, probably through the rumen wall, indicating that the forestomach epithelium may have been damaged (Minuti *et al*. 2014).

Nutrition can be managed to some extent to reduce metabolic or infectious diseases, as well as the tissue damage responsible for inflammation. Unfortunately, complete prevention of any inflammatory condition is impossible. Nonetheless, any attempt to reduce the inflammatory response and to accelerate resolution could be useful. All these aspects can be affected by the genome, as well as nutrition, because some nutrients can influence the gene expression (Grimble 2001). The first nutrients suggested that might reduce the inflammatory response in humans were ω3-polyunsaturated fatty acids (PUFA) and antioxidants, such as Se, vitamin C, vitamin E, β-carotene and polyphenols. The ω3-PUFA, but also conjugated linoleic acid (Williams 2000), appear to modulate several nuclear transcription factors, such as PPARα and NF-kB, that influence the expression of some genes that affect inflammation (Calder 2008). Preliminary results from our Institute on the use of nutrients to attenuate or avoid inflammation in transition dairy cows indicated promising possibilities for animal husbandry (Trevisi *et al*. 2008). The importance of antioxidants as potential nutrients for reducing inflammation is self-evident, because reactive oxygen molecules are known to release NF-kB – a nuclear activator of PICs gene expression – from the inhibitory unit (Rimbach *et al*. 2002). Other possible anti-inflammatory nutrients are amino acids, such as glutamine, which improves intestinal barrier function, and the sulfur-containing amino acids, which are involved in the antioxidant systems (Grimble 2002). Osorio *et al.* (2013, 2014) provided evidence of supplemental rumen-protected methionine as beneficial to alleviate inflammation and oxidative stress during transition period of dairy cows. A recent addition to the list is the active form of vitamin D_3, which downregulates PICs production by Th1 cells in favour of Th2 cell production of anti-inflammatory cytokines (Hewison 2012).

A new concept of nutritional involvement that goes beyond the anti-inflammatory involvement is to help eliminate inflammation altogether (Serhan *et al*. 2008). In this case, lipoxins, resolvins and protectins derived from essential PUFA provide potent signals that selectively stop infiltration of neutrophils and eosinophils and stimulate non-phlogistic recruitment of monocytes, which can occur without producing pro-inflammatory mediators.

Conclusions

There are interactions among the functionality of the immune system, the inflammatory response and nutrition and the consequences of inappropriate activation of the immune system or excessive inflammation may be very costly to the animal. Performance is impaired, as is efficiency and health. For these reasons, the activity of immune system and inflammation are maintained as low as possible by natural mechanisms and are activated only when needed and stopped as soon as possible.

Most farmers are aware of the need to prevent infections, parasitism and tissue damage, and employ methods of hygiene, vaccination, metaphylaxis, immunonutrition, auxinic use of antibiotics, pre- and probiotics, or other ways to avoid digestive disorders. These methods are primarily aimed at reducing the activation of the immune system, thereby reducing inflammation indirectly. This approach assumes that the immune system and the inflammatory response are always involved together, which is not always the case.

Inflammation is partly an independent defence mechanism that can occur without significant intervention of the immune system, as occurs during metaflammation or chronic inflammation. Therefore, in addition to the tools that we have discussed to avoid activation of an immune response, it may be useful to intervene directly in some of the specific causes of inflammation as well as on its mechanisms. Where nutrition is concerned, there are two main approaches. First, avoidance of any deficiency, excess or toxicity of particular nutrients to prevent tissue damage, or metaflammation, and, at the same time, optimising the immune system capacity and reducing susceptibility to infection. Second, the use of long-chain fatty acids, such as ω3 and conjugated linoleic acid, antioxidants, and/or trace elements, such as selenium, vitamin D, or glutamine. Further studies should:

- pursue the possibility of reducing the inflammatory response while maintaining good immune responsiveness;
- evaluate the phenotype of cows for immune system capacity and for the pro- or anti-inflammatory type; and
- explore a genetic solution by selecting animals with a low susceptibility not only to disease, but also to the inflammatory response.

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