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Interaction between inflammation and metabolism in periparturient dairy cows

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Introduction

A large body of work has been conducted to elucidate the link between the loss of viability, sensitivity to pro-inflammatory mediators and the impairment of antimicrobial functions affecting the innate immune cells, the occurrence of uncontrolled inflammations, and the sudden alteration of the metabolism during the transition from pregnancy to lactation in high-producing dairy cows. Despite this massive effort, a clear link is still missing. The intent of this review is to summarize our current knowledge on the subject and attempt to propose a link. In the first part of this review we provide an overview of the physiological adaptation during the transition from pregnancy to lactation focusing on the alterations affecting the innate immune system and the inflammation occurring during this phase. In the second part of the review, we propose a relationship between the function of the innate immune system, the inflammatory conditions, and the metabolism in dairy cows during the transition from pregnancy to lactation with the intent to elucidate the driving cause of immune alterations occurring in this phase. In the third and final part, we review some novel dietary strategies to optimize the function of the innate immunity in dairy cows describing their mode of action and their applicability as an aid for dairy cows during the peripartal phase.

Peripartum Period and Immune Dysfunction

In dairy cows, peripartum period includes the last 2 mo of gestation and the first month of lactation. Within the peripartum period, the 3 wk prior to and the 3 wk following parturition are termed the transition period (**TP**). The TP is known as the most challenging phase during the life of all mammals, including cattle (Drackley, 1999; Van Knegsel et al., 2014). Reduced immune competence typically affects innate immune cells during the TP (Goff and Horst, 1997). The impairment of the immune system is driven by a transcriptomic change in polymorphonuclear (**PMN**) cells between –1 and 2 wk from calving that negatively affects viability, survival, and sensitivity to pro-inflammatory mediators as well as their chemotaxis, phagocytosis, respiratory burst, and antioxidant systems (Cai et al., 1994; Kimura et al., 1999; Mehrzad et al., 2001; O'Boyle et al., 2012; Crookenden et al., 2016; Crookenden et al., 2017). Thus, a delayed migration of hypofunctional neutrophils is believed as one of the causes of a hypo-responsive state in cows during their peripartum period (Sordillo, 2016). Such a condition increases the likelihood of developing infectious diseases (Minuti et al., 2015a).

A systemic inflammatory status accompanies the reduction of PMN function in early lactation, which is a physiological consequence of events related to parturition (i.e., fatigue, psychological stress, tissue trauma, altered epithelial permeability, uterine infections; Trevisi et al., 2011a; Trevisi and Minuti, 2018). Systemic inflammations are often accompanied by the acute phase response in liver, which implies severe loss of the ability of the liver to perform its normal functions mostly due to altered synthesis of liver proteins (Cappa et al., 1989; Trevisi et al., 2005; Hotamisligil, 2006; Loor et al., 2007; Bertoni et al., 2008). During the acute phase, the liver produces more α-globulins, known as positive acute phase proteins (**APP**); i.e., serum amyloid alpha (**SAA**), haptoglobin, ceruloplasmin, and orosomucoid (Fleck, 1989;

Abbreviations

APP	acute phase proteins
CLA	conjugated linoleic acid
COX	cyclooxygenase
DHA	docosaheaenoic acid
DMI	dry matter intake
EPA	eicosapentaenoic acid
ETE	eicosatrienoic acid
GH	growth hormone
IFNγ	interferon gamma
IGF-1	insulin-like growth factor-1
LDA	left displacement of abomasum
NDF	neutral detergent fiber
NEB	negative energy balance
NEFA	nonesterified fatty acids
NEL	net energy for lactation
NFC	non-fiber carbohydrates
NF-κB	nuclear factor-κ beta
PPARs	peroxisome proliferation-activated receptors
peNDF	physical effective NDF
RP	retained placenta
PUFA	polyunsaturated fatty acids
SFA	saturated fatty acids
PEB	positive energy balance
SAA	serum amyloid alpha
PON	paraoxonase
TNF	tumor necrosis factor
PI	physiological imbalance
PICs	pro-inflammatory cytokines
TP	transition period
PMN	polymorphonuclear

Ceciliani et al., 2012). Conversely, the liver reduces the synthesis of albumin, retinol binding protein, paraoxonase (**PON**), and lipoproteins, known as negative APP (Schreiber et al., 1982; Bertoni et al., 2008) and sequesters minerals from circulating blood as zinc and iron (Bertoni and Trevisi, 2013).

Plasmatic trends of positive APPs has been proposed as a biomarker of the severity of inflammation, as they reflect the alteration of liver functions induced by the acute phase response (Castell et al., 1989; Fleck et al., 1989; Trevisi et al., 2012). Nevertheless, positive APPs have different sensitivity to the acute phase, as they are released at different intervals from the onset of systemic inflammation. Among positive APPs, haptoglobin is the most promising biomarker of inflammation in dairy cows (Bionaz et al., 2007; Huzzey et al., 2011). In fact, it has a longer plasma half-life relative to other positive APPs (i.e., SAA), requiring 60 to 96 h to return to normal circulating levels after an acute phase response (Giblett, 1961). Relation of haptoglobin concentration with WBC function has been investigated by Nightingale et al. (2015), who grouped 240 Holstein transition dairy cows into three classes according to their postpartum haptoglobin level: low (0 to 8.4 μg/mL), moderate (8.5 to 458 μg/mL), and high (459 to 1,757 μg/mL). Animals with the highest haptoglobin levels had a lower neutrophil count in blood, likely due to the recruitment of PMNs to inflamed peripheral tissues. Furthermore, PMNs from cows with the highest haptoglobin level produced higher amounts of tumor necrosis factor alpha (**TNF**), had an increased expression of *SELL*, and a greater respiratory burst activity, confirming that the level of plasma haptoglobin was related to the activation of PMNs, and thus to the inflammatory condition of the animals.

Immune Dysfunction in Peripartum Period: Causes and Effects

The exact cause of immune dysfunction in cows during peripartum period has never been clearly identified. Sudden changes in body homeostasis are—to a certain extent—physiological during the TP (Trevisi et al., 2011a). Severe stressful events that occur during late pregnancy (i.e., inadequate dry-off procedures, psychological stressful conditions resulting from overcrowding or uncomfortable equipment, heat stress, nutritional impairment, poor hygienic conditions) could induce such changes that exceed the control of homeorhetic and homeostatic mechanisms, inducing a physiological imbalance (**PI**) condition.

High circulating pro-inflammatory cytokines levels during the dry period may impair the immune system post-partum

Even though rare clinical signs are reported before calving, recent studies highlighted the dry-off as a challenging event that could activate innate immune system inducing metabolic inflammation (Mezzetti et al., 2020). The occurrence of a PI condition before calving could exacerbate inflammatory events in early lactation (Calamari et al., 2014; Minuti et al., 2020), although the connection between inflammatory events that occur during dry period and the severity of the acute phase response in early lactation is still unknown. Likely, excessive levels of circulating pro-inflammatory cytokines (**PICs**) prior to calving could increase the severity of inflammatory conditions at the onset of lactation through impairing the capacity of the adaptive immune system to intervene during inflammatory processes and delaying the recovery of normal function of tissues (Jahan et al., 2015; Trevisi et al., 2015). This could arise from the dysfunctional activation of dendritic cells driven by PICs, which are known to block the activation of T-lymphocytes (Joffre et al., 2009). This hypothesis is consistent with data by Nightingale et al. (2015), who found a lower production of interferon gamma (**IFNγ**) by whole blood cells after an LPS stimulation in cows having high haptoglobin levels after calving, reflecting an impairment of T-lymphocytes and adaptive immunity, and suggesting the interaction between the innate and adaptive immune systems was reduced as compare with cows having low haptoglobin levels after calving (Nightingale et al., 2015). Recent evidences suggest that cows having inflammatory conditions during the dry period are more prone to an impairment of pivotal body functions in early lactation (e.g., increased body temperature and reduced feed intake, likely as a consequence of inflammation after calving), increasing the risk in developing metabolic disorders (Mezzetti et al., 2019).

Limitations of maternal immune responses against the allogeneic conceptus

Reduced immune competence reported in TP could partially arise from the normal maternal immunotolerance against the allogeneic conceptus during the late gestation period (Esposito et al., 2014). Other than fluctuation in steroid hormones, immunotolerance is also triggered by specific immune cells (i.e., M2 macrophages, γδ T-cells, and T regulatory cells) that can inhibit inflammation and T-cell responses (Majewski and Hansen, 2002; Padua et al., 2005; Esposito et al., 2014). In particular, M2 macrophages are involved in inhibition of inflammatory conditions that could increase the risk of developing uterine infections (Esposito et al., 2014).

Alteration in the hormonal patterns

Steroidal changes, such as an increase of estradiol and a reduction of progesterone, occur before calving, while increases of protein homeorhetic hormones, such as prolactin, growth hormone (**GH**), insulin-like growth factor-1 (**IGF-1**), and insulin, occur after calving (Bauman and Bruce Currie, 1980; Tucker, 1985). The occurrence of a PI condition could alter the normal hormonal patterns in peripartum period. For instance, cortisol levels depend on the liver synthesis of a specific carrier protein, termed corticosteroid binding globulin. When inflammation occurs and liver protean syntheses are impaired, reduced production of corticosteroid binding globulin triggers an initial increase in free cortisol, which indicates more bioactivity (Pugeat et al., 1989). Then, negative feedback prevails and the hypophysis-pituitary-adrenal axis secretes less cortisol (Trevisi et al., 2013a). A direct relationship with immune functions has been well documented for most of the hormones aforementioned (Table 1), although these trends can only partially account for immune dysfunction in TP, as they do not overlap with the entire duration of the immune alterations.

Mastectomized pregnant cows face a shorter and less marked immune suppression status during calving as compared with animals with mammary glands, without any alterations in circulating WBCs (Nonnecke et al., 1993; Kimura et al., 1999; Kimura et al., 2002). These results suggest that the largest effect of reducing immune competence during calving could result from endocrine assets that alter body homeostasis in order to satisfy lactation requirements. Thus, an indirect effect on immune functions (which is discussed in detail in the following section) should be considered for most of the hormones fluctuating during TP (Table 1).

Alteration in nutrient availability

Cows entering the dry period are in a positive energy balance (**PEB**) condition (Mäntysaari and Mäntysaari, 2015). Three weeks prior to calving, nutrient requirements of the growing fetus reach maximal levels (Bell, 1995; Dingwell et al., 2001). Furthermore, as soon as milk production starts, mammary glands change the metabolic priorities in nutrient redistribution to start copious milk synthesis, which induces a drastic increase in energy, protein, and mineral requirements (Drackley, 1999; Leroy et al., 2008). These massive requirements cannot be satisfied from the feed intake during early lactation. The feed intake in this phase is limited by a combination of an insufficient rumen volume, as it is reduced during the dry period (Dirksen et al., 1985; Sordillo et al., 2009), and other not well-defined factors (Ingvartsen and Andersen, 2000), including alterations of the rumen microbiota due to dietary changes (Odensten et al., 2005; Calsamiglia et al., 2008; Minuti et al., 2015b), hormonal changes due to the parturition process, stress induced by calving, moving cows between pens (Ingvartsen, 2006; Nordlund, 2006), and the anorexic effect of PICs released due to calving or metabolic and/or infectious diseases (Jahan et al., 2015; Trevisi et al., 2015; Trevisi et al., 2016). Insufficient feed intake leads to a negative energy balance (**NEB**) that has been quantified to be >12 Mcal/d in Holstein dairy cows having an average milk yield of 45 kg/d during the first 3 wk of lactation (Rastani et al., 2001). Studies conducted on a model of feed restriction using mid-lactation cows (i.e., an early lactation-like NEB condition without the endocrine alteration related to calving) revealed that lack of energy affects the transcription of genes important for immune-competence in PMN, including down-regulation of genes encoding for defensins, cytokines, antigen presentation, respiratory burst, and inflammatory response (Moyes et al., 2010; Crookenden et al., 2017). The NEB also represses the expression of genes involved in the inflammatory response and chemotaxis in PMN during inframammary infection with *Streptococcus uberis* (Moyes et al., 2010). At the same time, greater mRNA expression of anti-inflammatory genes occurred, indicating a greater likelihood of developing additionally infectious diseases (Moyes et al., 2010) or in establishing chronic pathological conditions. Inflammation has a main role in aggravating the NEB condition at the onset of lactation, as TNF produced by activated leukocytes during inflammatory events could induce an insulin-resistance status though inhibiting solute carrier family 4 (*SLC2A4*), reducing glucose uptake in peripheral tissues (except for mammary gland and immune cells) and increasing lipolysis by the adipose tissue (Kushibiki et al., 2001; Bradford et al., 2009) (Table 1).

Glucose is the main energy source used by immune cells, and the effect sorted by NEB on immune cells at the beginning of lactation is driven by an insufficient availability of glucose in peripheral tissues due to the prioritization of milk synthesis (Sordillo et al., 2009). Data obtained in Holstein lactating cows after a stimulation with LPS indicated that an acutely activated immune system uses >1 kg of glucose within 720 min from the onset of inflammation (Kvidera et al., 2017). During mid-lactation, the activated immune system can compete for glucose though an up-regulation of *SLC2A1* and *SLC2A4* on immune cells (Moyes et al., 2016), reducing glucose availability for the mammary gland and, thus, reducing milk yield. This was supported by the study from Kvidera et al. (2017), who evaluated milk yield, acute phase response and lipid metabolism parameters in mid-lactating cows treated with LPS. They observed that LPS group had a marked acute phase response, resulting in severe milk loss compared to a control group. The authors also observed that maintaining glycemia through an euglycemic clamp did not reduce inflammation and, more importantly, did not prevent the reduction of milk synthesis. This could be due to the direct contribution of LPS in affecting the transcriptome of the mammary gland (Minuti et al., 2015c; Moyes et al., 2016), that could have decreased its milk synthesis independently from glucose availability. Conversely, a reduced expression of the solute carrier family 2, the main glucose transporter in immune cells, has been reported during the TP (O'Boyle et al., 2012), and this could make cells of the bovine immune system less competitive for glucose as compared with what is used for milk production in early lactation (Sordillo, 2016).

Alternative energy sources for immune cells include glutamine and nonesterified fatty acids (**NEFA**) (Calder, 2013), while ketones are not utilizable as an alternative energy source by leukocytes and have been shown to inhibit the immune response when their concentration is relatively high (Ingvartsen and Moyes, 2015). In early lactation, NEFA and glycerol are released into blood as a result of induced adipose tissue lipolysis. Circulating NEFA are completely oxidized in the liver to acetyl coenzyme A that enters the Krebs cycle to produce energy (Drackley, 1999; Herdt, 2000). Excessive lipid deposition that occurs during the dry period and/or severe and prolonged NEB increase the magnitude and duration of mobilization at the beginning of lactation. When mobilization is massive, NEFA can exert anorexic effects, further reducing the dry matter intake (**DMI**) and worsening the NEB (Ingvartsen and Andersen, 2000; Allen et al., 2009). As soon as lipomobilization becomes severe, the Krebs cycle becomes overloaded by NEFA, leading to their partial oxidation and to the diversion of acetyl coenzyme A to the production of ketone bodies (Drackley

Table 1. Trends of main hormones during transition period and their effect on immune functions

Class	Hormone trend[1]	Altering factors[2]	Effect on immune system[3]	References
Glucocorticoids	Cortisol (+) dry-off and calving time	(±±) Stress induced by milk yield higher than 25 kg/d at dry-off, pen movements, re-socialization, environment, weather, diet, parturition	Immune competence (D-): Down-regulation of *selectin-L* and *cluster of differentiation-18 adhesion molecules* on PMN[4], impairing their chemotaxis and diapedesis; altered cytokines production through impairment of *NF-κB*[5] functions Immune competence (I-): Reduce feed intake favoring lipomobilization. Induce increased expression of *PPARα*[6], which leads to coordinate induction of enzymes involved in plasma transport, intracellular trafficking and metabolism of fatty acids Inflammation (D±): Stimulates haptoglobin release from parenchymal liver cells	Burton et al., 1995; Drackley, 1999; Drackley et al., 2005; Bertulat et al., 2013; Putman et al., 2018
Catecholamines	Epinephrine, norepinephrine, dopamine (+) dry-off and calving time	(±±) Stress induced by pen movements, re-socialization, environment, weather, diet, parturition	Immune competence (D-): Activation of genes encoding for a variety of cytokines through the *cAMP-RBP*[7] activation Immune competence (I-): Provide the primary stimulus for increased mobilization of NEFA[8] from adipose tissue	Higuchi et al., 1994; Burton et al., 1995; Drackley, 1999; Padgett and Glaser, 2003; Do Nascimento et al., 2004; Cooke et al., 2012
Steroids	Progesterone High levels during gestation and rapid fall at calving Estrogen (+) late pregnancy	(Decrease) Deficiency of dietary n-3 fatty acids (Increase) Excess of dietary n-6 fatty acids	Immune competence (D-): Decrease functional capabilities of lymphocytes and PMN[4], reduce capacity to face bacterial infections Immune competence (I-): Decrease feed intake favoring mobilization of body fats	Roth et al., 1982; Davis, 1998; Drackley et al., 2005; Lamote et al., 2006; Kelley et al., 2007; Sordillo, 2016
Protein hormones	Insulin (+) late pregnancy; (-) early lactation	(Altered sensitivity) TNF released by leukocytes during systemic inflammations induce insulin resistance	Immune competence (I-): Increased insulin resistance of peripheral tissues reduces glucose uptake in peripheral tissues increasing negative energy balance condition, mobilization of body fats, liver ketogenesis and accumulation of triglycerides	Bell, 1995; Davis, 1998; Kushibiki et al., 2001; Lucy, 2001; Taylor et al., 2004; Kelley et al., 2007; Bradford et al., 2009; Sordillo, 2016
	Growth hormone (GH) (+) early lactation IGF-1 (-) early lactation		Immune competence (I-): Down-regulation of liver GH receptor during NEB[9] increase GH and decrease IGF-1 blood concentration, increasing lipolysis and gluconeogenesis	Lucy, 2001
	Leptin Falls in late pregnancy and remain low postpartum		Immune competence (I-): Can influence feed intake and contribute to peripheral insulin resistance in peripartum, increasing NEB[9] condition	Esposito et al., 2014

[1]Trend of main hormones: (-) indicates hormones that undergoes a reduction and (+) indicates hormones that increase during transition period.
[2]Main factors altering normal hormonal trends and their effects: (±) indicates an augmented magnitude of transition period trends; (Increase) indicates an upregulation and (Decrease) a down-regulation in the average hormonal production.
[3]Effect of the hormone on the immune system: (I) and (D) indicate an indirect and direct mode of action respectively; (+) and (-) indicate a positive or negative effect on immune function, respectively.
[4]Polymorphonuclear cells.
[5]Nuclear factor-κB.
[6]Peroxisome proliferation-activated receptor, alpha.
[7]Cyclic adenosine monophosphate response element-binding protein.
[8]Non-esterified fatty acids.
[9]Negative energy balance.

et al., 2006; Ingvartsen, 2006). Contemporaneously with the mobilization of NEFA, a massive mobilization of amino acids from muscle tissue occurs to meet the growing requirements of the mammary gland (Komaragiri and Erdman, 1997; Doepel et al., 2006), including the partial utilization of amino acids as gluconeogenic sources (Herdt, 2000). Deficiency of methionine and lysine worsens during NEB, while glutamine is one of the most scarcest amino acids in early lactation, since up to 74% of it is completely oxidized for energy production (Newsholme et al., 1985; Calder et al., 1990; Newsholme et al., 1999). Finally, mineral deficiency, particularly for calcium and magnesium, also occurs when milk production starts (Mulligan and Doherty, 2008). Calcium and magnesium deficiencies can be aggravated when the close-up rations contain excessive amounts of positively charged minerals (i.e., potassium > 1.4% on DM basis) that are known to affect mineral equilibrium in TP (Nightingale et al., 2015).

Thus, the lower efficiency of utilizing alternative energy sources (Sordillo, 2016), the direct toxic effect of certain metabolites at high concentration, and the deficiency of amino acids and minerals that are essential for immune cells (Calder, 2013) could partially explain the reduced immune competence reported with NEB conditions at the beginning of lactation (Table 2). Data indicate these encompass the impairment of phagocytosis, chemotaxis, and diapedesis of PMN (Stevens et al., 2011). In a recent ex vivo experiment (Sipka et al., 2020) data suggested a role of nutrient deficiency on the response of PMN in early lactating cows to inflammation via PI3K/AKT/mTORC1 kinase pathway. This pathway is involved in maintaining a critical balance between immune regulation and inflammation (Cobbold, 2013; Katholnig et al., 2013), and in preventing exaggerated innate immune responses (Weichhart et al., 2008; Troutman et al., 2012; Vergadi et al., 2017). Compared with a control media, PMNs from early lactating dairy cows incubated in vitro with a mixture of glucose, amino acids and insulin had a higher transcription of the anti-inflammatory cytokine IL-10 and decreased the transcription of the PICs IL12B and TNFA. When mixture of nutrients was provided in PMNs stimulated with LPS the increased transcription of the PICs was prevented (Sipka et al., 2020). Based on these data, a pivotal role of the nutrient availability could be hypothesized in the occurrence of exaggerated inflammatory events in early lactating cows. The adipokines released during NEB status could also be supposed to contribute to developing inflammatory condition, as these metabolites are known to serve as pro-inflammatory signals (Makki et al., 2013). Based on these data, a pivotal role of the nutrient availability could be hypothesized in the occurrence of exaggerated inflammatory events in early lactating cows.

Changes in fatty acid profiles in cell membranes due to large mobilization of NEFA early post-partum may also have a role in altering the production of oxylipids that act as immune mediators (Calder, 2006; Raphael and Sordillo, 2013). In normal conditions, palmitic (C16:0) and stearic acid (C18:0) are the main saturated fatty acids (**SFA**) present in the cell membranes of dairy cows, while oleic (C18:1, n-9) and linoleic (C18:2, n-6) acid are the main unsaturated fatty acids (**UFA**) (Contreras et al., 2010). In early lactation, plasmatic amounts of SFA increase as compared with mid-lactation, accounting for >35% of total plasmatic long chain-fatty acids after calving, while UFA account for the remainder (Drackley, 1999; Douglas et al., 2007). Thus, the proportion of several SFA, including lauric (C12:0), myristic (C14:0), and C16:0, increases in cellular membranes (Drackley, 1999; Douglas et al., 2007). Conversely, the amount of UFA, particularly polyunsaturated fatty acids (**PUFA**) ascribed to the n-3 series as eicosatrienoic acid (**ETE**; C20:3, n-3), eicosapentaenoic acid (**EPA**; C20:5, n-3), and docosaheaenoic acid (**DHA**; C22:6, n-3), decreases substantially in cellular membranes as compared with mid-lactation cows (Douglas et al., 2006; Sordillo et al., 2009). Such alterations could reduce the production of pro-resolving oxylipids, which "promote resolution of inflammation, clearance of microbes, reduction of pain, and promotion of tissue regeneration via novel mechanisms" (Serhan, 2017). Besides changes in fatty acids composing the cellular membrane, the fatty acids that compose NEFA can also directly affect immune functions, as summarized in Table 3.

Oxidative stress status

Oxidative stress has commonly been reported during TP of dairy cows (Bionaz et al., 2007; Celi, 2011; Celi and Gabai, 2015). Oxidative stress consists in a loss of reduction-oxidation (redox) homeostasis and in a consequent damage to various organelles and tissues (Sordillo, 2016). Such condition results from the accumulation of excessive amounts of oxidants, such as ROM and reactive nitrogen species, leading to the depletion of antioxidant defenses. The main components of ROM include oxygen ions (i.e., superoxide anion), free radicals (i.e., hydroxyl radical), and hydroperoxides (i.e., lipid and hydrogen peroxides), while nitric oxide can be considered as the main reactive nitrogen specie (Cipak Gasparovic et al., 2017). Increased in oxidative stress in TP can be the consequence of changes in metabolic adaptation of cows that occurs during this phase, as summarized in Table 4.

Oxidative stress causes damage to DNA, proteins, and lipids and can thus contribute to dysfunction of the immune system (Sordillo et al., 2009). Proteins are highly susceptible to oxidative stress, and their oxidation alters the function of receptors, transporters, or structural elements involved in the immune response (Celi and Gabai, 2015). As a significant amount of protein functions as enzymes, the effect of oxidation on one molecule is greater than stoichiometric, as enzymes serve as catalytic mediators in cells (Dalle-Donne et al., 2005). Furthermore, oxidized proteins can generate new antigens, inducing or exacerbating the inflammatory response (Halliwell and Whiteman, 2004). Oxidation of lipids is involved in immune dysfunctions as immune cells are highly susceptible to lipid peroxide chain reaction, due to the high PUFA content of their membranes (Calder, 2008). Lipid peroxidation generates the reactive electrophile species malondialdehyde, that cause toxic stress in cells (Del Rio et al., 2005). Damage includes altered cellular functions and signal transduction, which may exacerbate the inflammatory response and contribute to the dysfunction of the vascular endothelium in TP (Lacetera et al., 2005; Sordillo et al., 2007; Sordillo et al., 2009).

Oxidative stress also increases the pro-inflammatory phenotype of immune cells acting on redox-regulated pro-inflammatory factors (Cao et al., 2000; Weaver et al., 2001; Sordillo et al., 2009), and is also related to the up-regulation of pro-inflammatory genes related to leukocyte extravasation (i.e., intracellular adhesion molecule-1 and vascular adhesion molecule-1) that are known to induce pathologic pro-inflammatory reactions (Maddox et al., 1999; Sordillo et al., 2008). Oxidants can also serve as messengers in a wide range of signaling pathways, including pathways related to nuclear factor-κ beta (**NF-κB**) and mitogen activated protein kinase, that are involved in the production of cytokines, oxylipids, and immunoregulatory factors (Finkel, 2011; Brown and Griendling, 2015; Serhan, 2017). Activation of NF-κB via oxidative stress is the main cause of the greater production of TNF by monocytes of

Table 2. Main metabolites related to the negative energy balance status, their trend during transition period, their effects on immune cells and their mode of action

Metabolite trend[1]	Cell	Effect[2]	Mechanism	References
Glucose (-) late gestation and after calving	Macrophages, polymorphonuclear cells	Immune competence (-): Decrease of proliferation, differentiation, viability, chemotaxis and phagocytosis	Primary energy source for leukocytes. Low efficiency in alternative energy sources utilization	Barghouthi et al., 1995; Gamelli et al., 1996; Pithon-Curi et al., 2004; Sordillo, 2016
	Lymphocytes	Immune competence (-): Reduced mitogen-induced activation	Proliferation and secretory activities are glucose-dependent	Sordillo, 2016
NEFA (+) after calving	Polymorphonuclear cells	Immune competence (-): Inhibition of phagocytosis and synthesis of DNA	Impairment of cell viability	Lacetera et al., 2004
	Monocytes	Immune competence (-): Decreased diapedesis and secretion of IgM[3], TNF[4], and IL-6[5]	Reduced expression of mRNA encoding for L-selectin, TNF[4] and IL-6[5]	Lacetera et al., 2004
	Macrophages	Inflammation (±): Increase respiratory burst and induce apoptosis and necrosis	Increase of ROM[7] production	Scalia et al., 2006
	Lymphocytes	Immune competence (-): Altered proliferation, decreased secretion of IgM[3] and IFNγ[6]		Lacetera et al., 2004
Beta-hydroxybutyrate (+) early lactation	Macrophage, polymorphonuclear cells	Immune competence (-): Decreased chemotaxis, respiratory burst and superoxide anion production	Decrease cell viability as are useless as alternative energy source	Calder et al., 1990; Hoeben et al., 1997; Sartorelli et al., 1999; Suriyasathaporn et al., 1999
	Lymphocytes	Immune competence (-): Decreased blastogenesis, mitogenic responses and IgM[3] production	Decrease cell viability as are useless as alternative energy source	Targowski and Klucinski, 1983; Nonnecke et al., 1992; Takeuchi et al., 2010
Glutamine (-) late gestation and early lactation	Macrophage, polymorphonuclear cells	Immune competence (-): Reduced production of IL-1B and IL-6, reduced phagocytosis	Glutamine availability drive those functions (high oxidation efficiency)	Wallace and Keast, 1992; Ogle et al., 1994; Yassad et al., 1997
		Reduced production of nitric oxide (macrophages) and superoxide anion (polymorphonuclear cells)	Glutamine is related to the production of NADPH, that is essential in the respiratory burst	
	Lymphocytes	Immune competence (-) Reduced cell division and synthesis of lactate	Glutamine is precursor of purine and pyrimidine: essential in anabolic functions	Newsholme et al., 1985; Newsholme et al., 1999; Pithon-Curi et al., 2004

[1]Trend of main metabolites related to immune cells functions during transition period: (-) indicates metabolites that undergoes a reduction, (+) indicates metabolites that increase during transition period.
[2]Effect of main metabolites related to negative energy balance condition on immune functions: (-) indicate a depressive effect, (+) indicate a stimulating effect.
[3]Immunoglobulins M.
[4]Tumor necrosis factor, alpha.
[5]Interleukin-6.
[6]Interferon, gamma.
[7]Reactive oxygen metabolites.

Table 3. Main fatty acids, their trend during transition period, their effects on immune cells and their mode of action

Metabolite trend[1]	Cell	Effect[2]	Mechanism	References
Saturated fatty acids (SFA) (±) after calving; (+) C12:0; C14:0; C16:0	White blood cells	Altered lymphocytes activation, antibodies production and inflammation driven from the inhibition of *CD14*[7] and LPS-induced TNF[4] production	SFA can covalently modify proteins trough fatty acylation, altering membrane fluidity, influencing how proteins anchor to plasma membrane and affecting the formation of glycolypoproteins composing lipid raft, that are involved in lymphocytes activation, antibodies production and inflammation	Drackley, 1999; Raphael and Sordillo, 2013; Sordillo, 2016
	Polymorphonuclear cells	Inflammation (±): Activation of *NF-κB* through toll-like receptors (TLRs) 2 and 4, increased apoptosis and necrosis	C12:0, C14:0 and C16:0 are PAMPs[9] similar to the lipid A associated with bacterial LPS, that activates *NF-κB*[10] mediated gene expression, increasing inflammation and respiratory burst activity	Lee et al., 2003, 2004; Scalia et al., 2006; Shi et al., 2006; Sordillo et al., 2009; Esposito et al., 2014
	Macrophages	Immune competence (-): Decreased secretion of IgM[3], IFNγ[6], TNF,[4] and IL-6[5]. Altered ROM[8] production		
		Reduced phagocytosis, diapedesis, antigen presentation and synthesis of DNA	Impaired cell viability for the low efficiency in utilization as energy source	
Unsaturated fatty acids (UFA) (-) after calving; (-) C18:1 n-9; C18:2 n-6; C20:3 n-3; C20:5 n-3; C22-6 n-3	Polymorphonuclear cells	Inflammation (±): Increased ROM[8] production, increased phagocytosis	C18:2 n-6 interacts with *PPARG*[11]. C20:5 n-3 and C22-6 n-3 interacts with *TLR2*, *TLR4*, *PPAR* and sterol response element binding protein family of transcription factors. All these genes are involved in *NF-κB*[10] activation and UFA could act both as pro or anti-inflammatory factors. The lack of these fatty acids in the post partal period could induce uncontrolled inflammations	Lee et al., 2003; Lee et al., 2004; Gorjão et al., 2006; Scalia et al., 2006; Lee et al., 2010; Moallem, 2018
		Inflammation (±): Reduced expression of mRNA for IL-10 and IL-8, stimulated expression of *IL-1B* and *ICAM1*, altered expression of cyclooxygenase2 (*COX2*) and *TNF*		
	Monocytes	Immune competence (-) Reduced antigen presentation to lymphocytes	C20:5 n-3 and C22-6 n-3 reduce *MHC II*[12] and *ICAM1*[13] expression decreasing IFNγ[6] production	Lee et al., 2003, 2004; Gorjão et al., 2006; Scalia et al., 2006
	Macrophages	Inflammation (-) Increased phagocytosis, inhibition of TLRs	C20:5 n-3 and C22-6 n-3 inhibits *TLR2* and *TLR4* reducing expression of *NF-κB*[10] and sorting anti-inflammatory effects	Calder et al., 1990; Lee et al., 2003; Lee et al., 2004
	Lymphocytes	Inflammation (-) Increase the production of IL-10, TNF, and IFNγ[6] Increase the production of IL-4 in circulating T-cells	C20:5 n-3 and C22-6 n-3 inhibits the production of prostaglandin E2, that is known to reduce IFNγ[6] synthesis and lymphocytes proliferation	Hughes and Pinder, 2000; Trebble et al., 2003; Gorjão et al., 2006; Brassard et al., 2007

[1]Trend of main fatty acids during transition period: (-) indicates fatty acids that undergoes a reduction and (±) indicates those that increase during transition period in plasma; (-) indicates fatty acids that undergoes a reduction and (+) indicates those that increase during transition period in plasmatic membranes.
[2]Effect of main fatty acids on immune functions: (-) indicate a depressive effect, (+) indicate a stimulating effect.
[3]Immunoglobulins M.
[4]Tumor necrosis factor, alpha.
[5]Interleukin-6.
[6]Interferon, gamma.
[7]Cluster of differentiation 14.
[8]Reactive oxygen metabolites.
[9]Pathogen-associated molecular patterns.
[10]Nuclear factor-κB.
[11]Peroxisome proliferation-activated receptor, gamma.
[12]Major histocompatibility complex, II.
[13]Intercellular adhesion molecule.

Table 4. Main biological process related to calving and involved in the development of the oxidative stress status in dairy cows during the transition period: their site of occurrence, their biological function and the mechanism by which they contribute in altering redox status

Biological process	Site	Function	Mechanism	References
Cellular respiration	All tissues	Conversion of nutrient to energy aimed to face requirements for milk synthesis and secretion	ROM[1] are formed in mitochondria as byproduct of electron transport chain and their massive production deplete antioxidant systems	Bell, 1995; Hodgkinson et al., 2007; Sordillo et al., 2007; Valko et al., 2007; Sordillo and Aitken, 2009
Colostrogenesis	Mammary gland			
Fatty acid metabolism	Liver		ROM[1] are formed in peroxisome consequently to beta-oxidation	Drackley, 1999; Grum et al., 2002
Respiratory burst	Phagocytes	Kill microbial pathogens during inflammation	ROM[1] are formed in phagocytes from NADPH[2] oxidase system; Macrophages produce nitric oxide as a cytotoxic agent; Neutrophils releases hypochlorous acid through the myeloperoxidase activity, generating di-tyrosil residues from serum albumin	Babior, 1999; Dedon and Tannenbaum, 2004; Bordignon et al., 2014
Oxylipid biosynthesis	Cellular membranes	Regulation of inflammatory process and immune response	Lipid peroxide and superoxide anion are byproduct of the oxidative reactions of PUFA[3] triggered by COX[4], LOX[5] or cytochrome P450	Raphael and Sordillo, 2013
Reduced dietary intake	Gut, tissue and blood	Adaptation to physiological imbalance related to calving	Reduced plasma concentrations of serum-derived micronutrients (i.e., vitamins and minerals) with antioxidant properties	Spears and Weiss, 2008; Sordillo and Mavangira, 2014
Increased utilization of antioxidant systems	Blood and tissues	Facing metabolic stress occurred in transition period; Satisfying increased vitamins requirements of growing fetus		
Lipomobilization and triglycerides deposition	Liver cells	Supply to growing energy demand	Liver damage and dysfunction reduce plasma cholesterol and high-density lipoproteins, which bound paraoxonase, an important antioxidant enzyme, to the blood	Turk et al., 2005
Inflammatory status		Face tissue damages and infections related to calving		

[1]Reactive oxygen metabolites.
[2]Nicotinammide adenine dinucleotide phosphate.
[3]polyunsaturated fatty acids.
[4]Cyclooxygenase.
[5]Lipoxigenase.

transition cows as compared with monocytes of mid-lactating cows (Sordillo et al., 1995). This is consistent with the reverse relationship between TNF production by PMNs and the availability of antioxidants highlighted by O'Boyle et al. (2006) in transition cows.

Immune dysfunction and the incidence of disease in transition cows

The occurrence of disease is known to increase during the TP, which impairs performance in the following lactation (Pinedo et al., 2010; Trevisi et al., 2011b). Multiple diseases tend to occur during the TP in dairy cows rather than isolated diseases (Sordillo, 2016). The occurrence of one of these diseases (primary) significantly increases the risk of developing secondaries diseases, with substantial economic impact on the dairy industry (Curtis et al., 1985; Ingvartsen, 2006). The relationship between the various diseases typical of the TP and immune dysfunction is complex and has not been fully elucidated.

Examples of metabolic diseases related to TP are fatty liver, milk fever, retained placenta (**RP**), ketosis, left displacement of abomasum (**LDA**), and lameness (Kelton et al., 1998; Ingvartsen, 2006). As most of these metabolic diseases occur at the beginning of lactation whereas immune dysfunction seems to begin earlier, it is possible that several of the factors affecting immunocompetence reviewed in the previous sections are also involved in the occurrence of metabolic disorders. Most of metabolic disorders are known to further impair the PI conditions, increasing the risk ratio of secondary diseases, either metabolic or infectious, as summarized in Table 5. For example, excessive deposition of triglycerides in the liver of dairy cows has been suggested to increase the production of haptoglobin. In this situation, an increase of haptoglobin production is in direct response to a lipid infiltration in the liver occurred during dry period, which acts as a harmful stimulus for parenchymal liver cells (Katoh et al., 2002), and liver lipidosis could thus increase the risk of developing metabolic inflammations in early lactation. Conversely, the occurrence of a severe acute phase reaction in the liver during the TP (i.e., due to an endotoxemia) has been reported to reduce the DMI, thus promoting liver lipidosis through increasing the mobilization of NEFA (Bobe et al., 2004; Bertoni et al., 2006a). In both cases, the negative effect of lipid mobilization-related metabolites on immune response of leukocytes and their dysregulation consequential to the severe acute phase response, could account for the increased mastitis and metritis incidence reported after fatty liver (Van Winden and Kuiper, 2003; Ametaj et al., 2005).

Different from metabolic disorders, increased incidence of infectious disease at the beginning of lactation could be clearly interpreted as a direct effect of impaired immune competence around calving (Ingvartsen, 2006). Previous studies found that cows that developed endometritis and metritis had reduced prepartal leukocytes phagocytosis (Kim et al., 2005), a reduced glycogen concentration in circulating neutrophils at calving (Galvão et al., 2010), and reduced TNF expression in monocytes after stimulation with *E. coli* (Galvão et al., 2012). Furthermore, some modifications of immune function detected in PMNs during TP (e.g., reduced chemotaxis, delayed migration, reduced antimicrobial activity, and ROM production) are also consistent with the increased susceptibility to mastitis, endometritis, and metritis reported in transition cows, and may also account for the escalated severity of diseases registered as compared with mid-lactating animals (Hill, 1981; Cai et al., 1994; Shuster et al., 1996).

Nutritional Strategies to Prevent Immune Dysfunction in the Transition Period

Strategies to improve immune functions of dairy cows during the TP include management adjustments aimed to minimize the environmental stressors (i.e., accurate dry-off routine, optimal hygienic conditions, good animal well-being, calm and easy parturition) during this phase and nutritional strategies aimed to sustain the immune cells. Management and environmental strategies have been widely reviewed elsewhere (Aleri et al., 2016), while this review will be focused mainly on nutritional strategies to optimize dairy cows immunity. These should be focused on reducing the degree of PI early post-partum, as this condition could be referred to as a common denominator between immune dysfunction and an increased likelihood of disease. Provision of a balanced and healthy diet should be considered as a focal point in this respect (Bertoni et al., 2015; Bertoni et al., 2016). Although optimal dietary concentrations of fermentable carbohydrate, fiber, sugar, and starch for transition cows are still being defined, NRC provided guidelines for diet formulations that fit most nutritional requirements of this phase (NRC, 2001).

Management of the energy balance through modulating diet concentration

Avoiding excessive lipid deposition during the dry period and minimizing NEFA mobilization processes in early lactation is crucial to reduce NEB-related dysfunctions of leukocytes. Thus, monitoring BCS of dairy cows and applying an energy plan aimed to decrease the early lactation-NEB are essential points to consider during the TP. Dairy cows should enter the dry period with a BCS of 3.5 out of 5 (Agricultural Development and Advisory Service, 1986), in order to minimize the amount of stored triglycerides. An energy content of 1.25 Mcal/kg DM is considered the ideal net energy for lactation (NE_L) that should be provided between dry-off and 3 wk prior to parturition to minimize the BCS gain during the dry period (NRC, 2001). Such a low energy diet should be provided with a high-fiber content, aimed to increase the rumen capacity so to help maximize feed intake early post-partum (Contreras et al., 2004; Esposito et al., 2014).

An energy content of 1.54–1.62 Mcal/kg DM is considered to be the ideal NE_L value that should be provided during the last 3 wk prior to parturition to meet the growing requirements of the fetus and ensure a BCS of approximately 3.5 at calving (Overton and Waldron, 2004). This phase is also fundamental in allowing a smooth increase of dietary fermentable starch till enriching early lactation-levels, as a sudden increase of starches in the diet could induce a reduction of rumen pH resulting in acidosis condition. Rumen acidosis could alter rumen fermentations and the permeability of epithelium (Minuti et al., 2015b), reducing DMI in early lactation and increasing the severity of NEB conditions in this phase (Allen et al., 2009). Increasing non-fiber carbohydrates (**NFC**) or highly digestible neutral detergent fiber (**NDF**) levels since 3 wk prior to calving (in rations with adequate physical effective NDF [**peNDF**] amounts) improves the development of rumen papillae and ameliorates the VFA absorption, minimizing the likelihood of developing rumen acidosis in early lactation (Rabelo et al., 2003). Furthermore, such a strategy increases levels of propionate, improves gluconeogenesis, and bacterial protein synthesis at rumen level (Overton and Waldron, 2004), sorting positive effects on glucose availability and reducing liver triglycerides content, with a reduction of the incidence of metabolic disorders and reproductive issues in early lactation

Table 5. Time course relationship between main transition period diseases, their effect on physiological imbalance conditions and possible secondary diseases triggered from it

Primary	Effect on physiological imbalance	Secondary	References
Retained placenta	Raise of PIC[1]; depression of DMI[2]; increase of NEB[3] and lipomobilization; acute phase response	Mastitis, ketosis	Dohoo and Martin, 1984a; Emanuelson et al., 1993; Trevisi and Bertoni, 2008
Ketosis	Ketone bodies production; depression of DMI[2]; increase of NEB[3]; impairment of immune functions; decrease of vitamin A and increase of bilirubin	Mastitis, metritis, left displacement of abomasum	Oltenacu and Ekesbo, 1994; Duffield, 2000; Rodriguez-Jimenez et al., 2018
Milk fever	Depression of DMI[2]; increase of NEB[3] and lipomobilization; decreased smooth muscle function (essential for digestive tract); increased cortisol secretion	Ketosis; left displacement of abomasum; retained placenta	Dohoo and Martin, 1984b; Loor et al., 2013; Esposito et al., 2014
Left displacement of abomasum	Depression of DMI[2]; increase of NEB[3] and lipomobilization	Ketosis	Dohoo and Martin, 1984a
Fatty liver	Increased haptoglobin production and inflammation; increased PIC[1] production; depression of DMI[2]; increase of NEB[3] and lipomobilization; acute phase response	Metritis, laminitis, displacement of abomasum, mastitis	Van Winden and Kuiper, 2003; Ametaj et al., 2005; Bertoni et al., 2006a
Infectious diseases	Decreased glutamine concentrations due to tissue and immune cells consumption; repression of genes related to inflammatory response and PMN[4] chemotaxis; greater expression of mRNA for anti-inflammatory genes and oxidative stress	Metritis, mastitis, infectious diseases	Holtenius et al., 2004; Moyes et al., 2009

[1]Pro-inflammatory cytokines.
[2] Dry matter intake.
[3]Negative energy balance.
[4]Polymorphonuclear cells.

(Gong et al., 2002). Nevertheless, some studies reported this increased energy concentration to be associated with an increased susceptibility to the inflammatory response at calving time (Janovick et al., 2011; Graugnard et al., 2013), suggesting a condition that mimics metaflammation in humans (Egger and Dixon, 2009).

Avoiding excessive amounts of NFC and highly fermentable NDF is pivotal during the first month of lactation, as one of the limiting factors for feed intake is the chemical effect of metabolites related to the oxidation of fuels in this phase, and excessive propionate productions could directly contribute in reducing DMI (Choi and Allen, 1999). Conversely, rumen availability of starch, NFC, and fermentable fiber should be incremental, likely since the second to third month of lactation only, when the peak of lactation occurs and cows have overcome the NEB condition. In fact, feed intake is limited from gut fill in this phase, and increased production of propionate, driven from the increased fermentable substrate, increases insulin concentration and reduces lipomobilization without affecting DMI (Drackley, 1999).

Supplementation of lipids

Fat supplementation may have a main role in affecting immune functions during TP. Fatty acid composition of lipid sources fed during the TP affect the lipid composition of cell membranes and the NEFA profile in blood (Calder, 2002; Calder, 2008). The modulatory effect of fatty acids on immune functions is well-known (Table 3). Thus, an effective strategy to modulate the immune response in TP could be the administration of rumen-protected PUFA aimed to shift the fatty acid composition of cell membranes (Table 6). N-3 PUFA and conjugated linoleic acid (**CLA**) are known to affect the inflammatory response and modulate the expression of nuclear transcription factors, such as peroxisome proliferation-activated receptors (**PPARs**) and NF-kB (Bertoni et al., 2016), that are known to play an important role in the regeneration of tissues, differentiation, insulin signaling, overall lipid metabolism, and immune response (Bionaz et al., 2013a; Bionaz et al., 2013b). Ensuring a n-6:n-3 ratio equal to 2:1 has been suggested as the ideal value to provide in the ration (Moallem, 2018). A relevant role of dietary n3-PUFA in modulating the activity of immune cell and improving the immune response of dairy cows is supported by a large number of studies, as previously reviewed (Moallem, 2018). The response to n-3 supplementation is however dependent on the dose and physical form of the n-3 source used (Michael A. Ballou et al., 2009).

Providing a high-fat diet to dairy cows during the dry period has also been hypothesized as a strategy to induce the peroxisomal beta-oxidation process (Drackley, 1999), reducing the incidence of diseases and liver lipidosis in the peripartum period (Bertoni et al., 1989; Drackley, 1999). Thus, a positive effect on leukocytes function through mitigating NEB-related dysfunctions could be expected. In comparison to mitochondrial beta-oxidation, peroxisomal beta-oxidation is catalyzed by an oxidase (Acyl-CoA-oxidase) that produces hydrogen peroxide rather than reduced NAD, which releases a larger amount of heat and less reduced cofactors (Drackley, 1999). Moreover, peroxisomes do not contain any electron chain linked to ATP production and thus this process is not regulated by the energy demand of the cell. Consequently, induction of peroxisomal beta-oxidation could provide an aid to the mitochondrial pathway during the NEB condition, when a NEFA overflow occurs (Drackley, 1999). Such a strategy has been suggested to reduce the hepatic accumulation of triglycerides at

Table 6. Main nutritional supplements aimed to modulate dairy cow's immunity during transition period and their mode of action on immune cells

Supplement	Effect	Mechanism	References
n-3 PUFA (C20:5 n-3; C22:6 n-3)	Inflammation (-) Mitigation of pro-inflammatory response (reduced TNF[1] and IL-6[2] production) of immune cells to high NEFA[3] concentrations (as those observed with high lipomobilization) Immune competence (±) Improved lymphocytes and mononuclear cells function in transition period: improved cell-mediated immune response; increased phagocytosis and decreased oxidative stress damages in PMN[4], leading to improved uterine and udder health in early lactation; modified mononuclear cells/PMN[4] ratio	Decrease the amount of arachidonic acid in cell membranes, shifting the oxylipid profile: increased production of resolvins, protectins and lipoxins/ reduced production of PGF2A[8] from endometrium (that exert pro-inflammatory effect) and of prostaglandin E2 (that impairs IFNγ synthesis and lymphocytes proliferation). Decreased expression of adhesion molecules involved in inflammatory interactions between leukocytes and endothelial cells; Decreased liver ketogenesis; Direct action on Toll-like receptor 4 inhibiting the LPS-induced *NF-κB* activation reduces the expression of transcription factors and PICs[5]. Activates PPARG reducing the production of TNF by leukocytes and partially reversing the insulin resistance caused by this cytokine, thus increasing the glucose available for leukocytes	Kushibiki et al., 2001; Lee et al., 2003; Trebble et al., 2003; Lessard et al., 2004; Mattos et al., 2004; Brassard et al., 2007; Ballou et al., 2009b; Trevisi et al., 2011b; Contreras et al., 2012b; Contreras et al., 2012a; Bionaz et al., 2013a; Dirandeh et al., 2013; Minuti et al., 2015a
n-6 PUFA (C18:2 *cis-9 trans-11* and *trans-10 cis-12*)	Inflammation (-) Increased albumin and cholesterol concentrations in early lactation Immune competence (±) Enhanced neutrophils function in transition period	Modulation of the *NF-κB*[9] inhibiting the LPS[10]-induced inflammatory activity in macrophages Protection of paraoxonase against oxidative inactivation, reducing oxidative stress status; Increased secretion of VLDL[11] and apolipoprotein B100 (involved in lipid redistribution through tissues), decreasing cellular accumulation of triglycerides from palmitic acid, increasing DMI[12], reducing NEB[13] and lipomobilization (lower NEFA[3] and BHB[14] levels in blood)	Cheng et al., 2004; Trevisi and Bertoni, 2008; Silvestre et al., 2011
Vitamin A	Prevention of oxidative stress status	β-carotene prevents fatty acid peroxidation chain reaction	Sordillo, 2016
Vitamin C	Mitigation of oxidative stress status	Ascorbic acid act as a radical scavenger	Sordillo, 2016
Vitamin E	Mitigation of oxidative stress status	α-tocopherol disrupts fatty acid peroxidation chain reaction	Trevisi et al., 2011b; Sordillo, 2016
Vitamin D_3	Inflammation (-) Down-regulation of PICs[5] in favor of AICs[6] production	Inhibits Th1 sub-family of lymphocytes in favor of Th 2	Bertoni et al., 2015
Selenium	Mitigation and prevention of oxidative stress status	Active component of thioredoxin reductase and glutathione peroxidase enzymatic complexes, that controls redox signaling and reduce ROM[15] production	Sordillo, 2016
Copper	Mitigation and prevention of oxidative stress status	Active component of ceruloplasmin, that exert oxidase activity as peroxyl radical scavenger, and superoxide dismutase, that converts cytosol superoxide to H_2O_2	Osorio et al., 2016; Sordillo, 2016
Zinc	Mitigation and prevention of oxidative stress status	Active component of superoxide dismutase, that converts cytosol superoxide to H_2O_2, and metallothionein, which is a cysteine-rich radical scavenger	Sordillo, 2016
Manganese	Mitigation of oxidative stress status	Active component of superoxide dismutase that converts cytosol superoxide to H_2O_2	Osorio et al., 2016; Sordillo, 2016
Iron	Mitigation of oxidative stress status	Active component of catalase, that converts H_2O_2 to water	Sordillo, 2016
Choline	Reduced hepatic triglycerides abundance and fat infiltrations; mitigation of oxidative stress status	Quasi-vitamin that is a structural component of phosphatidylcholine, that is required for the synthesis of VLDL[11] by the liver; important sources of the intracellular antioxidants glutathione and taurine	Esposito et al., 2014; Zhou et al., 2016

Table 6. Continued

Supplement	Effect	Mechanism	References
Methionine and lysine	Reduced hepatic triglycerides abundance and fat infiltrations; mitigation of oxidative stress status	They affect mitochondrial beta-oxidation of fatty acids in liver and export of triglycerides as VLDL[11]; important sources of the intracellular antioxidants glutathione and taurine	Esposito et al., 2014; Zhou et al., 2016
Acetylsalicylic acid	Inflammation (-): Reduced positive APPs[7] abundance and improved liver synthesis	Inhibition of cyclooxygenase enzymatic complex reducing the synthesis of pro-inflammatory oxylipids	Trevisi et al., 2003; Bertoni et al., 2007; Trevisi and Bertoni, 2008; Shin et al., 2010; Kim et al., 2012; Grossi et al., 2013
Hottuynia cordata extract	Inflammation (-): Reduced production of TNF[1] and pro-inflammatory oxylipids		Shin et al., 2010; Kim et al., 2012
Aloe arborescens Mill. extract	Inflammation (-): Increased negative APPs[7] concentration	Reduced mobilization of body fats and improved liver synthesis	Trevisi et al., 2013, 2017

[1]Tumor necrosis factor.
[2]Interleukin-6.
[3]Non-esterified fatty acids.
[4]Polymorhonuclear cells.
[5]Pro-inflammatory cytokines.
[6]Anti-inflammatory cytokines.
[7]Acute phase proteins.
[8]Prostaglandin 2, alpha.
[9]Nuclear factor κB.
[10]Lypopolysaccharides.
[11]Very low-density lipoproteins.
[12]Dry matter intake.
[13]Negative energy balance.
[14]Beta-hydroxybutyrate.
[15]Reactive oxygen metabolites.

calving, thus decreasing the likelihood of developing fatty liver syndrome (Bertoni et al., 1989), and could also be effective in mitigating any negative effects sorted by NEFA on immune cells. Large transcriptomics analysis of the liver of dairy cows that were fed-restricted or overfed during the close-up period appear to support such hypothesis (Shahzad et al., 2014). The data indicated that fed-restricted cows had higher circulating NEFA prepartum and this induced fatty acid oxidation via activation of PPARs. Nevertheless, this hypothesis still lacks scientific evidence where cows are supplemented fat before calving. In fact, from the best of our knowledge, the induction of peroxisomal beta-oxidation driven by administering high-fat diets to dairy cows during the dry period has never been demonstrated in any experimental study to date.

Supplementation of antioxidants

Other than the increased production of oxidant species, altered redox homeostasis that occurs in TP is triggered by the consumption or lack of a proper antioxidant system. An effective strategy to reduce negative effects of oxidative stress status on immunity could be the supplementation of minerals and vitamins involved in the antioxidant system during the late gestation and early lactation period (Table 6). Vitamins and trace minerals have critical roles in a variety of physiological process, particularly antioxidant defense, and a deficiency may depress immunity especially in peripartal or transition cows (Spears and Weiss, 2008). Inflammatory-like status that commonly occurs after calving is known to reduce circulating minerals (i.e., zinc, iron, and copper), sequestering them in liver (Osorio et al., 2016) and thus contributing to the development of an oxidative stress condition in early lactation that negatively affects WBC function.

Methyl donor supplementation

Methyl donor species are involved in lipid metabolism and lipoprotein synthesis. In dairy cows, their availability is limited by the extensive degradation in the rumen (Zhou et al., 2016). At the beginning of lactation, the availability of such compounds is suddenly reduced, as milk from dairy cows is high in methylated compounds and the levels secreted into milk are maintained even at the cost of depleting liver tissue reserves (Pinotti et al., 2002; Zhou et al., 2016). Lower levels of methyl donors negatively affect lipid metabolism, which increases NEFA accumulation and ketone body production. This condition will reduce feed intake, further increasing lipomobilization and enhancing the negative effects sorted by NEFA on WBC. Thus, supplementation of methyl donors during late gestation and early lactation phases could ameliorate the utilization of lipid sources, reducing the likelihood of developing ketosis and liver lipidosis in early lactation and mitigating the negative effects of excessive lipomobilization on immune cells. Furthermore, methyl donors are important sources of the intracellular antioxidants glutathione and taurine (Zhou et al., 2016) and thus their administration in TP could mitigate oxidative stress, which would ameliorate leukocyte functions and reduce the degree of inflammation (Table 6).

Anti-inflammatory product supplementation

Nutritional additives could be used in TP to transform the animal from a pro- to an anti-inflammatory phenotype to a certain extent (Bertoni et al., 2015). Among these, vitamin D3 and plant extract could provide an aid in modulating over-exuberant inflammatory responses during calving. Acetylsalicylic acid is a common drug, formerly derived from plants, that has been successfully used in dairy cows to attenuate their systemic response to inflammation during TP (Bertoni et al., 2004; Trevisi and Bertoni, 2008; Bertoni et al., 2013). Providing 15 g/d of acetylsalicylic acid to dairy cows for 3 to 4 d after calving reduced the severity of inflammation and the incidence of clinical diseases in early lactation, thus exerting positive effects on their milk yield and fertility (Trevisi and Bertoni, 2008), likely because of its positive impact on the resolution pathways of inflammation (Serhan, 2017).

Other plant extracts, as *Hottuynia cordata* supercritical extract, have been suggested to be potential anti-inflammatory drugs, although the effects of *Hottuynia cordata* have not been evaluated in dairy cows in TP. However, in murine models, the extract reduced TNF production and inhibited pro-inflammatory oxylipids synthesis by cyclooxygenase (**COX**) enzymatic complex (Shin et al., 2010; Kim et al., 2012). *Aloe arborescens Mill.* has been successfully utilized to modulate the inflammatory status of transition cows (Trevisi et al., 2013b). Administration of 150 g d^{-1} of *Aloe* extract during the 4 wk around calving did not affect the production of positive APPs, but reduced mobilization of body fats, improved liver metabolism, and mitigated the negative APPs drop after calving (i.e., albumin, PON, cholesterol, lipoproteins and retinol binding proteins).

Finally, treatment with cytokines during TP has been hypothesized to be a potential strategy to reduce the severity of inflammatory phenomena. In an in vitro model of swine alveolar macrophages, 0.5 UI/mL of interferon-alpha reduced the expression of the TNF gene (Amadori, 2007), suggesting it could be a potential strategy to mitigate inflammatory status during TP of dairy cows. Nevertheless, daily oral administration of either 10 or 0.5 IU/kg BW of interferon-alpha to dairy cows during TP increased the severity of inflammatory phenomena after calving (Trevisi et al., 2009). Such an effect could be driven by lymphocytes in the rumen liquor of dairy cows, that could have counteracted and inverted the antiphlogistic signal of interferon-alpha.

Conclusions

Proper function of the innate immune system is essential to ensure protection against pathogens and to avoid the occurrence of uncontrolled inflammations. Thus, mitigating the immune dysfunction that occurs during TP in dairy cows is a pivotal goal in preventing infectious and metabolic diseases typical of early lactation. Although there is a vast amount of scientific literature regarding this topic, the cause of immune dysfunction in TP remains unclear. The sudden metabolic changes occurring during this phase make it challenging to identify the driving mechanism of immune alterations. It is very likely that there is not a single cause, but multiple factors are at play. The lack of clarity on the cause of immune dysfunction is the main reason it is still a major issue in early postpartum cows. The physiological adaptation to lactation, mostly driven by hormonal changes, and needed dietary alterations to face the tremendous increase in requirements during the onset of lactation can be also additional causes of the immune dysfunctions. This is probably more acute during PI. The adoption of nutritional strategies and the supplementation with feed additives aimed to improve white blood cells functions and to exert an anti-inflammatory action could mitigate the negative effects related to immune dysfunctions in transition dairy cows. We can conclude that, although feed additives and nutritional strategies could be

effective in mitigating immune alterations during TP, the adoption of proper management practices aimed to mitigate the risk of a PI from dry-off to early lactation, could be the most effective strategy for improving the immune competence in the peripartum period.

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Conflict of interest statement

The authors declare no real or perceived conflicts of interest.

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