

# Climate change, nutrigenomics, immune function and diseases and production in dairy cattle: a comprehensive review



Hassan H. Musa<sup>a</sup> | Joram M. Mwacharo<sup>b</sup> | Saber Y. Adam<sup>c</sup> | Demin Cai<sup>d</sup> |

Abdelkareem A. Ahmed<sup>aef</sup>  

<sup>a</sup>Biomedical Research Institute, Darfur University College, Nyala, Sudan.

<sup>b</sup>Department of Genetics, International Center for Agricultural Research in the Dry Areas, Addis Ababa, Ethiopia.

<sup>c</sup>Department of One Health, Medical and Cancer Research Institute, Nyala, Sudan; Animal Welfare Center, Nyala, Sudan.

<sup>d</sup>College of Animal Science and Technology, Yangzhou University, Yangzhou 225009, PR China.

<sup>e</sup>Department of Veterinary Sciences, Faculty of Animal and Veterinary Sciences, Botswana University of Agriculture and Natural Resources, Private, Bag 0027, Gaborone, Botswana.

<sup>f</sup>Department of Physiology and Biochemistry, Faculty of Veterinary Science, University of Nyala, Nyala, Sudan.

**Abstract** Climate change is considered a main factor that negatively impacts agriculture and animal production. In addition, it also influences the animal's immune functions and diet intake, making it susceptible to infectious diseases. Recent nutritional research involving genomics proposes a rational ability to prevent disease occurrences. Scientific evidence in genomic sequencing discloses opportunities for discovering diet health associations and prospective for individual phenotypes and genotypes based on dietary suggestions. This review covers climate change, nutrition, and immune function on dairy cows' health and diseases. Strategies to increase dairy cow milk productive yield through nutritional interventions offer the prospect of improving their milk production performances and animal welfare. This review also addresses how such nutrition manipulations can enhance dairy cows' immune function and productivity. The principal competencies covered in this review are the evolutionary impacts of climate change on animals, climate change on livestock diseases, nutrition and clinical practice in dairy cows, and the influences of malnutrition on dairy cow diseases. In addition, the article discussed a common origin for immunity and digestion, the evolution of transgenerational immunity, nutrition, and immune function, and their impact on cattle. Moreover, the review covered the interaction between nutrition and immune function and their influence on the health problems of dairy cows. Finally, the review discussed the application of nutrigenomics and nutrigenetics in milk production in dairy cows and strategies for preventing disease during early lactation.

**Keywords:** climate change, dairy cow, immune function, nutrition

## 1. Introduction

Changing climatic conditions, directly and indirectly, impact biotic and abiotic processes and represent a robust basis for novel selection pressures for adaptive evolution (Merilä and Hoffmann 2016). In addition, climate change can affect development by altering the patterns of hybridization (Sanchez-Guillen et al 2013; Canestrelli et al 2017), changing population size (Knape and de Valpine 2011), and shifting patterns of gene flow in landscapes (Sork 2016). Known that the scientific evidence for rapid evolutionary adaptation to the spatial variation (Liu et al 2014) both in biotic and abiotic ecological conditions corresponding to that shown in modifications brought by climatic change is ubiquitous, continuing climate change is predicted to have large and extensive evolutionary impacts on animal biodiversity (Bellard et al 2012). Therefore, rapid evolution changes species in real-time. However, phenotypic plasticity (Vedder et al 2013; Merila and Hendry 2014), migration (Seebacher and Post 2015), and different kinds of ecological and genetically constraints (Franks and Hoffmann 2012) can prevent the animal from developing much in response to the climate change, and a generalization about the rates and magnitudes of expected responses seem to be challenging to make for several reasons (Hetem et al 2014; York et al 2017).

The impact of animal microevolutionary responses to climate change is a hot area of investigation (Boutin and Lane 2014). In contrast, interest in the evolutionary impacts of climate change goes back to early paleontological (macroevolutionary) studies focused on prehistoric climate changes and microevolutionary research that started only in the late 1980s (Gibbons 2010). The microevolutionary discipline has attracted the actual attention of scientists in the 2000s after the fundamental concept of climate change became essential to the universal public and funding organizations (Biedenkopf 2017). However, to date, no scientific conclusion has yet emerged. In addition, the complication of biotic changes has been



activated by novel climatic conditions, submitting predictions on strength and patterns of natural selection. Moreover, predictions are complicated due to the expression of genetic variability in traits of environmental consequence varying with ecological situations, influencing and expected responses toward climate-mediated selection (Weed et al 2013).

This review covers climate change, nutrition, and immune function on dairy cows' health and diseases. Strategies to increase dairy cow milk productive yield through nutritional interventions offer the prospect of improving their milk production performances and animal welfare. This review also addresses how such nutrition manipulations can enhance dairy cows' immune function and productivity.

## 2. Heat stress

All living organisms have a thermal comfort range that is a range of surrounding environmental temperatures. These temperatures are optimal for biological functions. Throughout the day, ruminants keep their body temperature within a range of  $\pm 0.5$  degrees centigrade (Henry et al 2012). Once body temperature increases more to the critical temperature of the normal range, the animals start to suffer from heat stress (Belhadj Slimen et al 2016). Then the animals developed a physical and phenotypic response to the source of stress, for example, heat, called acclimation. It has been reported that exposure to ambient temperature decreased feed intake (Pearce et al 2014), water intake (Bruno et al 2011), reduced productive and reproductive performance (Das et al 2016), and affected respiratory system function (Polsky and von Keyserlingk 2017). The influences of heat stress on livestock are dependent on temperature, humidity (Robert et al 2014), genetic potential (Das et al 2016), species, life stage, and nutritional status (Krishnan et al 2017). It is known that livestock in higher latitudes are less influenced by the increase in temperatures while livestock reared in lower latitudes are more subjected to heat stress (Kielland et al 2010) because animals in lower latitudes are habitually better acclimatized to high heat stress and droughts (Thornton et al 2009). Closed systems of livestock production are found to have more control of conditions over climate exposure (Flamenbaum and Galon 2010). Heat stress reduces diet intake (Das et al 2016), milk production (Yano et al 2014), feed conversion efficiency (Quinteiro-Filho et al 2010), and reproductive performance (Boni et al 2014). Humid and warm conditions cause heat stress (Gao et al 2017), which affects animal behavior (Allen et al 2015) and metabolic rates in livestock (Belhadj Slimen et al 2016) or even mortality (Bishop-Williams et al 2015). In the overall process, the impacts of heat stress on dairy cows include feed intake, feed nutrient utilization, production, reproduction performance, health, and mortality.

## 3. Heat stress and milk production

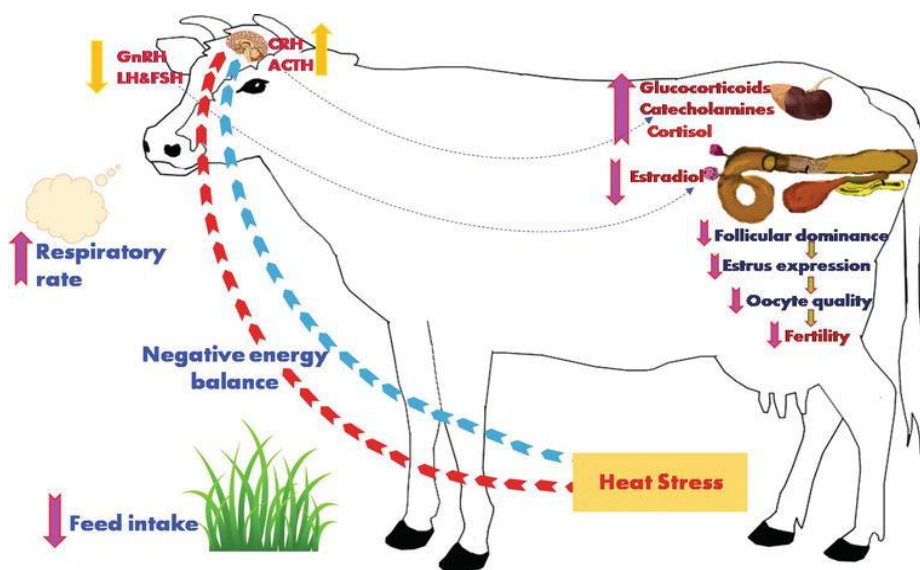
Heat stress is one of the main factors that cause production capacity reduction in the dairy and beef industry (Bernabucci et al 2014; Das et al 2016) and economic losses (St-Pierre et al 2003). High-yielding dairy cows produce more metabolic heat than low-yielding dairy cows (Moallem et al 2010; Garner et al 2016). Consequently, the high-yielding dairy cows are more sensitive to heat stress than zebu cattle (Hansen 2004; Berman 2011). Therefore, the increased metabolic heat production, and the increased heat stress, are accompanied by declined milk production (Reyad et al 2016). Heat stress also has negative impacts on sheep (Sevi and Caroprese 2012), goat (Mabjeesh et al 2013), and buffalo (Kapila et al 2016) milk production. Heat stress also negatively impacts milk composition and amount (Liu et al 2017).

The mechanism underlying the reduction of milk production by the heat stress is that dairy cows mainly depend on glucose for energy requirements; therefore, during the milk production period, less glucose is directed to the mammary glands, and this process will decline in milk production. Negative energy balance during lactation is associated with several metabolic alterations implemented to maintain the dominant physiological status of lactation (Fatima et al 2014). Apparent changes in glucose and lipid metabolisms ensure the partitioning of dietary constituents and tissues that originate nutrients to the mammary gland (Wheelock et al 2010; Tian et al 2016). Many of these metabolic alterations are mediated via endogenous reproductive hormones, which are usually hormones, throughout the periods of negative balance due to heat stress (Hansen 2009; Takahashi 2012; Dash et al 2016; Roth 2017). The milk constituents are also greatly influenced by heat stress (Tian et al 2016; Liu et al 2017). In addition, the studies on breed differences of ruminant species regarding their response to heat stress will provide an essential new window in the next quarter-century and, therefore, will allow dairy cattle selection based on resistance to heat stress as global warming continue (Matthews et al 2017; Rojas-Downing et al 2017).

## 4. Impact of heat stress Impact on the endocrine and reproductive system of dairy cow

Heat stress has adverse effects on reproductive capacity through negative energy imbalance and alterations in dairy cows' reproductive hormone concentrations (Figure 1) (Liu et al 2017). Various studies confirmed that heat stress negatively affects the fertility and reproductive performance of livestock via compromising the reproductive physiology system (O'Doherty et al 2014) through the imbalance of reproductive hormones (De Rensis et al 2017), reduced quality of oocytes (Al-Katanani et al 2002; Ferreira et al 2011), decreased semen quality (Hamilton et al 2016) (Al-Kanaan et al 2015), and decreased embryo development (Sakatani 2017) and survival (Silva et al 2013). Heat stress reduces the secretion of luteinizing hormone (Vanselow et al 2016) and estradiol (Bridges et al 2005), resulting in decreased length and intensity of the estrus cycle (Schüller et al 2017), an increased incidence of anoestrus (Das and Khan 2010) and silent heat in farm animals (Kadokawa et al 2012;

Dash et al 2016). Thermal stressed oocytes lose their fertilization competence (Silva et al 2013) and development (Hansen 2013) into the blastocyst stage (Lawrence et al 2004; Wang et al 2009), which in turn results in reduced fertility (Jordan 2003; Whitfield 2016) due to the poor quality oocytes (Satrapa et al 2011) and thus the embryos (Sakatani et al 2012; Sakatani 2017). In addition, low progesterone concentrations (De Rensis and Scaramuzzi 2003) limit the functions of endometrial (Kobayashi et al 2013), and consequently embryo development (Silva et al 2013). Moreover, the high concentration of endometrial prostaglandin F<sub>2</sub>- $\alpha$  during heat stress threatens the continuance of pregnancy (Kobayashi et al 2013). It was found that the increase in each unit of the temperature-humidity index over 70 decreased the percentage of conception rate by 4.6 (Nabenishi et al 2011). Heat stress during pregnancy also retarded fetal growth (Tao and Dahl 2013) and results in low birth weight (Tao et al 2012). The negative influence of heat stress on livestock health and production can be reduced through adapting appropriate scientific strategies, including management, modification optimization of environmental conditions, genetic development, and nutritional management. In addition, the applications of advanced technologies in reproductive science can be countered by including timed artificial insemination, hormonal treatments, and embryo transfer, that ultimately can increase the choices for establishing pregnancy in dairy cow.



**Figure 1** Effects of heat stress on reproductive performance in dairy cow. *Source:* Liu et al (2017).

## 5. Climate change and livestock diseases

Increasing greenhouse gas (GHG) emissions have been rising over the last century due to the increase in the planet's mean air and ocean temperatures (O'Reilly et al 2012; Drijfhout et al 2015; Ji et al 2016). These changes substantially impact the epidemiology of infectious diseases in livestock (Bett et al 2017). These effects can be direct and indirect progressions associated with climate change and livestock infectious diseases (Koneswaran and Nierenberg 2008). A few previous studies show a positive link between temperature and spreading out of the geographical arrays of arthropod vectors (Negev et al 2015; Flahault et al 2016). In contrast, most of the studies illustrated an opposite impact of climate change on the prevalence of infectious diseases (Kurane 2010; Ramasamy and Surendran 2012). Temperature (Ju et al 2015) and humidity (Jaworski and Hilszczański 2013) increases the rate of insects development (Ju et al 2011; Savopoulou-Soultani et al 2012), survival (Kreppel et al 2016) and production (Norhisham et al 2013). Thus increasing the incidence and prevalence of various diseases (Gray et al 2009; Dantas-Torres 2015; Robinson et al 2015). Higher temperatures may also motivate an infected host species to stay winter in larger populations (Aliabadi et al 2011), enlarge the population size and increase their habitat range (Negev et al 2015). Yet, the impact of these alterations on cattle disease in the Arctic has not been fully understood. In addition, whether these alterations can be transmitted to the offspring remain unknown. The roles of climate change on the incidence of infectious diseases are summarized in table 1.

## 6. Climate and mortality rate

Humid, warm climate conditions can cause heat stress that increases livestock mortality. They recommend sprinklers, shade, or similar management practices to cool the animals as a mitigation measure. Sirohi and Michaelowa (2007) linked livestock mortality to several heat waves between 1994 and 2006 in the United States and northern Europe. More information is needed concerning how heat stress affects feed nutrient utilization and feed intake, animal production, reproduction, and

health. With more excellent knowledge related to livestock's nutritional and metabolism processes, management practices could be adapted to increase animal performance.

## 7. Nutrition and clinical practice

The impact of climate (Koluman Darcan and Silanikove 2017), nutrition (Ingvarsten and Moyes 2013) on animal health (Feleke et al 2016), immunity, disease (Rahal et al 2014), and reproductive capacity (Manjunathareddy et al 2017) has long been the issue of investigation, from its influences on animal evolution during the Paleolithic period to be the critical factor in causing several diseases (Barnosky and Kraatz 2007; Merilä and Hoffmann 2016). Recent scientific evidence in the genomic field has explored climate-nutrition-health interaction revealing the potential for genotype-based nutrition references (Rauw and Gomez-Raya 2015). However, double edging in nutritional field research and genomics disclose evidence preventing livestock diseases and supporting optimal health (Baye et al 2011). These issues have not been actively utilized nor given critical importance throughout ruminants health, production, nutrition, and disease control conferences (McNamara 2012). New window in biotechnology applications shows new approaches for advance climate, immunity, and nutritional genomics tools for analyzing biological mechanisms underlying in animal diseases. As climate change and nutrition are an important environmental factor that ultimately predispose animal disease, immunity based nutrition can potentially improve overall animal health (Asmare 2014). Through nutritional strategy based on animal genotype (James 2009), we will then outfitted to enhance animal immunity and prevent and control animal disease based on nutrition and climate change.

**Table 1** Effects of climate change on the incidence of infectious diseases.

Environmental change	Disease example	Animal Species	Reference
Dams	Schistosomiasis	Bovine, Humans	(Li et al 2007)
Canals	Schistosomiasis	Bovine, Humans	(Colley et al 2014)
River	Rift Valley fever	Bovine	(Drake et al 2013)
Weather	Foot and Mouth Disease	Bovine	(Dong et al 2016)
Management	Milk fever	Bovine	(Thilsing-Hansen et al 2002)
Irrigation	Fasciolosis	Bovine	(Suon et al 2006)
Migration& Globalization	Tuberculosis	Bovine	(Humblet et al 2009)
Global warming	Trypanosomiasis	Bovine	(Moore et al 2012)
Drought	Johne's disease	Ovine	(Bush et al 2006)
Wildlife	Anthrax	Bovine, Caprine, Ovine	(Miller et al 2013)
Global Warming	<i>Cryptococcus neoformans</i>	Mammals	(Garcia-Solache and Casadevall 2010)
Seasonal changes	Bluetongue	Bovine, Caprine, Ovine	(Samy and Peterson 2016)
Land use	Pasteurellosis	Bovine, Caprine, Ovine	(Wilson and Ho 2013)
Depopulation	Corynebacterium	Bovine, Caprine, Ovine	(Spier and Azevedo 2017)
Evaporative cooling	Mastitis	Bovine	(Arcaro et al 2013)
High humidity	Rinderpest	Bovine	(Morand 2015)
Grazing system, land cover	Lumpy Skin Disease	Bovine	(Alkhamis and VanderWaal 2016)

With modern progress in the field of nutritional genomics (Loor et al 2013), environmental genomics (Shafer et al 2016), immunological genomics (Shen et al 2013; Raszek et al 2016), and the promotion of customized, genotype-based diets (Ferrell et al 2006; Seo et al 2013), management for optimal animal health is more common in developed countries veterinary medicine. However, these opportunities are missing in underdeveloped countries (Bayne et al 2015), particularly in Africa. Nevertheless, these approaches also correspond with animal welfare philosophy lobes in Eastern developed countries, which pressure their governments toward improving animal welfare (Szucs et al 2012). Several nutritional concepts in animal production and disease control have generally not been adopted by ministries of veterinary worldwide (Perry and Grace 2009; Thornton 2010). However, as both developing and developed countries (Thompson 2010; Cornish et al 2016) possess different weaknesses and strengths concerning biotechnology applications (De Simone and Serratosa 2005), as well an analysis of an integrated approach to animal immunity and nutrition (Warne 2014) therefore, could be accomplished by selecting the advantages of both approaches based on the knowledge and practice. Combining both approaches may thus create a



comprehensive, all-inclusive concept of veterinary medicine, providing holistic systems and improved animal welfare from both systems.

## 8. Malnutrition and dairy cattle diseases

Malnutrition and infection have constantly been intricately associated (Katona and Katona-Apte 2008). It is considered the main factor which causes immunodeficiency worldwide (Duggal et al 2012), and scientists are searching more and more to understand the pathogenesis of this relationship. Deficiencies of both micronutrients and macronutrients have apparent effects on immune function (Banos et al 2013), susceptibility to infectious diseases (França et al 2009), decreases in milk production (Raboisson et al 2015), abortion, dystocia (Hickson et al 2006), and fetal growth retardation (Long et al 2012), congenital fetal diseases (Hill et al 2009), skeletal abnormalities (Dittmer and Thompson 2015) and increased mortality rate (Whiting et al 2012). It is well known that parasitic infestation causes malnutrition, particularly the cestodes (Kumar et al 2013). However, exactly which malnutrition increased parasitic infestation is not well documented; therefore, this issue must be addressed. Nutritional deficiencies during pregnancy are associated with decreased immune defense against infectious diseases (Katona and Katona-Apte 2008; Cunningham-Rundles et al 2009) since colostrums may partially compensate for this immune dysfunction; the best way to protect calves from infection diseases (Yang et al 2015; Ontsouka et al 2016). Malnutrition (Müller and Krawinkel 2005) and nutritional alterations (Joy et al 2014), a major complications of both human and animal problems in developing countries (Jin and Iannotti 2014; Mosites et al 2016; Kaur et al 2017). However, the disease-specific nutrition formula to improve the nutritional condition and functional reproductive performance in dairy cows remain scarce. Therefore, here we recommend further studies to address the disease specific nutrition formula in the field of livestock production particularly in dairy cattle.

## 9. A Common Origin for Immunity and Digestion

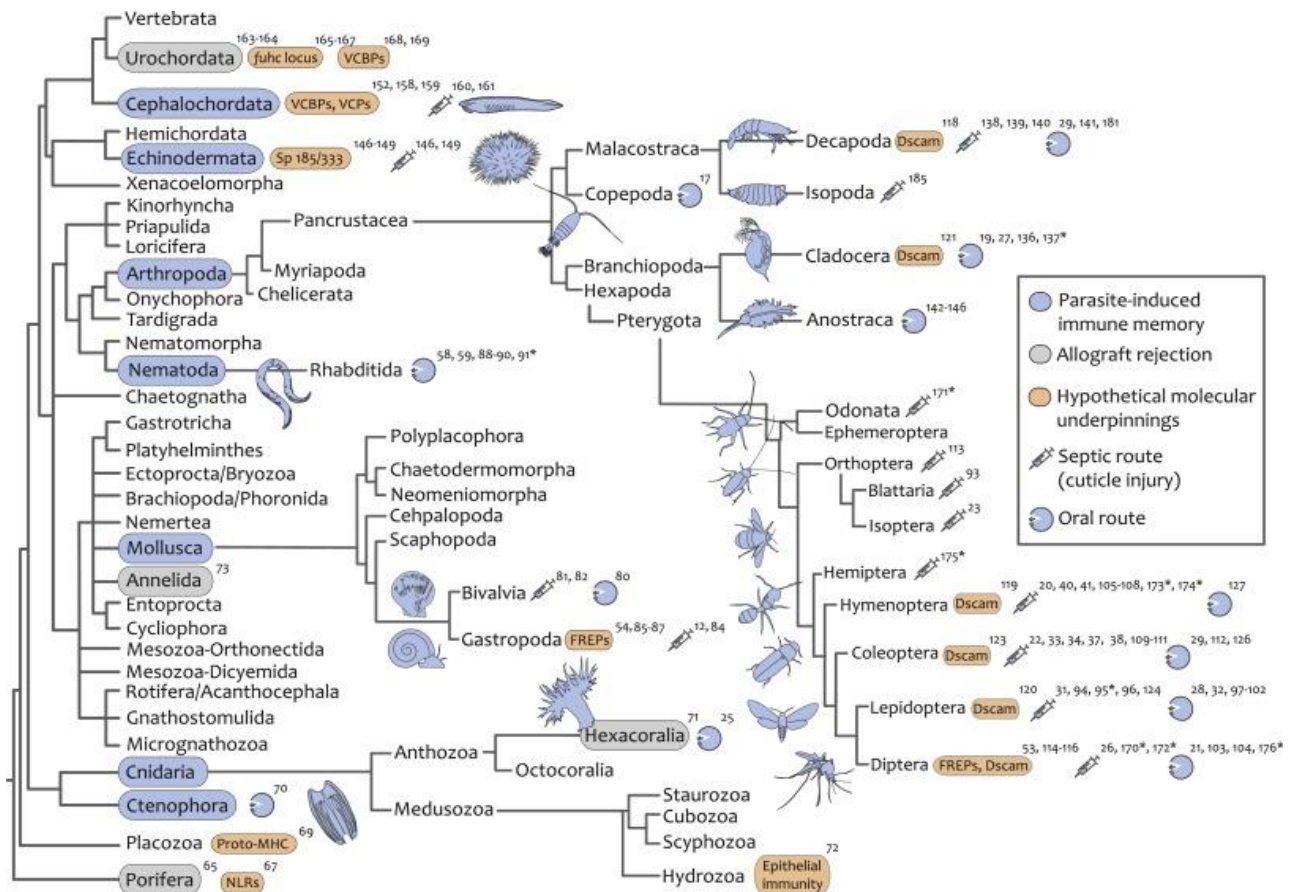
From an evolutionary view, scientific evidence on relationships between immunity and nutrition has shown an ancient connection in embryonic development and function (Broderick 2015; van Niekerk and Engelbrecht 2015). Historically, the immune and digestive systems have been observed and analyzed as separate entities. However, recent scientific evidence revealed that both systems shared vital similarities and common join functions, both in nutrient gaining and host defense and the origins common to both organs (Round and Mazmanian 2009; Sotolongo et al 2012). This concept provides a new and possibly novel method to visualize the emergence and evolution of host defense mechanisms (Broderick 2015). Unicellular organisms are known to phagocytose for gaining food (Esteban et al 2015) and defense (Oczypok et al 2013), and the phagocytosis process represents the main ancient and ubiquitous form of food acquisition and protection against foreign insult (Sanjuan and Green 2008). Multicellular vertebrates and invertebrates possess special phagocytic cells that function for defense and have evolved more complex processes (Morella and Koskella 2017) attributed to immunological defense cells, which became specialized for carrying out humoral immune and cellular responses (Buchmann 2014). From the oral cavity to the end of the intestine, the tubular gastrointestinal tract is well equipped and adapted with specialized cells, tissues, and organs that coevolved to remain forever together (Van den Abbeele et al 2011).

Host response against invading pathogens is an essential physiological reaction in all living organisms (Govers et al 2017). Since the development of the first eukaryotic cells, several defense mechanisms (Kono and Rock 2008; McGhee and Fujihashi 2012) have evolved to protect cellular integrity (Randow et al 2013), homeostasis (Marques et al 2016), and host survival (Nakad and Schumacher 2016). Invertebrate organisms from the protozoans to metazoans contain cellular receptors (Price et al 2016) that bind to antigens (Klose et al 2016) and consequently discriminate self from non-self (Chaplin 2010). In multicellular animals, this rudimentary capability is associated with phagocytes, known by different names (e.g., coelomocytes, hemocytes, amebocytes) in different group's species of organisms such as sponges (Dzik 2010), round worms, cnidarians (Davy et al 2012), mollusks (Terahara and Takahashi 2008), crustaceans (Vazquez et al 2009), chelicerates (Buchmann 2014), insects (Browne et al 2013), annelid worms and echinoderms (Hirano 2016). The macrophage-like cells, function, and related repair are most important even at the earliest evolutionary stage (Sunyer 2012). They have well-conserved molecular structures such as pathogen-recognizing receptors (Moretti and Blander 2014) and pathogen-related molecular patterns (Santoni et al 2015). However, the impact of climate change on livestock adaptation with the dynamics of parasitic, bacterial, and viral infections is missing. In addition, whether the global climate change will modify the fundamental animal immune reactivity for prenatal and postnatal needs to be investigated.

## 10. Evolution of transgenerational immunity

The discovery of transgenerational immunity in invertebrates changed an existing paradigm on the lack of sophistication of their immune system (Pigeault et al 2016). However, the incidence of this paradigm and the environmental factors motivating its evolution in invertebrates remain less understood. Invertebrate immunity was commonly assumed over a decade ago due to the lack of the most complicated components of the vertebrate immune system (Loker et al 2004; Rowley and Powell 2007). The ability of invertebrate's immunity to mount an acquired response (Cooper and Eleftherianos 2017) where

memory effectors produced during an infection protects the offspring (transgenerational) (Little et al 2003) or individual (within-generational) (Jokela 2010) against later infections. Yet, recent investigations have shown that invertebrates possess spectacularly plastic immune effectors, which can produce accurate novelty and functional immune responses after exposure to pathogens (Armitage et al 2015). Scientific shreds of evidence of within-generational immune confirmation in invertebrates have been documented considerably in the last decade (Schmid-Hempel 2005). It has been reported that a variety of invertebrates species including Hymenoptera (Sadd and Schmid-Hempel 2006), Decapoda (Witteveldt et al 2004), Diptera (Rodrigues et al 2010), Lepidoptera (Tidbury et al 2011), Branchiopoda (McTaggart et al 2012), Coleoptera (Roth et al 2009). Interestingly, transgenerational immunity has been therefore far reported in a wide range of invertebrate species (Figure 2) (Milutinovic and Kurtz 2016; Huang and Song 1999; Little et al 2003; Sadd et al 2005). However, relevant information on mammals generally and ruminants is missing. In addition, the mechanisms underlying the transgenerational immune protection in dairy cows remain unknown. Thus, this review strongly recommends the research work in such a direction.



**Figure 2** Transgenerational immunity invertebrate species. *Source:* Milutinović and Kurtz (2016)

### 11. Nutrition and immune function in livestock model: the cattle

Studies in animal nutrition analysis and animal immunity, especially in invertebrates, have been extensively investigated, given newer discoveries and insights (Ponton et al 2011; Valtonen et al 2011; Pigeault et al 2016). Increased milk production and the structural changes in the dairy technology are the main factors that caused significant problems and alterations in feeding (Thanh and Suksombat 2015), housing (Popescu et al 2013), management (Das et al 2016) and behavior of the dairy cattle and buffalos (Seerapu et al 2015; Polsky and von Keyserlingk 2017). However, as better improvements have occurred in animal production and efficiency (VandeHaar et al 2016), the disease prevalence, based on veterinary reports, does not improve (Ducret et al 2011; Peiso et al 2011; Awan et al 2014; Brugere et al 2017). Previous review articles have enclosed critical periods, for instance, the transition period in the dairy cow and its impact on health and immune function (Ingvarsen and Moyes 2013), the interaction between the immune system, endocrine system and nutrition and immune function (Ingvarsen and Moyes 2013). Well, scientific establishment on these issues is fundamental for our understanding of animal disease risk and our attempt to expand animal health and welfare-improving approaches, including practical management for preventing infectious diseases and decreasing the severity of diseases. The health problems during the periparturient period signal the dairy cows' complexity in adapting to the nutrient requirements for lactation (Sun et al 2016; Ruiz et al 2017). This may result in physiological imbalance (Moyes et al 2013). In this situation, the regulatory mechanisms are inadequate for the



cow to function optimally, resulting in a high risk of complex digestive (Abdela 2016), metabolic (Sundrum 2015) and infectious problems (Moosavi et al 2014). The compromised immune status increases the risk of infectious diseases in the animal (Ingvarstsen and Moyes 2013). It is well recognized that nutrition status plays a critical role in the organism's immune response (Pae et al 2012), and the influence of nutrition can be directly through nutrients (Sordillo et al 2009; Ponton et al 2011) or indirectly via metabolites (Sordillo 2016), for example, in situations of physiological imbalance (Ingvarstsen and Moyes 2013). Yet, these complex associations between immune function and metabolic status and the interactions enhance the risk of diseases during the lactation period. Therefore, special care should be taken into account on the vital energetic supplements which presently known to be used by immune cells, such as non-esterified fatty acids (Ster et al 2012), glucose, beta-hydroxybutyrate (Hillreiner et al 2016), and glutamine (de Oliveira et al., 2016). In addition, how specific metabolic states, for example the degree of negative energy balance and risk of physiological imbalance, contribute to immunosuppression during the periparturient period is critical, and therefore, it should give special attention.

## 12. Nutrition, immune function, and health problems of dairy cattle

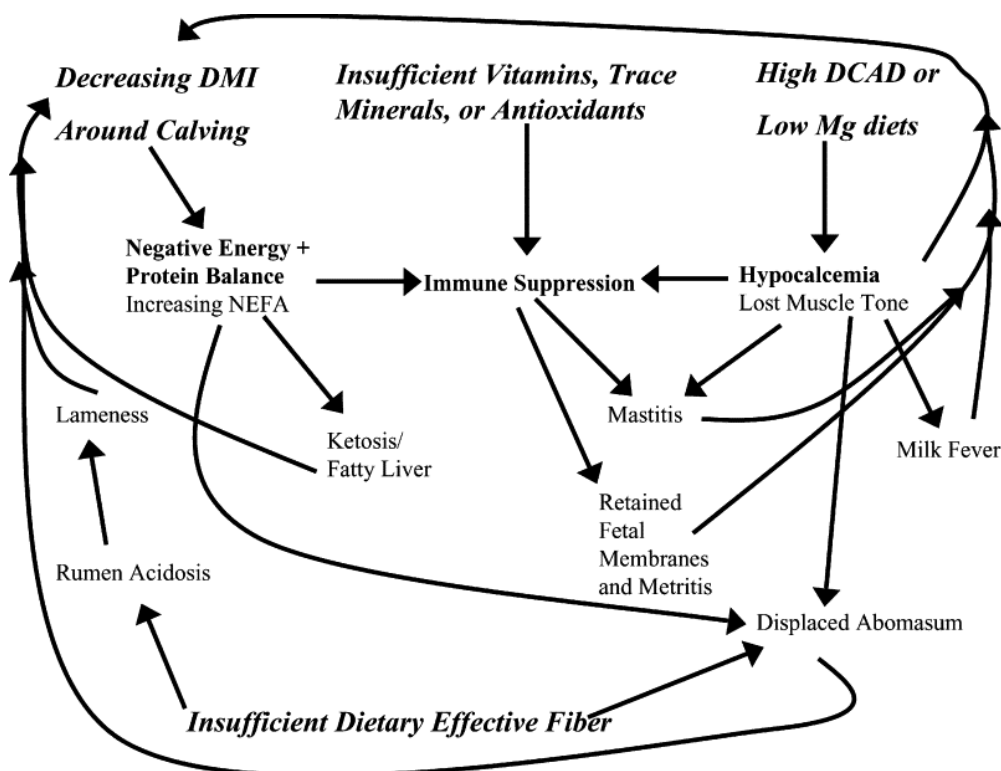
The most common health problems in the dairy cow occur during the parturition period (Villarroel and Lane 2010; Palombi et al 2013). Previous reviews have discussed that decreased immune competence and physiological imbalance are the main predisposing and risk factors for disease rather than milk production (Ingvarstsen and Moyes 2013). Several outstanding previous articles have enclosed critical periods, for instance, the transition period in dairy cows and its impact on animal health and immune function (Mulligan et al 2006; Mulligan and Doherty 2008), the interaction between the endocrine system and immune function (Burdick et al 2011; Banos et al 2013), nutrition and immune function (Sordillo 2016). The period of periparturient (Trevisi et al 2012) and particularly the transition period of dairy cattle are distinguished by dramatic alteration in metabolism (Sundrum 2015) and host defense mechanisms which are found to be associated with an increased risk of disease (Mordak and Anthony 2015). Predominantly, the transition period is the most demanding (Gross et al 2011) for the majority of mammals that may intimidate both animal health and animal welfare (Beggs et al 2015) if the challenges go beyond the coping mechanisms of the animal (Aitken et al 2009; Sordillo 2013; Aleri et al 2016). Both periods are found to be associated with an increased incidence of metabolic (Mordak and Anthony 2015) and other non-infectious (Sundrum 2015) and infectious diseases (Eckel and Ametaj 2016) such as fatty liver (White 2015), milk fever (Thilsing-Hansen et al 2002), retained placenta (Beagley et al 2010), metritis (Sheldon et al 2008), ketosis, left-displaced abomasums (Sexton et al 2007; Mueller 2011), lameness (Randall et al 2016) and clinical mastitis (Lundberg et al 2016). During the early lactation period, ruminants remobilize large amounts of nutrient reserves, mainly lipid from adipose tissue, to support milk production. Demobilization of lipids is a common physiological adaptation mechanism in mammals to counter those physiological conditions, such as in the periparturient period, but excessive demobilization of lipids has been associated with an increased risk of diseases (Vernon 2005; Contreras and Sordillo 2011).

The nutrient requirements increase significantly during late pregnancy and mainly in early lactation (Dunlap et al 2015). In late pregnancy, the nutrient demand is found to increase as a result of fetal development (Bell et al 1995; Dunlap et al 2015), which remarkably increases glucose (Brett et al 2014) and amino acids (Dunlap et al 2015; Tedeschi et al 2015). The extensive milk production acceleration, seen particularly in the last week of *prepartum* and in the first 2 weeks of lactation, mirrors the spectacular increase in nutrients requires at the onset of lactation. A dairy cow with a milk yield of 50 kg was found to secrete approximately 2 kg of milk fat per day, 2.5 kg of lactose, 1.6 kg of milk protein, 50 g of P, 65 g of Ca, and 8 g of Mg. All of these nutrients ultimately increase requirements for energy (Mair et al 2016), protein (Imaizumi et al 2010) and minerals (Bhandari et al 2016). In the late stage of pregnancy, the nutrient demand and particularly the nutrient requirements for lactation induce a coordination mechanism of the biological processes in different tissues, resulting in metabolic alterations that ensure that dairy cows reach their highest genetic potentiality for milk yield.

Physiological imbalances in dairy cows have been known as cows whose parameters deviate from routine and thus have an elevated risk of developing production diseases and decreased reproduction and production capacity (Moyes et al 2013) A well-known example of physiological disturbances would be the extreme mobilization, due to over malnutrition or conditioning, in other cases, for extended periods in early lactation (Elizondo Salazar et al 2013; Sun et al 2016). During excessive mobilization of lipids, lipogenesis rates undergo very low (Contreras et al 2017), while lipolysis rates become very high (Humer et al 2016), resultant in high plasma non-esterified fatty acids (NEFA) concentrations (Adewuyi et al 2005; Contreras et al 2010) and glycerol (Melendez et al 2017). The interaction of these processes increased NEFA, which in turn reduces dry matter intake (Allen et al 2009) and, therefore, the low plasma glucose concentration with increased ketogenesis (Vicente et al 2014) and consequently elevated plasma ketone body levels (Enjalbert et al 2001). These metabolic changes associated with excessive lipid mobilization definitely serve as secondary factors to diseases, such as stress, displaced abomasum, and lameness (Gellrich et al 2015). The information mentioned above illustrates that, in general, more metabolic parameters are influenced by excessive lipid mobilization, stress, pain and disease (Goff 2006) (Figure 3).

## 13. Nutrigenomics and nutrigenetics in animal health and production

Traditional research work regarding animal nutrition mostly deals with either excess or deficiency of the specific nutrient, which causes a reduction in animal production or may cause health problems. Nutrigenomics (Ferguson 2009) and nutrigenetics (Raqib and Cravioto 2009) are new disciplines in the improvement of milk production in ruminant species (Table 2), which concern the influence of food at the genetic level (Martin and Król 2017). Nutrigenomics studies how bioactive components of foods and their supplements influence animal metabolism by changing gene expression (Bouchard-Mercier et al 2013) and connects various fields: nutrition (Ferguson 2015), bioinformatics (Malkaram et al 2012), molecular biology, genomics (Doo and Kim 2015), functional genomics (Hocquette et al 2007), epidemiology (Boeing 2013), and epigenomics (Bishop and Ferguson 2015; Carlberg et al 2016). Multi-disciplinary tool utilization provides new windows to explore the complex interactions between the genome and the diet. These new approaches emphasize the appropriate role of nutrition-genetics interactions on various physiological and metabolic processes with a high influence on economically associated traits such as milk and meat quality. Thus, multidisciplinary studies interest is essential to face these new complicated issues. However, the studies on basic concepts and technologies involved in nutrigenomics and nutrigenetics research in the dairy field are lacking. In addition, research on how nutrition affects genes expression involved in lipid metabolism before parturition and during lactation period needed to investigate.



**Figure 3** Metabolic pathways in the situation of excessive lipid mobilization, stress, pain and related disorders. *Source:* Goff et al (2006).

#### 14. Strategies for preventing disease in the dairy cow during early lactation

The transition from late gestation to early lactation is the main metabolically demanding stage in the lactation cycle of a dairy cow (Sundrum 2015). There is growing evidence associates the degrees of nutrient balance with immunity function and risk of both infectious and non-infectious diseases (Lacasse et al 2017), minimizing the severity and period of negative nutrient balance during the periparturient period (García et al 2011), which is very important for improving animal health (Abuelo et al., 2015) and welfare and decreasing economic losses to farmers (de Ondarza and Tricarico 2017). In this review, it is not difficult to discuss all of these factors that affect the levels of nutrient balance, their quality, management, environmental factors, and risk factors of disease during early lactation in the dairy cow. Here we will cover the significant strategies of management that have been applied previously and are currently being established, focusing on the improvement of transition in dairy cows.

Dairy cows experience temporary decreases in dry matter intake before parturition, further aggravating the imbalance between energy requirements (Grummer et al 2004) and energy supply (Buhler et al 2017). Intake of dry matter usually decreases up to 32% before 3 weeks of parturition, and about 89% of these reductions occur throughout the last week before the calving (Hayirli et al 2002). Greater immersion in intake of dry matter at this time has been linked with elevated blood NEFA (Imhasly et al 2015) and ketone bodies, particularly BHBA (Imhasly et al 2015) and accumulation of liver triglycerides during early lactation (Sejersen et al 2012), thus increasing the risk factor of both infectious and non-infectious diseases (Janovick et





al 2011). The strategies designed to minimize this natural fall in dry matter intake have revealed improvements in metabolic profiles, including the decreases in blood NEFA, ketone bodies and decreases in liver triglycerides accumulation. In addition, it has shown a decreased incidence of metabolic disorders in the dairy cow during the early lactation period.

Recent research work has shown the association between overconsumption during the dry period and the severity of energy balance (Smith et al 2017), decreased liver functions (Roche et al 2017) and increased the incidence of metabolic diseases throughout early lactation (Dann et al 2006; Sundrum 2015; Sun et al 2016). Previous nutritional strategies application showed significant changes in dry matter intake and energy balance, reduced the magnitude of body condition scoring modifications and decreased blood NEFA and BHBA levels and triglycerides accumulation in the liver. However, recent scientific evidence indicates that restriction of energy intake prepartum did not negatively impact primiparous dairy cows (Janovick et al 2011). Therefore, we here suggest future studies are needed to clarify if comparable responses are obvious in other cattle breeds, particularly Jerseys.

**Table 2** Applications of nutrigenomics and nutrigenetics technology in ruminants.

Species	Type of Application	Tissue	Title of the study	Reference
Bovine	Gene expression	Muscle	Effect of the feeding system on the fatty acid composition, expression of the $\Delta 9$ -desaturase, Peroxisome Proliferator-Activated Receptor Alpha, Gamma, and Sterol Regulatory Element Binding Protein 1 genes in the semitendinous muscle of light lambs of the Rasa Aragonesa breed	(Dervishi et al 2010)
Bovine	Gene expression	Muscle	Estimates different levels of protein supplementary diet on gene expressions related to intramuscular deposition in early-weaned yaks	(Zhang et al 2014)
Caprine	Gene expression	Mammary gland	Negative effects of long-term feeding of high-grain diets to lactating goats on milk fat production and composition by regulating gene expression and DNA methylation in the mammary gland	(Tian et al 2017)
Caprine	Gene expression	Muscle	Selection of Reference Genes for Gene Expression Studies Related to Intramuscular Fat Deposition in <i>Capra hircus</i> Skeletal Muscle	(Zhu et al 2015)
Caprine	Gene expression	Mammary gland	Effects of different model diets on milk composition and expression of genes related to fatty acid synthesis in the mammary gland of lactating dairy goats.	(Zhang et al 2015a)
Caprine	Gene expression	Liver	Long-term effects of subacute ruminal acidosis (SARA) on milk quality and hepatic gene expression in lactating goats fed a high-concentrate diet.	(Dong et al 2013)
Bovine	Gene expression	Muscle	Effects of different levels of protein supplementary diet on gene expressions related to intramuscular deposition in early-weaned yaks	(Zhang et al 2014)
Bovine	Gene expression	Adipose tissue	Effects of dietary energy level on lipid metabolism-related gene expression in subcutaneous adipose tissue of Yellow breed $\times$ Simmental cattle	(Zhang et al 2015b)
Caprine	Gene expression	Mammary gland	Feeding a High Concentrate Diet Down-Regulates Expression of ACACA, LPL and SCD and Modifies Milk Composition in Lactating Goats.	(Tao et al 2015)
Bovine	Gene expression	Muscle	Dietary conjugated linoleic acids increase intramuscular fat deposition and decrease subcutaneous fat deposition in Yellow Breed $\times$ Simmental cattle	(Zhang et al 2016)
Bovine	Gene expression	Cells	Neuronal Nicotinic Acetylcholine Receptors on Bovine Chromaffin Cells: Cloning, depression, and Genomic Organization of Receptor Subunits	(Campos-Caro et al 1997)
Bovine	Gene expression	Adipose tissue	Effects of dietary energy level on lipid metabolism-related gene expression in subcutaneous adipose tissue of Yellow breed $\times$ Simmental cattle.	(Zhang et al 2015b)
Bovine	Gene expression	Mammary glands	Conjugated linoleic acid-induced milk fat reduction associated with depressed expression of lipogenic genes in lactating Holstein mammary glands	(Han et al 2012)
Bovine	Gene expression	Mammary glands	Expression and nutritional regulation of lipogenic genes in the ruminant lactating mammary gland	(Bernard et al 2008)
Bovine	Gene expression	Liver	Dietary supplementation of selenium in inorganic and organic forms differentially and commonly alters blood and liver selenium concentrations and liver gene expression profiles of growing beef heifers	(Liao et al 2011)

Bovine	Transcriptome	Liver	Hepatic transcriptome profiles differ among maturing beef heifers supplemented with inorganic, organic, or mixed (50% inorganic:50% organic) forms of dietary selenium. (Matthews et al 2014)
Bovine	Gene expression	Adipose tissue	Effect of Diet Supplementation on the Expression of Bovine Genes Associated with Fatty Acid Synthesis and Metabolism (Joseph et al 2010)
Caprine	Gene expression	Mammary gland	Effects of different model diets on milk composition and expression of genes related to fatty acid synthesis in the mammary gland of lactating dairy goats (Zhang et al 2015a)
Ovine	Gene expression	Mammary gland	Sheep and goats differences in CLA and fatty acids milk fat content in relation with mRNA stearoyl-CoA desaturase and lipogenic genes expression in their mammary gland. (Tsiplakou et al 2009)
Bovine	Gene expression	Liver	Lipopolysaccharide derived from the rumen down-regulates stearoyl-CoA desaturase 1 expression and alters fatty acid composition in the liver of dairy cows fed a high-concentrate diet. (Xu et al 2015)
Bovine	Gene expression	Muscle	Expression of genes involved in lipid metabolism in the muscle of beef cattle fed soybean or rumen-protected fat, with or without monensin supplementation (Oliveira et al 2014)
Ovine	Gene expression	Ruminal epithelial cells	Conjugated linoleic acids influence fatty acid metabolism in ovine ruminal epithelial cells. (Masur et al 2016)
Ovine	Gene expression	Muscle	The effect of feeding system in the expression of genes related with fat metabolism in semitendinous muscle in sheep (Dervishi et al 2011)
Ovine	Gene expression	Muscle	Effect of vitamin E supplementation or alfalfa grazing on fatty acid composition and expression of genes related to lipid metabolism in lambs. (Gonzalez-Calvo et al 2015)
Bovine	Gene expression	Mammary gland	Bovine Mammary Gene Expression Profiling during the Onset of Lactation
Bovine	Gene expression	Milk	Differential expression of genes in milk of dairy cattle during lactation (Yang et al 2016)
Bovine	Transcription	Mammary gland	Transcriptional profiling of mammary gland in Holstein cows with extremely different milk protein and fat percentage using RNA sequencing. (Cui et al 2014)
Caprine	Transcriptome	Mammary gland	Transcriptome analysis of the mammary gland from GH transgenic goats during involution. (Lin et al 2015)
Bovine	Transcription	Whole blood	Whole blood transcriptional profiling comparison between different milk yields of Chinese Holstein cows using RNA-seq data. (Bai et al 2016)
Bovine	Gene expression	Mammary gland	Deep sequencing shows microRNA involvement in bovine mammary gland adaptation to diets supplemented with linseed oil or safflower oil. (Li et al 2015)
Bovine	Gene expression	Mammary gland	Targeted imputation of sequence variants and gene expression profiling identifies twelve candidate genes associated with lactation volume, composition and calving interval in dairy cattle. (Raven et al 2016)
Bovine	SNP	Milk	Genome-wide association study for endocrine fertility traits using single nucleotide polymorphism arrays and sequence variants in dairy cattle. (Tenghe et al 2016)
Bovine	Gene expression	Mammary gland	Expression variants of the lipogenic AGPAT6 gene affect diverse milk composition phenotypes in Bos taurus. (Littlejohn et al 2014)
Bovine	GWS		Multibreed genome wide association can improve precision of mapping causative variants underlying milk production in dairy cattle. (Raven et al 2014)
Bovine	Gene expression	Mammary gland	Function of SREBP1 in the milk fat synthesis of dairy cow mammary epithelial cells. (Li et al 2014)
Caprine	Gene expression	Mammary gland	Overexpression of SREBP1 (sterol regulatory element binding protein 1) promotes de novo fatty acid synthesis and triacylglycerol accumulation in goat mammary epithelial cells. (Xu et al 2016)

Caprine	Gene expression	Mammary gland	Peroxisome proliferator-activated receptor delta facilitates lipid secretion and catabolism of fatty acids in dairy goat mammary epithelial cells. (Shi et al 2017)
Caprine	Gene expression	Mammary gland	SCD1 Alters Long-Chain Fatty Acid (LCFA) Composition and Its Expression Is Directly Regulated by SREBP-1 and PPAR $\gamma$ 1 in Dairy Goat Mammary Cells. (Yao et al 2017)
Caprine	MicroRNA	Mammary gland	MicroRNA-24 can control triacylglycerol synthesis in goat mammary epithelial cells by targeting the fatty acid synthase gene. (Wang et al 2015)
Bovine	Transcription	Review paper	TRIENNIAL LACTATION SYMPOSIUM: Nutrigenomics in dairy cows: Nutrients, transcription factors, and techniques. (Bionaz et al 2015)
Caprine	Gene expression	Mammary gland	Peroxisome proliferator-activated receptor $\gamma$ 1 and $\gamma$ 2 isoforms alter lipogenic gene networks in goat mammary epithelial cells to different extents. (Shi et al 2014)
Caprine	Gene expression	Mammary gland	Overexpression of SREBP1 (sterol regulatory element binding protein 1) promotes de novo fatty acid synthesis and triacylglycerol accumulation in goat mammary epithelial cells. (Xu et al 2016)
Bovine	Gene expression	Liver	Rumen-protected conjugated linoleic acid supplementation to dairy cows in late pregnancy and early lactation: effects on milk composition, milk yield, blood metabolites and gene expression in liver. (Sigl et al 2010)
Bovine	Gene expression	Mammary gland	A commonly used rumen-protected conjugated linoleic acid supplement marginally affects fatty acid distribution of body tissues and gene expression of mammary gland in heifers during early lactation. (Kramer et al 2013)

## 15. Final considerations

Climatic factors, for example, humidity, temperature and rainfall, are well known to influence the insect's population dynamics and transmission of disease potentiality. Shifting from the specific climatic condition is known to cause compromised health, immune functions and productivity in livestock. Climatic changes affect disease incidences in livestock breeds by influencing their heat stress which affects diet intake, metabolism, immune function, the virulence of pathogens, and increases transmission methods. Due to climate change, elevated temperature leads to increased infectious agents' development rates. Severe dehydration and heat stress ultimately affect the immune dysfunction in dairy cows due to climate changes. Most fitness problems in dairy cows occur around parturition, related to dairy cows facing difficulty in adapting nutrient requirements for milk production. Complex associations between immune function, nutrition and metabolic status have potentially affected disease risk. These disturbances decrease immune competence and increase the risk for the disease since metabolites and nutrients can affect numerous vital aspects of immune response and thus potentially resistance to diseases. Feeding strategies should avoid the physiological imbalance in dairy cows to improve immune function, thus disease resistance and health promotion.

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Not applicable.

## Conflict of Interest

There was no conflict of interest.

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