The Transition Period of Dairy Cows

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Considerable literature exists on the severe challenges faced by dairy cows at their transition from calving to lactation. Most studies focus on the transition period (TP) phase, which begins three weeks before calving and spans the first three weeks of lactation. Typically, this physiological phase implies severe alterations in the metabolic asset of dairy cows. These alterations are driven by sudden changes in hormonal trends and nutrient partitioning as well as by the adaptation of the animal's metabolism to the negative energy and protein balance conditions driven by late pregnancy and early lactation requirements.

Keywords: metabolic disorders ; immune dysfunctions ; inflammation ; parturition ; transition management

1. Introduction

Considerable literature exists on the severe challenges faced by dairy cows at their transition from calving to lactation. Most studies focus on the transition period (TP) phase, which begins three weeks before calving and spans the first three weeks of lactation [1]. Typically, this physiological phase implies severe alterations in the metabolic asset of dairy cows. These alterations are driven by sudden changes in hormonal trends and nutrient partitioning [2][3] as well as by the adaptation of the animal's metabolism to the negative energy and protein balance conditions driven by late pregnancy and early lactation requirements [4][5][6][7][8][9]. Dairy cows are also prone to developing immune dysfunctions in this phase. Such dysfunctions consist of two phenomena: (1) a reduced competence of the immune system, triggering a hypo-responsive state in polymorphonuclear cells (PMN) and lymphocytes starting about 2–3 weeks before calving, and reaching lowest efficiencies between the time of calving and two days after [10][11][12], and (2) the occurrence of systemic inflammation that triggers the acute phase response after parturition [13]. Recently, Lopreiato et al [14] reported that increasing the release of proinflammatory cytokines (PICs-interleukin-6 and interleukin-1β) upon PEG-rbG-CSF treatment in dairy cows after parturition did not result in increased systemic inflammation (as reflected by haptoglobin and ceruloplasmin plasma levels). This latter finding highlights that mechanisms and/or molecules other than PICs are likely to drive the acute phase response occurring in dairy cows after parturition. Thus, despite reduced competence of the immune system and systemic inflammation commonly appear together in dairy cows at their transition to calving [15], these should be probably considered as two distinct phenomena. A recent review [16] hypothesizes that a multifactorial etiology could be responsible for these dysfunctions and that their severity is directly related to the magnitude of metabolic changes faced by dairy cows. Together, these metabolic and immunologic challenges during the peripartal period are important factors that limit the ability of most cows to achieve optimal performance and balanced immune-metabolic status in early lactation.

The risk ratio of both metabolic and infectious diseases in early lactation is directly related to the magnitude of metabolic alteration and the degree of immune dysfunction faced by dairy cows during the periparturient period [17][18][19]. In turn, the occurrence of disease (infectious and/or metabolic) in this physiological phase could further challenge the metabolism of dairy cows and impair the function of leukocytes, increasing the likelihood of other diseases [20][21]. This vicious circle increases drug costs and could impair fertility of the animals, frequently resulting in their culling [22][23].

2. How to Manage a "Good" Transition Period

2.1. Management Strategies and Facilities to Optimize Animal Welfare

Typically, transition cows flow successively into four pens: dry, prefresh, maternity, and fresh [24]. Cows should enter the prefresh pen 21 days before expected parturition. Then, cows should be moved to the contiguous maternity pen, where they should stay alone for no longer than three days to avoid any distress from prolonged isolation. Finally, cows should be moved to the fresh pen, where they should stay for approximately 21–30 days postpartum, allowing closer monitoring and perhaps being fed a different diet from lactating cows (see **Table 1**).

Table 1. Performances inputs, dietary recommendations, and sample diets for a medium-performance dairy cow undergoing the lactation, far-off, close-up and fresh phases (adapted from NRC [25]).

Item [1]	Unit	Phase			
		Lactation	Far-Off	Close-Up [4]	Fresh
Inputs					
Days [2]	day	90	240	270	11
Body weight [3]	kg	680	730	751	680
BCS	-	3	3.3	3.3	3.3
Age	months	49	57	58	58
Milk production	kg	35	-	-	35
Butterfat	%	3.5	-	-	3.5
True protein	%	3	-	-	3
Lactose	%	4.8	-	-	4.8
Dry matter intake	kg	23.6	14.4	13.7	15.6
Daily weight change	kg	0.3	0.67	0.67	−1.6
Days to gain one condition score	day	316	na	na	-
Days to lose one condition score	day	-	na	na	55
Dietary recommendations					
NE_L	Mcal/day	34.8	14	14.4	34.8
NE_L	Mcal/kg DM	1.47	0.97	1.54–1.62	2.23
MP	g/day	2407	871	910	2157
Diet MP	%	10.2	6	6.6	13.8
RDP	g/day	2298	1114	1358	1634
Diet RDP	%	9.7	7.7	9.9	10.5
RUP	g/day	1291	317	172	1405
Diet RUP	%	5.5	2.2	1.3	9
Diet NDF min	%	25–33	33	33	25–33
Diet ADF min	%	17–21	21	21	17–21
Diet NFC max	%	36–44	42	43	36–44
Absorbable Ca	g/day	65	18.1	21.5	64
Diet Ca	%	0.61	0.44	0.45 (0.5–1.5)	0.79
Absorbable P	g/day	56.5	19.9	20.3	49
Diet P	%	0.35	0.22	0.3–0.4	0.42
Diet Mg	%	0.19	0.11	0.35–0.4	0.29
Diet Cl	%	0.26	0.13	0.15 (0.8–1.2)	0.4
Diet K	%	1.04	0.51	0.52	1.24
Diet Na	%	0.23	0.1	0.1	0.34
Diet S	%	0.2	0.2	0.2 (0.3–0.4)	0.2
Diet Co	mg/kg DM	0.11	0.11	0.11	0.11
Diet Cu	mg/kg DM	11	12	13	16

Item [1]	Unit	Phase			
		Lactation	Far-Off	Close-Up [4]	Fresh
Diet I	mg/kg DM	0.5	0.4	0.4	0.77
Diet Fe	mg/kg DM	15	13	13	22
Diet Mn	mg/kg DM	14	16	18	21
Diet Se	mg/kg DM	0.3	0.3	0.3	0.3
Diet Zn	mg/kg DM	48	21	22	73
Diet vitamin A	IU/kg DM	3169	5576	6030	4795
Diet vitamin D	IU/kg DM	864	1520	1644	1308
Diet vitamin E	IU/kg DM	23	81	88	35
DCAD	meq/kg DM	na	na	10 (−75 to 0)	na
Sample diet (ingredients listed as kg/day DM)					
Corn silage, normal	-	8.21	-	5.55 (5.40)	36.44
Grass silage, mid-maturity	-	-	8.1	2.48 (2.42)	-
Legume forage silage, mid-maturity	-	4.57	-	-	-
Legume forage hay, immature	-	-	-	-	20.17
Grass hay, mid-maturity	-	3.21	-	-	-
Sugar beet pup, dried	-	-	-	2.15 (2.09)	-
Corn grain, steam flaked	-	4.33	-	-	18.29
Soybean meal, 48% CP	-	1.62	-	0.79 (0.77)	2.53
Soybean meal, expellers	-	-	-	-	7.65
Blood meal, ring dried	-	-	-	-	1.02
Cottonseed, whole with lint	-	-	-	-	8.41
Calcium soaps of fatty acids	-	-	-	-	0.65
Vitamin and mineral premix	-	0.49	0.02	0.43 (0.42)	3.18
Calcium carbonate	-	0.07	0.46	-	0.56
Calcium phosphate (di-)	-	-	-	0.05 (0.03)	-
Calcium chloride	-	-	-	- (0.14)	-
Monosodium phosphate	-	0.02	-	- (0.07)	0.4
Sodium chloride	-	0.011	5.79	0.03	0.7
Magnesium oxide	-	-	-	0.05 (0.03)	-

[1] BCS is body condition score; NE_L is net energy for lactation; MP is metabolizable protein; RDP is rumen degradable protein; RUP is rumen undegradable protein; NDF is neutral detergent fiber; ADF is acid detergent fiber; NFC is nonfibrous carbohydrates; DCAD is dietary cation-anion difference (calculated as [(Na + K) − (Cl + S)]. [2] Days in milk while lactating, pregnant while dry. [3] With conceptus while pregnant. [4] Values enclosed within brackets are referred to anionic close-up diets. na is “not available”. -is “absent”.

In all transition pens, a soft and comfortable lying surface and adequate ventilation should be provided (i.e., dry and deep layer of shavings, straw, or sand as bedding material and a minimum airspeed of 1 m s^{-1}), as well as feed bunks with headlocks (76 cm wide)—these are preferred to post-and-rail design [26][27][28][29][30][31]. These requirements are essential as is the need for frequent caregiver examinations (keeping in mind that lockup time should be as short as possible). They also mitigate competition while feeding, providing subordinate cows a certain level of protection [32]. Overstocking should be minimized to ensure sufficient bunk and resting space (i.e., at least 13 m^2 per cow). Thus, each pen should be sized using 120-150% average calving rate (depending on average stay of the animals in each pen) to avoid overstocking when

calving rate is higher [24]. Grouping strategies should be planned carefully to avoid pointless movements that can lead to social stressors. Regrouping or inclusion of new animals requires the stabilization of social hierarchy, increasing agonistic and competitive behaviors [33][34][35]; these social interactions can have detrimental effects during the days closer to calving (i.e., reducing feed and water intake, increasing standing time and decreasing lying time) [36]. Furthermore, separating primiparous cows from the herd during their first pregnancy and lactation should be considered in large dairy farms, as these animals are more susceptible to adverse effects resulting from social interactions with dominant subjects [37][38].

Dry and prefresh pens can have either freestall or loose bedded pack layout. Maternity pens should guarantee the expression of innate maternal behavior through ensuring calm parturition in an appropriate environment, minimizing disturbances and risk of mistaken identity of the offspring [39]. Good results can be obtained both with individual and group pens, separated from the rest of the herd. Maternity pens should be designed to ensure adequate space (>13 m^2 per cow), a soft and clean surface (deep straw bedding is preferred), easy access, proximity to prefresh area, and options for hiding (i.e., a plywood barrier covering half of the pen) [40][41]. A series of papers [42][43][44] demonstrated that providing the maternity pen with additional space and a physical blind (created using plastic road barriers and plywood, a steel gate, and shade cloth) may benefit periparturient cows and heifers, facilitating natural calving behaviors and reducing inflammation before calving.

Immediately after calving, the calf is usually separated from the dam, although public concern about this practice is increasing [45]. As reviewed by Johnsen et al. [46] different dam rearing systems that maintain cow-calf contact for longer can be a viable option even in modern dairy farms, ensuring special attention is provided to hygiene and the control of transmissible diseases.

2.2. Nutritional Strategies and Modulatory Treatments to Improve the Adaptation of Dairy Cows to the New Lactation

Considerable literature exists on the best diet formulation strategies for dairy cows during the initial dry period, and subsequent new lactation [20][47][48]. These strategies focus on satisfying nutrient requirements avoiding metabolic challenges driven by sudden changes in diet composition. Furthermore, there is a growing interest regarding the inclusion of nutraceuticals on the diet of transition dairy cows due to their specificity in modulating metabolic pathways (i.e., energy metabolism and the immune functions), allowing a fine tuning on the metabolic processes that are more likely to exceed the control of homeorhetic mechanisms [49][50]. These compounds include probiotics, prebiotics, dietary lipids, functional peptides, phytoextracts, microminerals, vitamins, and methyl donors. However, the requirement of dairy cows for most of these active principles is very low and their direct dietary inclusion is hard to fit with the feeding routine adopted in most commercial dairy farms. Furthermore, each active principle mentioned above affects few metabolic pathways through a highly specific mode of action, while molecules interacting with multiple body compartments could likely provide a greater benefit against the multifactorial challenges affecting the metabolism of transition dairy cows. Thus, several commercial products containing a mixture of active substances have been developed to address these limitations, allowing direct dietary inclusion at the farm level. For example, Omnigen-AF (**OAF**) is known as an immune modulator that could be included in the diet of dairy cows from dry-off to the first month of lactation, providing positive effects on leukocyte function and a consequent reduction of the incidence of infectious diseases in TP [51][52]. Although a direct effect of OAF on the gene expression of neutrophils has been reported [53], a recent study found no effects on neutrophils diapedesis measured in-vivo or on the amelioration of liver metabolism and inflammation of dairy cows receiving the feed additive [54][55]. Nevertheless, the same study described dairy cows receiving OAF to have an increased abundance of lymphocytes at the blood level and improved leukocyte function after ex-vivo stimulation with LPS (lower lactate production and lower glucose consumption). These outcomes, paired with the improved rumination time and energy metabolism found in dairy cows receiving the additive, suggest that OAF has an indirect effect on immune function, likely mediated by positive effects on energy metabolism and feeding behavior.

Besides nutritional aspects related to diet formulation, recent interest in the alterations occurring in the immune functions of dairy cows during the peripartum period have promoted the development of specific treatments aimed at reducing their negative effects. Pegbovigrastim (Imrestor; Elanco Animal Health Greenfield, IL, USA) is a commercial product consisting of pegylated recombinant bovine granulocytes-colony stimulating factor (PEG-rbG-CSF), aimed at stimulating the circulating numbers, and possibly function of neutrophils. G-CSF is a cytokine that induces a state of neutrophilia, characterized by a ‘left-shift’ towards progenitor cells with a release of mature neutrophils and band cells from storage pools in bone marrow [56]. PEG-rbG-CSF only needs to be injected two times (a 15 mg injection approximately a week before parturition and a second injection within 24 h after parturition), addressing the limitations of rbG-CSF treatment (i.e., daily injections, leading to an impractical on-farm application). Some studies using this product have demonstrated substantial increases in circulating neutrophil, monocyte, and eosinophil counts for several weeks [57][31][58][59][60][61].

These were paired with modest increases in per-cell function, most consistently of extracellular release of myeloperoxidase [59][62]. From a molecular perspective, the abundance of mRNA in most genes involved in the cell adhesion (*ITGB2*, *ITGAL*, *TLN1*, *SELL*, *SELPLG*, and *CD44*), recognition and immune stimulation (*CD14*, *CD16*, *MYD88*, *TLR2*, and *TLR4*), antimicrobial activity (*MMP9*, *LTF*, and *LCN2*), and inflammation cascade (*CASP1*, *TNFRSF1A*, *IL1B*, *IL1R*, *IL18*, *IRAK1*, *NLRP3*, and *S100A8*), together with the expression of *SOD2* and *ALOX5,* increased in whole blood leukocytes from dairy cows treated with PEG-rbG-CSF during the TP [57][58]. Conversely, treated cows showed lower expression of *RPL13A*, *ALOX15*, *IL8*, and *TNF*. In another study, isolated neutrophils from the blood of cows receiving PEG-rbG-CSF had an increased expression of genes related to the chain of functional steps (*ICAM1*, *TLR2* and *PTGS2*), while those isolated from the uterus at 4 and 7 days postpartum showed 11 differentially expressed genes, which collectively suggested enhanced antimicrobial capacity [63]. Despite occurring only at the transcriptional level, these differences in gene expression suggest a possible improvement of migration, adhesion, and antimicrobial ability, and enhanced inflammatory response of leukocytes (especially neutrophils) with PEG-rbG-CSF. In turn, this could trigger immune cell activation and enhanced function allowing a complete activation of the immune machinery against the challenges occurring in post-partum. Recently, Lopreiato et al. [14] showed, for the first time, the effect of PEG-rbG-CSF in maintaining stable (with no drops) PIC levels during the first month after parturition. This reflects greater regulation of neutrophil recruitment, tracking, and maturation during the inflammatory response, providing evidence of the immunomodulatory action of PEG-rbG-CSF around parturition, when dairy cows are highly immune hypo-reactive. Several randomized controlled trials have demonstrated an approximately one-third relative reduction in the incidence of clinical mastitis in early lactation following treatment with PEG-rbG-CSF [62][64][65]. Conversely, two studies reported no differences in the incidence risk for retained placenta [60][62], and one study reported PEG-rbG-CSF to increase the incidence risk of metritis at 21 days postpartum [62]. Taken together, these results suggest that PEG-rbG-CSF do not consistently lead to a reduction in the incidence of diseases thought to be related to neutrophil function(i.e., retained placenta, metritis, and endometritis) [66], suggesting that a massive increase in the number of neutrophils available in circulation does not correspond to fewer diseases.

Finally, treatments that are classically adopted in transition cows to modulate rumen fermentation, recently revealed to have a potential role in mitigating the immune dysfunction occurring immediately before and after parturition. Monensin is known for its effect on rumen bacteria populations, resulting in increased propionic acid and reduced lactic acid and methane production [25][67][68]. Thus, modulation of rumen fermentation through monensin is an effective strategy to address the risk of both ketosis and acidosis in dairy cows at the onset of lactation [69]. These positive effect of monensin on rumen fermentation is reflected by trends of several plasma analytes (i.e reduced BHB and NEFA concentrations and higher plasma glucose) in cows treated with monensin [67][68][70]. A recent study [71][72] found reduced infiltration of T and B leukocytes in the rumen fluid from transition dairy cows that received a controlled-release capsule of monensin 21 days before the expected calving date (expected release rate, 335mg/d for 95 days). Such an outcome suggests monensin promotes the stabilization of rumen milieu, probably through mitigating pH alterations related to the adaptation of dairy cows to the lactation diet. This provides a new perspective on the utilization of ionophores to modulate the immune system of early lactating cows.

2.3. Early Detection of Risky Animals through Plasma Analytes Trends and Behavioral Patterns

Several studies have been performed on biological fluids of transitioning dairy cows (i.e., urine, blood, saliva, rumen fluid) using different analytical procedures. Research efforts have focused on identifying candidate biomarkers that might reflect ‘at risk’ condition for developing early lactation diseases (i.e., ketosis, mastitis, metritis, lameness, retained placenta, and milk fever) [73][74][75]. Plasma analytes reflecting metabolic and immune conditions represent a promising tool in this respect [13][76][77]. Besides considering single analytes as biomarkers for specific metabolic patterns of dairy cows, a valuable strategy could be the calculation of indexes aggregating trends of multiple plasma analytes detected at specific time points relative to the calving date. Several promising indexes have been developed on postpartal trends of plasma analytes reflecting liver function and the acute phase response. Bertoni et al. [8] calculated the liver activity index (**LAI**) by aggregating the albumin, cholesterol, and retinol concentrations measured 5, 15, and 30 days after calving. Similarly, Trevisi et al. [78] calculated the liver functionality index (**LFI**) aggregating the albumin, cholesterol, and bilirubin concentrations measured 3 and 28 days after calving. Retrospectively dividing a group of transition dairy cows based on their liver condition (as reflected by these indexes), three studies [19][79][80] consistently found animals with the lowest LAI or LFI values to have the most severe inflammatory condition in early lactation (i.e., higher PICs and oxidant species concentrations in blood and higher SCC in milk). Furthermore, animals with the lowest LAI or LFI values had the lowest milk yield, worst reproductive performances, and greatest disease incidence in early lactation. This suggests LAI and LFI calculations are valuable tools for following up the adaptation of dairy cows to the new lactation [15][81]. Recent research by the same group [82] provided new perspectives on the use of blood indexes as predictive biomarkers as they found the plasma AGR of late lactating cows to reflect their adaptation to subsequent calving and lactation.

Other promising predictive indicators include those related to the animal's behavior, such as rumination, activity, and lying times. The availability of sensors automatically monitoring these behavioral measures allows the detection of alterations that might reflect illness or disease risk in an animal [83][84][85]. Chewing and rumination times are affected by several factors [86], and their trends around calving reflect the likelihood of dairy cows developing severe inflammatory conditions or diseases in early lactation [87][88][89]. Cows with reduced rumination time before calving are known to maintain this even after calving, and these animals are more likely to develop health disorders during the peripartum phase (i.e., metabolic and digestive disorders and severe cases of mastitis and metritis) compared to cows with a greater rumination time ante-partum [88][90]. Recently, Abuelo et al. [1] extended such a relationship way beyond the TP, demonstrating that cows with the greatest reduction of rumination time at dry-off were more likely to develop ketosis or lameness in early lactation. Moreover, peripartum trends of plasma analytes from cows with a reduced rumination time during the first few days of lactation typically reflect a more marked inflammatory condition compared with those from cows having high rumination time at the onset of lactation [88][89]. This suggests that the occurrence of severe inflammation around parturition is associated with a slower increase of rumination time after calving. Saha et al., 2019 have found that cows undergoing a subclinical rumen acidosis condition (as reflected by the increased VFAs content, altered acetate to propionate ratio and decreased pH of the rumen fluid) spent a similar amount of time ruminating during the day as compared to healthy animals, but their RT differed after the morning feeding. Besides rumination time, time spent lying can predict the onset of several diseases, although this relationship has not been fully elucidated. Itle et al. [91] reported clinically ketotic cows to have a reduced lying time in the week preceding calving. Conversely, Rodriguez-Jimenez et al. [86] hypothesized that longer lying time (and reduced standing time) during the days leading to parturition could predispose dairy cows to postpartal ketosis through reducing DMI. Such a hypothesis is supported by the positive relationship between lying time, changes in plasma NEFA concentration, and the risk of developing ketosis (alone or paired with other diseases) detected by others during the first weeks of lactation [92][93]. In a recent paper on multiparous cows, Cattaneo et al. [23] reported cows developing retained placenta to have increased lying time during the last 3 weeks before calving, but no alterations in prepartal lying time were found for cows developing metritis. Conversely, Neave et al. [65] found that cows later diagnosed with metritis had reduced lying time and fewer lying bouts before calving, while Barragan et al. [3] detected an opposite trend in prepartal lying time for primiparous and no differences for multiparous cows developing metritis.

2.4. Genomic Information to Prevent Metabolic Dysfunctions

As TP severely challenges the metabolism and immunity of dairy cows, breeding cattle displaying lower susceptibility to disturbances could be a key step towards establishing resilient animal production systems [94]. The existence of genetic differences in dairy cattle to common health disorders was investigated and confirmed over the years [78]. Consequently, a growing interest in including health-related traits in genetic selection programs led to the concept of a comprehensive diseases prevention strategy, accounting also for genetic information [95][96][97]. The feasibility of such kind of breeding program has been reported by scientific literature [98][99] and implemented with the introduction of the genomic prediction Wellness Trait Index [100], which includes six disease resistance traits (mastitis, metritis, ketosis, retained placenta, displaced abomasum and lameness) in estimating differences in expected lifetime profit. Moreover, in 2018, the US genetic selection index (NM$18) was updated with the insertion of the Health Trait Subindex, which accounted for six disease resistance traits (milk fever, displaced abomasum, ketosis, mastitis, metritis and retained placenta) [101].

A feasible solution to improve the efficiency of current breeding programs at preventing transition cows diseases could be understanding the genetic architecture of specific biomarkers related to metabolism, immune system, and inflammation. Indeed, the genomic prediction quality of a model strictly depends on the trait's genetic architecture [102][103], and a control exerted by a large number of genes with small additive effect (polygenic control) is often to take into account when dealing with complex traits—such as health-related ones—[104]. Thus, identifying some intermediate phenotypes (or "endophenotypes"), which are measurable markers correlated to an illness—expected to be characterized by a simpler genetic control than the end-point phenotype—could improve our power in detecting candidate genes underlying the resistance to a disease [53][105][106].

In this respect, increased evidence of the role of genotype in modulating the inflammation process (mostly related to APOE genes) has already been reported in murine models [107][108]. Significant associations between genetic variants expressing different levels of inflammatory biomarkers and the occurrence of several diseases have been well investigated in human medicine [53][109][110]. Thus, identifying similar associations in the genome of dairy cows has the potential to drive breeding programs aiming to improve the effectiveness of animal responses to physiological and environmental stressors [111]. This represents a promising solution against the metabolic challenges occurring during the TP.

Recently, the genetic structure of several blood, hair, and milk biomarkers related to metabolism, immunity, inflammation, and oxidative stress response in Holstein and Simmental cows has been investigated [112]. Specific and precise genomic

regions were identified to be associated with three biomarkers levels, namely serum gamma-glutamyl transferase, paraoxonase and ceruloplasmin, all involved in anti-oxidant functions. Moreover, paraoxonase and ceruloplasmin are considered biomarkers of inflammation, as they are involved in the acute phase response as negative and positive acute phase proteins, respectively [15]. Interestingly, the identified genomic regions included the genes that directly code for each protein (GGT1 and GGT5 genes on chromosome 17 for gamma-glutamyl transferase, PON1 on chromosome 4 for paraoxonase and CP on chromosome 1 for ceruloplasmin), suggesting cis-regulation. Candidate causative variants were identified but are not yet validated.

Genetic resistance to ketosis and NEB-related diseases has already been explored and promising results have been obtained in dairy cows. RNA-seq studies performed on dairy cows undergoing different degrees of NEB have revealed that genes involved in fat metabolism have the greatest differences in transcription levels [113]. Although transcriptional and post-transcriptional regulation of gene expression do not relate differences in RNA transcripts found in this study to differences at the genotype level, energy metabolism genes were selected as suitable targets for genetic selection in subsequent years. Polymorphisms on the gene encoding for apolipoprotein B receptor (APOBR gene on chromosome 25) have been suggested to affect the likelihood of Holstein cows developing ketosis [114][115]. Accordingly, that gene was found to be significantly associated with glycerophosphocholine-phosphocholine ratio in milk, which was previously proposed as a ketosis biomarker [116]. It was suggested that cows with a high glycerophosphocholine-phosphocholine ratio were disposed to a greater ability in utilizing blood phosphatidylcholine as a source for milk fat synthesis. This likely reflects their lower susceptibility to developing severe lipomobilization processes that precede ketosis status. APOBR gene was suggested as promising candidate gene associated with metabolic status of dairy cattle also by Huang and colleagues [117]. In this study a genome wide association study (GWAS) on ketosis resistance in Chinese Holstein cattle was performed, finding out that genes explaining largest variance portions were all involved in either insulin or lipid metabolism. Several other SNPs and genes mostly located on chromosomes 6, 14, and 20 were found to have a significant genetic association with milk BHB concentration in dairy cows [118]. In particular, five genes (HSD17B10 and HTR2 on chromosome X; ABCA1 and ABCA2 on chromosome 8; LIPC on chromosome 10) were found to be positively related to the longitudinal concentration of BHB in Holstein milk [119].

Finally, further research is related to the resistance of infectious diseases, as the TP alters immuno-competences. A genetic effect on this phenotype was demonstrated in Canadian Holstein cattle [120] and subsequent studies focused on resistance to specific diseases, such as Bovine Respiratory Disease (BRD), tuberculosis and mastitis (reviewed in Raszek et al. [81]).

To conclude, genomics is helping in adding valuable information to the development of an efficient health management system. Each disease is characterized by a specific genetic architecture and correlations with other traits which should be properly investigated; independent functional validation of candidate causative variants is also crucial for the implementation of breeding programs. Finally, additional efforts in improving current disease recoding systems are required to ensure an easier estimation of genetic prediction.

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