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Invited review: Advances and challenges in application of feedomics to improve dairy cow production and health

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ABSTRACT

Dairy cattle science has evolved greatly over the past century, contributing significantly to the improvement in milk production achieved today. However, a new approach is needed to meet the increasing demand for milk production and address the increased concerns about animal health and welfare. It is now easy to collect and access large and complex data sets consisting of molecular, physiological, and metabolic data as well as animal-level data (such as behavior). This provides new opportunities to better understand the mechanisms regulating cow performance. The recently proposed concept of feedomics could help achieve this goal by increasing our understanding of interactions between the different components or levels and their impact on animal production. Feedomics is an emerging field that integrates a range of omics technologies (e.g., genomics, epigenomics, transcriptomics, proteomics, metabolomics, metagenomics, and metatranscriptomics) to provide these insights. In this way, we can identify the best strategies to improve overall animal productivity, product quality, welfare, and health. This approach can help research communities elucidate the complex interactions among nutrition, environment, management, animal genetics, metabolism, physiology, and the symbiotic microbiota. In this review, we summarize the outcomes of the most recent research on omics in dairy cows and highlight how an integrated feedomics approach could be applied in the future to improve dairy cow production and health. Specifically, we focus on 2 topics: (1) improving milk yield and milk quality, and (2) understanding metabolic physiology in transition dairy cows, which are 2 important challenges faced by the dairy industry worldwide.
Key words: omics, feedomics, dairy cow, milk yield and milk quality, transition period

INTRODUCTION

Great advances have been made in our knowledge of the roles that genetics, nutrition, and management have played in milk production from dairy cows over the past century. This has resulted in high yields of nutritious milk for human consumption produced ever more efficiently (McNamara and Lucy, 2017). This success has mainly been achieved by selective breeding and high-density nutrition using diets based on cereal grain and high-quality forage (Overton et al., 2017). However, this has increased susceptibility to metabolic diseases, reduced reproductive performance, and raised the incidence of mammary gland infectious disease (Zhang et al., 2017b). Indeed, up to 50% of high-performance dairy cows may be affected by different metabolic diseases during the transition period (LeBlanc, 2010). A major goal for the dairy industry now and in the future is to achieve more balanced breeding goals that not only emphasize production traits but also take into account health, welfare, and environmental sustainability traits (e.g., methane emissions, nitrogen waste secretion, heat stress tolerance, enhanced immune response, hoof health and so on; Miglior et al., 2017). To date, it remains challenging to identify the key regulatory mechanisms underlying the important biological processes and their roles in dairy cow productivity, well-being, and health (Baumgard et al., 2017). Therefore, a suite of tools to address these challenges is urgently needed. Long-term solutions to maintain sustainable production in the future should include advanced and novel strategies such as omics-based nutritional intervention and early diagnosis of metabolic disorders (e.g., using biomarkers and behavioral predictors). To do this, the research community has begun to collect large amounts of complex data using high-throughput techniques. However, most studies only focus on a single omics technology (we will refer to each omics approach as a "layer" of information, which together provide a more holistic understanding of the biological system), which usually misses important information from other biological layers as well as the interplay between different layers. The systematic collection and interpretation

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of these resulting large data sets and the application of this knowledge within production systems to improve animal performance are very limited.

Recently, feedomics has been proposed as an emerging approach to study food production animals with the aim of dissecting production- and health-related traits within each animal study. As the term implies, it includes many disciplines, principally combining feed science, animal nutrition, physiology, and metabolism, together with high-throughput omics technologies including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics (Sun and Guan, 2018). Feedomics is not just a combination of analytical tools; rather, it is a comprehensive approach to study animals with a system-wide overview of interactions among external stimuli (feed, environment, management, pathogen), internal molecular information (endo-phenotypes or intermediate phenotypes), and the symbiotic microbiome. In this way, feedomics can reveal the entire molecular profile resulting from different stimuli to present an unbiased image of the biological landscape.

In this review, we summarize published research on dairy cows from January 1901 to September 2018 that have used omics technology and that can contribute to feedomics. First, we present a brief historical description of research using the major omics technologies and their application. Second, we provide more details on their applications in 2 topics of major importance in dairy cattle research: milk yield and quality and the cow's metabolic status during the transition period. Last, we discuss current challenges and future directions of feedomics in dairy cattle research. This review provides new insights into the understanding of dairy cow production and metabolism and how the results from different biological layers may lead to a more efficient and sustainable dairy cow industry.

OVERVIEW OF OMICS IN DAIRY COW RESEARCH

Even though the term "feedomics" has been proposed only recently (Sun and Guan, 2018), the application of genomics technologies (as a layer of feedomics) in dairy cows started more than 25 yr ago. For example, one of the first studies was the confirmation of bovine leukocyte adhesion deficiency by DNA testing (Gilbert et al., 1993). Based on the Web of Science database (http://www.webofknowledge.com/), the number of papers published in the last 5 yr (up to September 2018) in each omics category is summarized in Figure 1A. In total, 1,832 published papers included the generic term "genomics," accounting for ~63% of total dairy cow omics studies (Figure 1A). The first "high density" panel of bovine genetic markers (SNP) was released commercially in late 2007, with a set of 54,001 SNPs. Its characterization (Matukumalli et al., 2009) together with the bovine genome sequence (Elsik et al., 2009) ushered in the era of genomic selection and provided the basis for all cattle omics applications. This breakthrough resulted in the rapid adoption of genomic selection in dairy cattle (Meuwissen et al., 2016), and more than 100,000 dairy cows have now been genotyped across the world (Wiggans et al., 2017). Official US genomic evaluations were released for Holstein in January 2009, followed by Jersey (August 2009), Brown Swiss (2013), and Ayrshire and Guernsey (2016; Wiggans et al., 2017). Wiggans and colleagues indicate that the rate of genetic improvement doubled in the United States as a result of decreased generation interval and increased selection accuracy, and a similar response has been reported in Canada (Miglior et al., 2012). Another advantage of genomics is the potential to increase the number of traits that can be genetically selected (Chesnais et al., 2016). To date, the outcomes of genomics-based dairy research have been extensively reviewed (Howard et al., 2017; Wiggans et al., 2017; Cole and VanRaden, 2018). Therefore, in this review, we will focus on omics approaches other than genomic selection, together with their wider potential impact, including improved management and the promise of precision dairy production.

Studies of the microbiome (sequencing of ribosomal RNA gene and the metagenome and metatranscriptome), the host (transcriptome, proteome, and epigenome), and their metabolic products (metabolome) have become hot topics in dairy cattle research. It has been extremely popular for researchers to apply marker gene [16S, 18S, and internal transcribed spacer (ITS) rRNA gene] sequencing-based microbiomics to study animals' symbiotic microbiome, mainly the rumen microbiota, which has led to the second largest group of publications (n = 396, Figure 1A). The first study using such an approach examined the phylogenetic diversity of the bacterial community in the rumen fluid of dairy cows in 1998 (Whitford et al., 1998). The numbers of papers in this category has been increasing in the last 5 yr (Figure 1A), suggesting that gene sequencing continues to play an important role in the field. The first papers that described epigenomics, transcriptomics, proteomics, and metagenomics approaches in dairy cows were all published around 2005. This reflects improvements in sequencing technologies and the international effort to sequence the cattle genome (Goodwin et al., 2016). Application of metabolomics and metatranscriptomics in dairy cows were first reported in 2009 (Bertram et al., 2009) and 2016 (Addis et al., 2016), respectively. It is notable that the integrated analysis of multiple omics approaches is now increasing, with 1, 2, and 8 papers

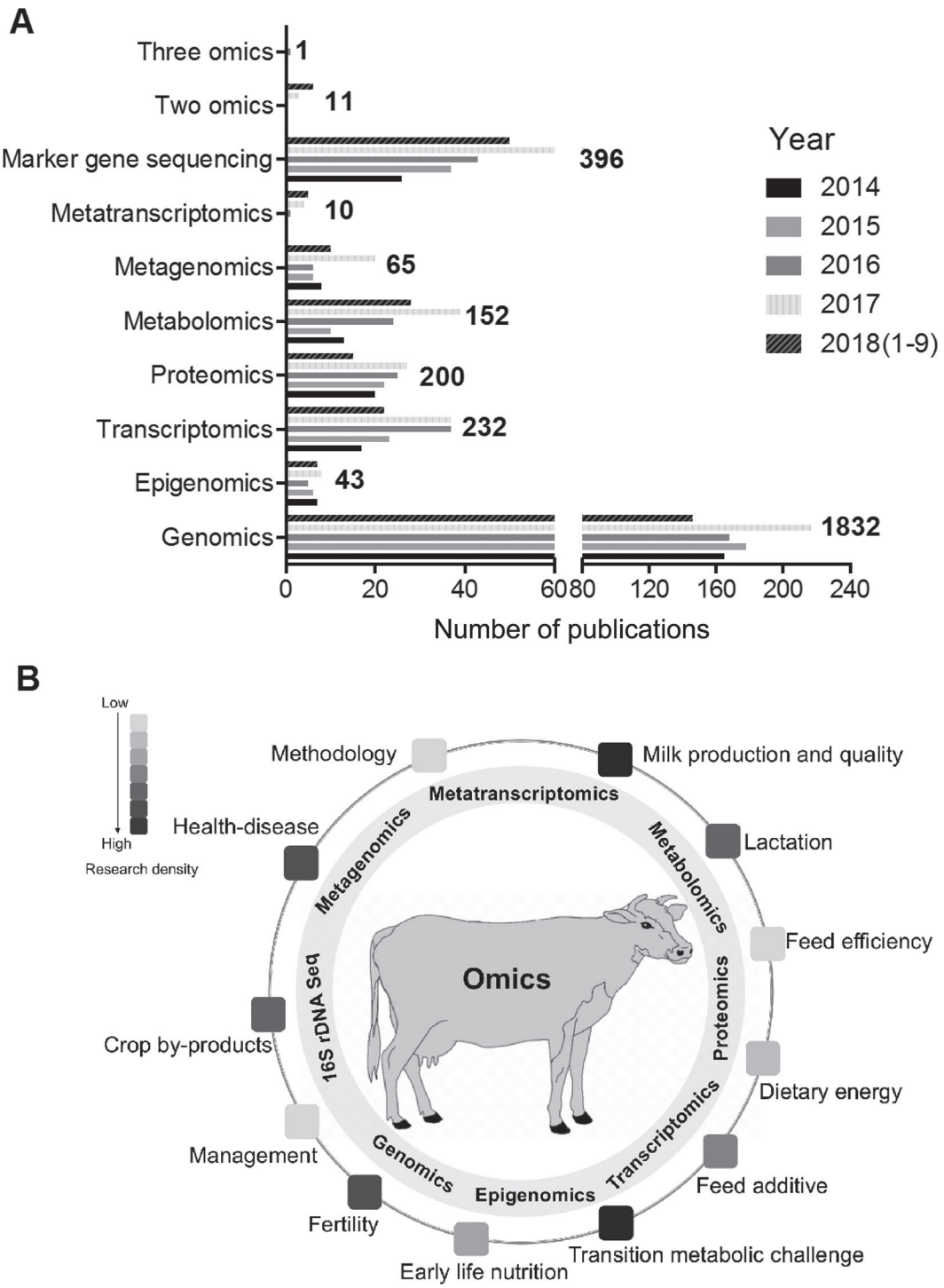

Figure 1. The numbers of papers published using different omics technologies and their applications in dairy cow research. (A) Number of papers published from 1900 to September 2018 using the names of different omics technologies in dairy cows based on the Web of Science database. The total number of published papers in each category is labeled. (B) Main applications of omics in dairy cow research areas; darker colors represent more omics papers published on the topic.

in 2016, 2017, and 2018, respectively (Figure 1A). To date, multi-omics analyses mostly used a combination of 2 omics technologies such as integration of metabolomics and 16S rRNA gene sequencing (Friedman et al., 2017; O'Callaghan et al., 2018; Wetzels et al., 2018), transcriptomics with 16S rRNA gene sequencing (Wirth

et al., 2018), metabolomics with transcriptomics (Sun et al., 2018), metabolomics with proteomics (Ceciliani et al., 2018), and transcriptomics with proteomics (Dai et al., 2018). Only one study used more: metabolomics plus 2 microbial genomics approaches (16S marker gene sequencing and metagenomics) to study the rumen microbiome of dairy cows with different feed efficiencies (Shabat et al., 2016). The results of that study showed the advantage of increasing the depth of information on microbial composition, function, and metabolism, providing a more convincing description of the contribution of the rumen microbiome to the feed efficiency trait and illustrating the proposed extension to feedomics studies.

To date, different omics technologies have mainly focused on the topics of milk yield and quality (Jiang et al., 2016; Do et al., 2017b; Ammah et al., 2018; Cai et al., 2018; Do et al., 2018; Li et al., 2018b; Liu et al., 2018; Pegolo et al., 2018; Wang et al., 2018; Wu et al., 2018; Xue et al., 2018b), transition metabolic challenge (Lima et al., 2015; Cersosimo et al., 2016; Bouvier-Muller et al., 2017; Derakhshani et al., 2017; Gessner et al., 2017; Zhang et al., 2017a; Dervishi et al., 2018; Hailemariam et al., 2018; Wei et al., 2018; Zandkarimi et al., 2018), early life nutrition (Song et al., 2018, 2019; Leal et al., 2018; Qi et al., 2018), utilization of crop by-products (Sun et al., 2016, 2018; Wang et al., 2016; Dai et al., 2017a; Wang et al., 2017; Dai et al., 2018), ruminal acidosis (Mann et al., 2018; Murovec et al., 2018; Xue et al., 2018a), mastitis (Dervishi et al., 2017; Abdelmegid et al., 2017; Song et al., 2017; Xi et al., 2017), heat stress (Min et al., 2016; Srikanth et al., 2017; Dado-Senn et al., 2018; Skibiel et al., 2018), lactation (Bionaz et al., 2012; Dai et al., 2017b; Sun et al., 2017; Yang et al., 2018), and fertility (Walker et al., 2013; Ribeiro et al., 2016; Bauersachs et al., 2017; Salehi et al., 2017; Moraes et al., 2018; Figure 1B). Improving milk yield and quality and the management of the transition dairy cow has attracted continued attention because these are prerequisites for sustainable profitability of dairy farms. Even though many advances have taken place related to these 2 topics, our understanding of complex regulatory and adaptive mechanisms underlying them remains limited. Some novel findings have been highlighted by these omics studies compared with traditional nutrition research. For example, researchers have expanded the current understanding to identify variables potentially linked to milk yield and quality at the transcriptomic level, as well as normal and abnormal metabolic profiles of transition dairy cows. However, we suggest that a more systematic feedomics approach is necessary to develop effective strategies to improve the understanding of all of the processes involved.

PROGRESS AND LIMITATIONS OF OMICS-BASED APPROACHES IN STUDYING MILK YIELD AND MILK QUALITY

Milk yield and milk quality (such as protein and fat content) are the most important economic traits in dairy production, and are affected by multiple factors such as breed, genetic potential, lactation stage, nutrition, environment, management, and disease (Oltenacu and Broom, 2010). Possible interventions at the genetic, physiological, and metabolic levels have been widely studied in the past decades. These have included use of genetic variants, regulatory genes, protein or metabolite biomarkers, symbiotic microbiota, interaction networks, and metabolic pathways by using different omics technologies (Suravajhala et al., 2016). Perhaps the clearest example is the impact of genomic selection.

We have summarized the main omics results related to milk yield and milk quality in dairy cows in Table 1. The "omics level," specific technology, breed, sample type and numbers, related milk traits, and references are also provided. In some cases, the findings are supported by different omics studies although the number of publications with overlapping results is still relatively low. For example, the diacylglycerol-acyl transferase 1 (*DGAT1*) gene has been identified as being associated with milk production traits in several studies (Grisart et al., 2002; Buitenhuis et al., 2014; Iso-Touru et al., 2016; Do et al., 2018; Yurchenko et al., 2018b). Similarly, the genes encoding lysine demethylase 5A (*KDM5A*; Pegolo et al., 2017; Yurchenko et al., 2018b), colony stimulating factor 2 receptor β common subunit (*CSF2RB*; Raven et al., 2016; Yurchenko et al., 2018b), signal transducer and activator of transcription 5A (*STAT5A*; Pegolo et al., 2016; Raven et al., 2016; Yang et al., 2016), and tribbles pseudokinase 3 (*TRIB3*; Cui et al., 2014; Ammah et al., 2018) have also been proposed as important gene markers for milk production and milk fat in different studies. Variations in the acetyl-CoA carboxylase α (*ACACA*) gene at both the genomic (Pegolo et al., 2016) and transcriptomic (Wang et al., 2018) levels have been shown to affect milk fat percentage. Although the transcriptome profiling of mammary gland tissue has been performed between high- and low-milk-producing dairy cows (Cui et al., 2014; Li et al., 2016), the relationship between genetic variation and expression of the differentially expressed genes that directly affect milk production is lacking. Also, research on genome-wide transcriptome profiling in the key organs (e.g., rumen, liver, gut tissues) that are involved in milk production is scarce, which prevents the application of the proposed gene markers. Therefore, identification of genes and their functional roles in milk synthesis within the whole animal is essential to en-

hance our understanding of milk production and could provide valuable resources for designing better breeding strategies to improve milk quality.

Consistent findings for other factors related to milk yield and milk quality at other molecular levels [e.g., microRNA (**miRNA**), metabolites] are shown in Table 1. Using RNA-sequencing-based miRNAome profiling, recent studies suggest that bta-miR-409a in mammary gland tissue might play a role as a regulator of milk protein in Chinese and Canadian Holstein dairy cows (Ammah et al., 2018; Wang et al., 2018). At the metabolite level, the relative concentration of hippuric acid was lower in milk with a high level of somatic cells compared with low-SCC milk (Sundekilde et al., 2013). It was also higher in the serum of cows with high compared with low milk protein yield (Wu et al., 2018), indicating that hippuric acid may be a metabolic marker linked to milk quality. In addition, the urine concentration of hippuric acid was elevated when cows were fed low-quality forages (such as corn stover and rice straw) compared with high-quality forage (alfalfa; Sun et al., 2016). This suggests that dietary forage type should be taken into consideration when using hippuric acid as a milk quality biomarker.

In addition, rumen microbes have been reported to be associated with milk production traits. It was reported that 13 and 2 bacterial genera, respectively, were positively and negatively correlated with milk yield (Xue et al., 2018b) and that 9 and 4 genera, respectively, were positively and negatively correlated with milk fat content. Meanwhile, 3 genera (*CF231*, *p-75-a5*, and an unclassified genus belonging to the family *Prevotellaceae*) and *Lachnospira* were positively and negatively correlated with milk protein content, respectively (Xue et al., 2018b). Some of these relationships have been identified in other studies (Indugu et al., 2017; Xu et al., 2017; Pitta et al., 2018), highlighting potential strategies for manipulating the rumen microbiota to improve milk yield and quality in dairy cows. However, a causal relationship between individual rumen microbiota and milk production needs to be further investigated and validated.

How and to what extent the molecular factors identified by current omics technologies can contribute to improving milk yield and milk quality in dairy cows is still largely unknown. Novel findings from different omics technologies tend to be reported rather than a systematic analysis of different omics approaches, a deficiency that often leads to inconsistent conclusions. It is also important to be aware of the limitations of omics-based studies. First, most of the published studies (except for those using genomic selection of genome-wide association studies, GWAS) were performed using a relatively small number of animals or samples; therefore, checking the probability of a given sample size with sufficient confidence (e.g., power analysis) is needed to reveal the biological relevance, rather than statistical significance (MacCallum et al., 1996). Meanwhile, for studies using a large number of samples, a batch effect between samples (e.g., different time of experiment or sample processing, reagent lots, human handling, and so on) may confound the discovery of real explanatory variables from large-scale omics data sets and should be evaluated to eliminate nonbiological differences (Goh et al., 2017). Second, current studies usually end with identifying one or several key factors (genes, transcripts, miRNAs, proteins, metabolites, microbial taxa) as putative, potential, or candidate indicators for milk yield and milk quality from substantial variables in omics data sets. Under this circumstance, a predictive model with optimal sensitivity (true positive rate) and specificity (true negative rate) is important and necessary to test biomarker performance (e.g., discrimination, probability, accuracy; Xia et al., 2015). Third, at a specific biological layer, the molecules (genes, proteins, or metabolites) can interact with each other and jointly affect internal reactions (Li et al., 2018a). Therefore, the correlation patterns (e.g., network analysis) among different molecules are needed to identify causal effects in these studies. Last, there is a scarcity of integrated analysis among different biological layers. It is well known that omics events at the genetic, epigenetic, transcriptional, translational, and metabolic levels are interrelated (Schwanhäusser et al., 2011). Similarly, the symbiotic microbiota could affect responses in the animal host. It is essential to describe the regulatory mechanism of milk yield and milk quality by constructing a "whole-feedomics" picture to determine causal relationships at multiple levels such as genomic variants, epigenetic events, gene activation or inhibition, miRNA interference, protein modification, metabolite-mediated pathways, and composition and function of the associated microbiota.

APPLICATIONS OF OMICS IN ANALYZING METABOLIC CHALLENGES DURING THE TRANSITION PERIOD IN DAIRY COWS

The transition period (mostly defined as the 3 wk before and after parturition) is an important and vulnerable period for high-producing dairy cows; it is characterized by abrupt changes in nutrition, physiology, and metabolism to fulfill the energy requirements for lactation (Drackley, 1999). Cows usually undergo different levels of negative energy balance during this period because of the increased nutrient demand to support gestation and lactation, which exceeds supply from feed intake. This results in high susceptibility to

Table 1. The molecular factors related to milk yield and milk quality in dairy cows identified using different feedomics technologies

Omics	Technology[1]	Breed	Sample type	Sample number	Trait	Molecular factors[2]	Reference
Whole-genome resequencing	Illumina HiSeq 2000 (PE200)	Holstein bulls	Semen	8	Milk protein and fat	*FCGR2B*, *CENPE*, *RETSAT*, *ACSBG2*, *NFKB2*, *TBC1D1*, *NLK*, *MAP3K1*, *SLC30A2*, *ANGPT1*, *UGDH*	Jiang et al., 2016
Genotyping	Illumina GGP HD150K	Buryat	Blood	24	Milk production	*HAL*, *LAP3*, *PCCA*, *TONSL*, ***DGAT1***	Decker et al., 2009, Daetwyler et al., 2014, Yurchenko et al., 2018a,b
		Yakut	Blood	26		***KDM5A***	
		Bestuzhev	Blood	19		*KLHL1*, ***DGAT1***	
		Yaroslavl	Semen	18		***CSF2RB***, *PCCA*	
		Kazakh Whiteheaded	Semen	20		*TONSL*, ***DGAT1***	
		Kholmogory	Semen	20		*LAP3*	
		Kalmyk	Semen	23		*ABCG2*	
		Kostroma	Semen	18			
	Illumina Genome Analyzer	Fleckvieh	Semen	25			
	Illumina BovineSNP50 BeadChip	Wagyu	Fossil bison bone specimens	19		*PCCA*	
	90K Affymetrix Axiom Buffalo SNP Array	Italian Mediterranean buffaloes	Blood	489	Milk fat yield	C allele at AX-85148558 and AX-85073877 loci; G allele at AX-85106096 locus	Liu et al., 2018
					Milk protein content	G allele at AX-85063131 locus	
	Illumina Bovine HD BeadChip	Danish Holstein (DH) and Danish Jersey (DJ) cattle	Milk	456 DH, 436 DJ	Milk fat	***DGAT1***, *SCD*, *ACSS3*	Buitenhuis et al., 2014
	Illumina BovineSNP50 BeadChip	Brown Swiss cows	Blood	1,011	Milk protein	Transcription factor (TF): *GFI1B*, *ZNF407*, *NR5A1*	Pegolo et al., 2018
					Milk fatty acid profiles	TF: *E2F3*, ***KDM5A***, and *BACH2*	Pegolo et al., 2017
		Canadian Holstein dairy cows	Hair follicles	3,796	Lactation persistency	*MAN1C1*, *MAP3K5*, *HCN1*, *TSPAN9*, *MRPS30*, *TEX14*, and *CCL28*	Do et al., 2017a
		Montbéliarde (MO), Normande (NO), and Holstein (HO) French dairy cattle	Milk	MO: 2,773; NO: 2,673 HO: 2,208	Milk protein	9 QTL on BTA2 (133 Mbp), BTA6 (38, 47, and 87 Mbp), BTA11 (103 Mbp), BTA14 (1.8 Mbp), BTA20 (32 and 58 Mbp), and BTA29 (8 Mbp)	Sanchez et al., 2016
		Nordic Red cattle	Semen	4,280	Milk protein yield	BTA14 (1.8 Mbp) located in ***DGAT1***; BTA25 (1.1Mbp) located in *UNKL*	Iso-Touru et al., 2016
					Milk fat yield	BTA14 (1.8 Mbp) located in ***DGAT1***	
					Milk yield	BTA14 (1.7 Mbp) located in *CPSF1* and *ADCK5*	
		Canadian Holstein cows	Hair follicles	1,200	Milk cholesterol	***DGAT1***, *PTPN1*, *INSIG1*, *HEXIM1*, *SDS*, and *HTR5A*	Do et al., 2018
		German Holstein cows		2,402	Milk fat yield	*RPGRIP1L*, *U6ATAC*, and *5 S rRNA*	Zielke et al., 2013
	Genome-wide association study	Holstein and Jersey dairy cattle		11,754 Holstein and 4.976 Jersey	Milk production	*BTRC*, *MGST1*, *SLC37A1*, ***STAT5A***, *STAT5B*, *PAEP*, *VDR*, ***CSF2RB***, *MUC1*, *NCF4*, and *GHDC*	Raven et al., 2016
	Illumina GoldenGate assay	Brown Swiss cows	Blood	1,158	Milk fat	*LEP*, *PRL*, ***STAT5A***, *CCL3*, ***ACACA***, *GHR*, *ADRB2*, *LPIN1*, *STAT1*, *FABP4*, *CSN2*	Pegolo et al., 2016

Continued

Table 1 (Continued). The molecular factors related to milk yield and milk quality in dairy cows identified using different feedomics technologies

Omics	Technology[1]	Breed	Sample type	Sample number	Trait	Molecular factors[2]	Reference
Transcriptomics	Illumina HiSeq 2000 (50-bp single reads)	Canadian Holstein dairy cows	Milk homogenized fat	9 animal × 8 time points	Milk production Milk lactose Lactation	miR-148a, miR-186, and miR-200a miR-18a, miR-221/222 Ratio: miR-29b/miR-363 and miR-874/miR-6254	Do et al., 2017b Do et al., 2017c
		Chinese Holstein dairy cows	Rumen	18	Milk protein	miR-21-3p	Wang et al., 2016
	Illumina HiSeq 2000 (50-bp single reads) Illumina NextSeq 500	Chinese Holstein dairy cows	Mammary gland tissues	12	Milk quality	38 differential expressed miRNA *SREBF1*, *KDR*, *KIT*, *IGF1*, *MYC*, *ADCY5*, ***ACACA***	Wang et al., 2018
	Illumina HiSeq 2000 (PE100+Single50)	Canadian Holstein dairy cows	Mammary gland tissue	12	Milk yield Milk fat content Milk protein content	Micro (mi)RNA–mRNA pairs (r = −0.599): bta-miR-183/*HNRNPA1*; bta-miR-183/*MAFF*; bta-miR-183/*MGME1*; bta-miR-183/*PPP2R5C*; bta-miR-183/*RHPN2* bta-miR-96/***TRIB3*** (r = 0.613) **bta-miR-409a**/*GALNT5* (r = 0.641)	Ammah et al., 2018
	Illumina Genome Analyzer	Chinese Holstein dairy cows	Mammary gland tissue	30	Milk fat	bta-miR-33a, bta-miR-152 and bta-miR-224	Shen et al., 2016
	Illumina HiSeq 2500 (PE125)	Chinese Holstein dairy cows	Mammary gland tissue	6	Milk protein	Long non-coding RNA: XLOC_059976	Cai et al., 2018
	Illumina HiSeq 2000 (PE100) + Illumina HiSeq 2500 (Single 50)	Chinese Holstein dairy cows	Liver tissue	9	Milk fat formation	*ARNTL*, *COL6A1*, *IGF1R*, *NGFR*, *INHBE*, *FGFR4*, *PKLR*, *NR0B2*, *S1PR1*, *SLC22A7*, *PPP2R2B*, *FADS2*	Liang et al., 2017
	Illumina HiSeq 2000 (PE100)	Chinese Holstein dairy cows	Blood	23	Milk yield	Specific metabolic and immunological pathways	Bai et al., 2016
		Chinese Holstein dairy cows	Mammary gland tissue	12	Milk protein content	*SERPINA1*, *CLU*, *CNTFR*, *ERBB2*, *NEDD4L*, *ANG*, *GALE*, *HSPA8*, *LPAR6*, and *CD14*	Li et al., 2016
		Chinese Holstein dairy cows	Mammary gland tissue	4	Milk protein and fat contents	***TRIB3***, *SAA* (*SAA1*, *SAA3*, and *M-SAA3.2*), *VEGFA*, *PTHLH*, and *RPL23A*	Cui et al., 2014
	Illumina HiSeq 2500	Chinese Holstein dairy cows	Milk	12	Milk production	***STAT5A***, *PRLR*, *NCF1*, and *PTGES*	Yang et al., 2016
	Microarray	Italian Holstein and Italian Simmental lactating cows	Blood	24	Milk protein yield	Specific metabolic and immunological pathways	Sandri et al., 2015
Metabolomics	GC-time-of-flight (TOF)/MS, HPLC-MS/MS	Chinese Holstein dairy cows	Serum	40	Milk protein yield	**Hippuric acid**, nicotinamide and pelargonic acid	Wu et al., 2018
	GC-TOF/MS	Chinese Holstein dairy cows	Mammary gland tissue	12	Lactation	Lactobionic acid, citric acid, orotic acid and oxamide	Sun et al., 2017
			Urine	16	Milk protein	**Hippuric acid**	Sun et al., 2016
			Rumen fluid, serum, milk and urine	16	Milk protein	Glycine, serine, and threonine pathway	Sun et al., 2015

Continued

Table 1 (Continued). The molecular factors related to milk yield and milk quality in dairy cows identified using different feedomics technologies

Omics	Technology[1]	Breed	Sample type	Sample number	Trait	Molecular factors[2]	Reference
	GC-MS	Friesian Holstein dairy cows	Milk	1,305	Milk protein	Myo-inositol-1-phosphate; phosphoenolpyruvic acid; pyroglutamic acid; spermidine; thiazole, 4-methyl-5-hydroxyethyl	Melzer et al., 2013
	Nuclear magnetic resonance	Danish Holstein-Friesian (DHF); Jersey dairy cows	Milk	DHF: 456; Jersey: 436	Milk SCC	Positive relation: lactate, butyrate, isoleucine, acetate, β-hydroxybutyrate Negative relation: **hippurate** and fumarate	Sundekilde et al., 2013
Proteomics	iTRAQ	Chinese Holstein dairy cows	Mammary gland tissue	12	Milk production	Proteins: isocitrate dehydrogenase 2 (IDH2), solute carrier family 7 member 8 (SLC7A8), sterol carrier protein 2 (SCP2), and collagen type IV alpha 2 chain (COL4A2)	Dai et al., 2018
Microbiomics	PacBio SMRT	Dairy cow	Fecal	9	Milk production	Core gut microbiota during peak lactation: *Bacteroides*, *Treponema*, *Ruminobacter*, *Alistipes*, *Oscillibacter*, *CF231*, *Clostridium*, *Succinivibrio*, *Prevotella*, *Phascolarctobacterium*, and *YRC22*	Li et al., 2018b
	Ion Torrent PGM sequencer	Holstein dairy cows	Rumen digesta	10	Milk fat	Unclassified *Lachnospiraceae*, *Butyrivibrio*, *Bulleidia*, and *Coriobacteriaceae*	Pitta et al., 2018
	Ion Torrent PGM sequencer	Holstein dairy cows	Rumen fluid	85	Milk yield	Positively correlated: *Prevotella*, *S24-7* and *Succinivibrionaceae* lineages	Indugu et al., 2017
	PacBio SMRT	Chinese Holstein dairy cows	Fecal	20	Milk yield	Negatively correlated: *Bacillus cereus*, *Paenibacillus barcinonensis*, and *Paenibacillus odorifer*	Xu et al., 2017
	Illumina MiSeq	Holstein Friesian dairy cows	Rumen fluid	146	Milk protein	*Ruminococcus flavefaciens*, *Prevotella* sp., *Clostridiales* sp., *Bacteroidales* sp.	Shabat et al., 2016
	Illumina HiSeq 2500 (PE250)	Chinese Holstein dairy cows	Rumen fluid	334	Milk yield	Positively correlated: *Lachnospira*, an unclassified genus in *Succinivibrionaceae* family Negatively correlated: 13 genera	Xue et al., 2018b
					Milk fat	Positively correlated: *Butyrivibrio*, *Pseudobutyrivibrio*, *Clostridium*, and *Moryella* and unclassified genera belong to the families *Christensenellaceae*, *Mogibacteriaceae*, *Ruminococcaceae*, *Clostridiales*, and S24-7, and the order *Bacteroidales*; Negatively correlated: *Lachnospira*, *Shuttleworthia*, *Treponema*, and an unclassified genus belonging to the *Succinivibrionaceae*	
					Milk protein	Positively correlated: *CF231* and *p-75-a5* and an unclassified genus belonging to the family *Prevotellaceae*; Negatively correlated: *Lachnospira*	

[1]GGP = GeneSeek Genomic Profiler; iTRAQ = isobaric Tags for Relative and Absolute Quantitation; SMRT = Single Molecule Real Time sequencing; PGM = Personal Genome Machine; Illumina = Illumina Inc., San Diego, CA; Affymetrix = Affymetrix Inc., Santa Clara, CA; PacBio = Pacific Biosciences of California Inc., Menlo Park, CA; Ion Torrent = Ion Torrent Systems Inc., Guilford, CT.

[2]Overlapping findings are highlighted in bold type.

postpartum diseases such as metritis, mastitis, hypocalcemia, and clinical ketosis (Suthar et al., 2013). It is reported that ~75% of diseases in dairy cows occur in the first month postpartum and 50% of dairy cows suffer from infectious and metabolic diseases during the transition period (LeBlanc, 2010). Omics technologies have been proposed as powerful tools to understand the adaptations of cows during the transition period at different molecular levels (or biological layers). These tools could play important roles in the early diagnosis of postpartum diseases to improve animal welfare, productive lifespan, and economic outcomes (Ceciliani et al., 2018). In this section, we summarize the main applications of omics technologies in transition dairy cows, including an understanding of metabolic adaptation mechanisms, early diagnosis of transition cow-related diseases, and the effects of alleviation strategies on metabolic disorders using feed additives.

Application of Omics to Understand Adaptations During the Transition Period

During the transition period, the diet of dairy cows usually shifts from greater fiber and less energy at prepartum to less fiber and greater energy after parturition, and both rumen microbiota and ruminal papillae need to adapt to such dietary changes (Pitta et al., 2014; Derakhshani et al., 2017). In a study that profiled the rumen fluid microbiota of 115 high-producing dairy cows, it was reported that the main differences in rumen microbiota were the abundances of *Christensenellaceae* and *S24-7* families between prepartum and postpartum (Lima et al., 2015). An increased prevalence of fungi was also found in the prepartum rumen microbiota and an increased prevalence of protozoa (*Litostomatea*) in the rumen during the postpartum period (Lima et al., 2015). High correlations were identified between bacterial groups and milk production (R^2 = 0.818, 0.817, 0.610, 0.714 for primiparous prepartum, primiparous postpartum, multiparous prepartum, and multiparous postpartum respectively; Lima et al., 2015). This suggests that the shift in rumen microbial populations might directly affect production traits during the transition periods. The enriched energy metabolism pathways of ruminal microbiota, increased proteolytic, amylolytic, and lactate-producing species (including *Prevotella*, *Streptococcus*, and *Lactobacillus*), and decreased fibrolytic genera (*Ruminococcus* and *Butyrivibrio*) were identified in postpartum dairy cows compared with prepartum cows (Derakhshani et al., 2017). These findings suggest that the ruminal microbiome acclimates, to some degree, to the nutrient-dense diet for lactation. In addition to bacteria and fungi, the rumen archaea also show significant differences during the transition period. For example, higher relative abundances of *Methanobrevibacter woesei* and *Methanobrevibacter millerae* and lower relative abundances of *Methanobrevibacter gottschalkii* and *Methanobrevibacter thaueri* were reported in the rumen of postpartum cows (Cersosimo et al., 2016). Another study also reported a significant increase in *Methanobacteriales* (from 80 to 89%, prepartum to postpartum) and a decrease in *Methanomassiliicoccales* (from 15 to 2%) in the rumen during the transition period (Zhu et al., 2017). However, whether and how the observed shifts in the rumen microbiome affect rumen function and subsequent performance are not clearly defined. Future metagenomics- and metatranscriptomics-based functional analysis along with metabolomics may give complementary information and drive more solid conclusions. Regardless, these findings provide novel insights into the roles of rumen microbiome community structure and activity in adapting to the dramatic changes in nutrition during the transition period.

The changes of diet and rumen microbiome (composition, function, and metabolites) in transition dairy cows will directly alter the nutrients provided for other tissues and organs, which may affect the corresponding functions. Several studies have revealed changes in metabolites and inflammatory responses in the liver (McCarthy et al., 2010; McCabe et al., 2012), uterus (Wathes et al., 2009), polymorphonuclear leukocytes (Agrawal et al., 2017), and granulosa cells (Girard et al., 2015) at the transcriptomic level when transition dairy cows were under negative energy balance. Another study using transcriptomics confirmed that the major hepatic functional changes in transition cows were related to fatty acid oxidation, cholesterol metabolism, and gluconeogenesis (Ha et al., 2017). They identified 9 key genes (*CYP7A1*, *APOA1*, *CREM*, *LOC522146*, *CYP2C87*, *HMGCR*, *FDFT1*, *SGLE*, and *CYP26A1*) involved in metabolic adaptation, which could serve as candidate genes for functional changes during transition. This was supported by other liver transcriptome studies (Akbar et al., 2015; Riboni et al., 2016). During the transition period, cows undergo many changes, which could be reflected in the blood. Using serum metabolomics, it was reported that the adaptation processes during the transition period in dairy cows were mainly associated with the glycerophospholipids and sphingolipids, especially the phosphatidylcholines C34:2 and C36:2 (Kenéz et al., 2016). In addition, the quantification of the cow plasma proteome showed obvious changes in the expression of 19 stress-associated (acute-phase response and defense response) proteins before and after calving (Ma et al., 2015). Metabolome- and proteome-based research could help us to identify new biomarkers and characterize multifaceted metabol-

ic adaptation of transition dairy cows, which provides new insights into understanding host physiological and metabolic responses to lactation and parturition stress.

In addition to nutritional changes, heat stress is another major factor affecting the health and production of dairy cows during the transition period (Do Amaral et al., 2009). Skibiel and colleagues reported that heat-stressed transition dairy cows suffered from mitochondrial dysfunction, increased oxidative stress, accumulation of hepatic lipids, and shifts in precursor supply for gluconeogenesis in liver using proteomics (Skibiel et al., 2018). These changes in expression of proteins and their functions may contribute to fatty liver and other transition-related diseases. Elevated malondialdehyde concentrations in plasma and enriched nuclear factor, erythroid 2 like 2 (Nrf2)-mediated oxidative stress response in adipose tissue were also found based on proteomics (Zachut et al., 2017), which identified the stress-induced phosphoprotein 1 (STIP1) protein in adipose tissue as a biomarker of heat stress in transition dairy cows. The hepatic transcriptome is strongly affected by parturition season in transition dairy cows; specifically, calving in the summer not only altered energy metabolism but also induced an inflammatory stress response in the liver (Shahzad et al., 2015). This leads to greater susceptibility to metabolic disorders and health problems in postpartum cows. Future research on the mechanisms involved in these metabolic, proteomic, and transcriptomic changes are needed to elucidate the overall biological processes during the transition period.

In summary, the above studies provided preliminary information to understand the effects of nutritional change or heat stress during the transition period on the rumen microbiome and tissue/blood transcriptome, proteome, and metabolome in dairy cows. However, holistic analyses of the changes on these "omes" in response to calving are scarce. This deficiency means there is a lack of understanding of how dairy cows adapt to nutritional and environmental changes by altering internal molecular phenotypes and related functions.

Applications of Omics to Predict the Risk of Transition-Related Diseases in Dairy Cows

The prevalence of periparturient diseases leads to reduced milk production, poor reproductive performance, early culling of cows, and associated economic losses. It is vital to diagnose early or predict the risk of these diseases. Metritis is a bacterial-caused inflammation of the uterus wall and affects about 40% of transition dairy cows in a herd (Sheldon et al., 2009). Cows with metritis have low rates of conception and poor fertility, even after successful treatment (Walsh et al., 2011). Many efforts have been made to use omics technologies to develop strategies to predict the risk of metritis and find susceptible animals to provide early treatment. Using targeted blood metabolomics, ornithine, pyroglutamic acid, D-mannose, glutamic acid, and phosphoric acid were identified as potential biomarkers for metritis at 4 wk prepartum (Hailemariam et al., 2018). Urine metabolomics revealed a combination of histidine, lysine, xylose, o-phosphocholine, threonine, *trans*-aconitate, isocitrate, and 3-aminoisobutyrate as potential biomarkers for metritis risk at 4 wk before parturition (Dervishi et al., 2018). Applying a more specific and sensitive metabolomic approach, Zhang et al. (2017) reported that lysine, lysophosphatidylcholine acyl C17:0, lysophosphatidylcholine acyl C18:0, isoleucine, and lysophosphatidylcholine acyl C16:0 and lysine, isoleucine, leucine, sphingomyelin C20:2, and lysophosphatidylcholine acyl C17:0 were predicted biomarkers at −8 and −4 wk before parturition, respectively. High accuracy (area under the curve >0.98) of diagnostic biomarkers (lysine, isoleucine, leucine, kynurenine, and phosphatidylcholine) at disease week were also reported (Zhang et al., 2017a). These findings suggest that serum metabolites have the potential to provide predictive, diagnostic, and prognostic strategies and reveal the pathobiology of metritis in transition dairy cows. However, these studies are limited by small sample size (e.g., only 6 metritic and 20 healthy dairy cows were used in Zhang et al., 2017a) and lack of standard cutoffs for proposed biomarkers. Therefore, the predictive accuracy of these biomarkers needs to be tested in a large cohort, and the baseline concentrations should be quantified. Another biomarker type, circulating miRNAs, was used to investigate prediction of bovine metritis. It has been shown that the highly expressed blood miRNAs, including bta-miR-15b, bta-miR-17-3p, bta-miR-16b, bta-miR-148a, bta-miR-26b, bta-miR-101, and bta-miR-29b, and lowly expressed miRNAs, including bta-miR-148b, bta-miR-199a-3p, bta-miR-122, bta-miR-200b, and bta-miR-10a, were associated with metritis in transition dairy cows (Kasimanickam and Kastelic, 2016). The relative expression level of targeted miRNAs was fully addressed in that study; however, the validation and functional mechanisms of these miRNA changes and their targeted genes should be studied further. The approaches may also be combined to investigate whether this improves accuracy.

Omics technologies have also been applied to the identification of predictive biomarkers for other transition diseases, such as ketosis and mastitis. Proteomics and metabolomics are the main technologies used to understand the etiological factors of transition-related disease. The metabolites carnitine, propionyl carnitine,

and lysophosphatidylcholine acyl C14:0 in plasma were significantly elevated in dairy cows with one or more periparturient diseases (metritis, mastitis, laminitis, or retained placenta; Hailemariam et al., 2014). These results may help to predict which cows would develop periparturient diseases. A research team from China systematically analyzed blood metabolic and urinary proteomic biomarkers of dairy cows with clinical ketosis and subclinical ketosis using nuclear magnetic resonance (NMR; Sun et al., 2014), GC-MS (Zhang et al., 2013), and liquid chromatography (LC)-MS–based plasma metabolomics (Li et al., 2014) as well as surface-enhanced laser desorption/ionization-time-of-flight-MS–based urinary proteomics (Xu et al., 2015). The 20 biomarkers identified in the above NMR study included His, Glu, Gln, Lys, Phe, glucose, lactate, myo-inositol, formate, citrate, Ala, Pro, Tyr, low-density lipoprotein, very low density lipoprotein, acetate, *N*-acetylglucosamine (NAG), BHB, acetoacetate, and acetone (Sun et al., 2014). Gas chromatography-MS–based metabolomics study detected 32 biomarkers, including lactic acid, glucuronic acid, L-Ala, glycolic acid, ribitol, pyroglutamic acid, galactose, 2,3,4-trihydroxybutyric acid, glucose, Gly, L-Ile, α-aminobutyric acid, aminomalonic acid, α-tocopherol, sitosterol, 3-hydroxy-3-methylglutaric acid, 3-hydroxyvaleric acid, palmitic acid, heptadecanoic acid, stearic acid, BHB, *trans*-9-octadecenoic acid, myristic acid, *cis*-9-hexadecenoic acid, 2-piperidinecarboxylic acid, L-Ser, 4-aminobutyric acid, melibiose, erythritol, 3-hydroxyvaleric acid, 2-methyl-3-hydroxybutyric acid, and xylitol (Zhang et al., 2013). The latter LC-MS results showed 13 biomarkers, including Val, Gly, glycocholic, tetradecenoic acid, palmitoleic acid, Arg, aminobutyric acid, Leu, Trp, creatinine, Lys, norcotinine, and undecanoic acid in plasma (Li et al., 2014). In the proteomic study, the authors proposed 11 proteins (VGF, amyloid precursor protein, serum amyloid A, fibrinogen, C1INH, apolipoprotein C-III, cystatin C, transthyretin, hepcidin, human neutrophil peptides, and osteopontin) in urine as diagnostic biomarkers for clinical ketosis (Xu et al., 2015). These results clarify some of the metabolic changes that occur in the pathogenesis of periparturient ketosis in dairy cows and may help in developing novel diagnostic and disease prevention strategies. However, comparative analysis among different technologies to determine the most accurate and easy method in practice is required. In addition, more research should be conducted to analyze the complex interactions among all of the metabolites detected during ketosis processes in transition dairy cows and to relate them to results from studies using other omics technologies.

Another highly prevalent and costly disease in transition dairy cows is clinical mastitis. Omics methods are now being used to investigate and identify predictive biomarkers to overcome the unsatisfactory performance (low accuracy, delayed discovery, time and labor consuming) of traditional indicators. For example, proteomic profiling revealed that plasma proteins including α1-acid glycoprotein, haptoglobin, and serum amyloid were dramatically increased in subclinical mastitis dairy cows in the transition period (Yang et al., 2012). Metabolomics profiling of serum showed that 3′-sialyllactose contributed the largest difference between healthy cows and those with clinical mastitis (Zandkarimi et al., 2018). Potential biomarkers in the blood may assist in developing predictive diagnosis and early treatment interventions for improving dairy cow health and welfare. However, future work should focus on integrating these tools with other omics technologies such as transcriptomics, microbiomics, and epigenomics to further understand the molecular mechanisms of transition disease. Moreover, biomarker validation in more experimental conditions as well as in commercial farms is required.

Omics to Evaluate the Effects of Feed Additives on Metabolic Changes in Transition Dairy Cows

There is an increasing interest in supplementing feed with micronutrients (e.g., biotin, nicotinamide, boron, zinc, manganese, copper) or functional by-products (e.g., grape seed, grape meal extract, linseed) to alleviate metabolic disorders in transition dairy cows (Sordillo and Aitken, 2009). The application of omics technologies would greatly extend our understanding of the effect of supplementation of feed additives on metabolic changes in transition dairy cows and whether and how they work (Chauhan et al., 2016). Investigations using metabolomics found that boron effectively prevented metabolic disorders in periparturient dairy cows by changing lipid-soluble metabolites in serum (Basoglu et al., 2017). Recently, it was reported that supplementation of biotin and nicotinamide significantly changed serum metabolites and the pathways of gluconeogenesis, glucose circulation, and oxidative stress alleviation in transition dairy cows using metabolomics (Wei et al., 2018). However, further exploration of the effective dose of biotin and nicotinamide supplementation is needed to determine the optimal treatment. Serum metabolomic analysis revealed impaired mitochondrial fatty acid β-oxidation with increased concentration of tiglylglycine and palmitoylcarnitine in cinnamon-supplemented dairy cows (Sadri et al., 2017), which suggests that supplementing cinnamon may damage rather than be helpful when aiming to overcome metabolic challenges in transition dairy cows.

Transcriptomics provides information on the regulation of gene expression and functional pathways in different tissues when using additive supplementation in transition dairy cow diets. Supplementing zinc, manganese, and copper from amino acid complexes during the transition period affected the transcription of a variety of genes involved in inflammation status, oxidative processes, and composition of the hoof in dairy cows with lameness (Osorio et al., 2016). These results expand our understanding of hoof biology and biological mechanisms of lameness. It remains to be discerned at the molecular level whether these supplementations significantly reduce the incidence of other hoof diseases in transition dairy cows. It was also shown that transition dairy cows fed grape seed and grape meal extract exhibited reduced endoplasmic reticulum stress-induced unfolded protein response and inflammatory processes using functional analysis based on differential liver transcriptomics (Gessner et al., 2017). Such treatment could help mitigate liver-associated diseases and improve milk performance. These studies focused only on molecular changes at the transcriptomic level and largely relied on predicted functions, which lack validation at downstream levels; for example, using proteomics to identify active proteins and verify post-translational changes.

At this stage, individual omics technologies have provided new information to elucidate the effects of supplementing feed additives on metabolic functions at various molecular levels in transition dairy cows. More detailed functional studies and integrated analysis with different feedomics technologies are required in the future.

CURRENT CHALLENGES AND FUTURE DIRECTIONS TO USE FEEDOMICS IN DAIRY CATTLE RESEARCH

Although different omics tools have been used in dairy cow research as stated above, the application of a true feedomics approach is still lacking. First, most research considers only part of the feedomics approach and lacks a comprehensive knowledge of the different biological layers. The dairy cow itself is a very complex biological system and contains numerous biological reactions: changes in one phenotype (especially for complex traits) can be regulated and reflected differently in the different biological layers. Typically, a single omics technology is only able to identify the key factors in one layer (gene, transcript, protein, metabolites, and microbial taxa, respectively); however, it does not determine which layer plays the central role. This, therefore, limits the investigation of the interactions among the different biological layers that drive the mechanisms underlying health or disease phenotypes (Camacho et al., 2018). Feedomics is a more promising approach to generate and incorporate multi-layered information and allow access to the interplay of components in each biological layer and to discover coherent and informative biological signatures. Second, most of the current omics studies in dairy cows have numerous limitations in terms of data processing and analysis. For example, many published studies lack an explanation of coverage and sequencing quality, which have a significant impact on the detection and quantification of low-abundance variables (Wang et al., 2011). This kind of parameter should be selected based on sample complexity and research objectives. The massive amounts of data generated by various omics approaches require sophisticated computer and statistical models for data processing and analysis to generate appropriate results. Completing this kind of work depends largely on bioinformatics knowledge and skills (Schneider and Orchard, 2011), which are in short supply in animal science. Bioinformatics, especially advanced machine learning and artificial intelligence approaches that give the computer the ability to learn without being strictly programmed, creates new opportunities to unravel and understand data-intensive processes (Liakos et al., 2018). Advanced bioinformatics can cope with extremely complex biological data in large quantities, which is one of the major bottlenecks for dairy cow research, and may therefore increase the pace of scientific findings.

To avoid errors and bias in data processing and analysis, suitable cutoffs (e.g., microbial relative abundance, gene expression threshold, metabolite similarity, differential expression cutoff, enriched function cutoff, significant impact value of pathways), data preprocessing options (e.g., data baseline filtering and calibration, peak alignment, deconvolution analysis, peak identification), data normalization, data transformation, and data scaling methods should be carefully considered and addressed within each future study. These are all essential for meta-analysis and global comparisons to draw valid conclusions. More research is warranted to focus on solid evidence and functional validation to help uncover biological mechanisms of the assumptions and speculations as proposed in current omics studies. In addition, feedomics should be exploited to help solve the following scientific issues in dairy cows in the future: (1) to apply metagenomics, metatranscriptomics, metaproteomics, transcriptomics, and metabolomics to reveal the mode of action of the symbiotic microbiome in the rumen and its explicit association with cow production and health traits; (2) to use epigenomics and transcriptomics to investigate stable epigenetic markers that can be included in production improvement programs in dairy cows; for example, using CRISPR-Cas9–based epigenome editing technology to directly gener-

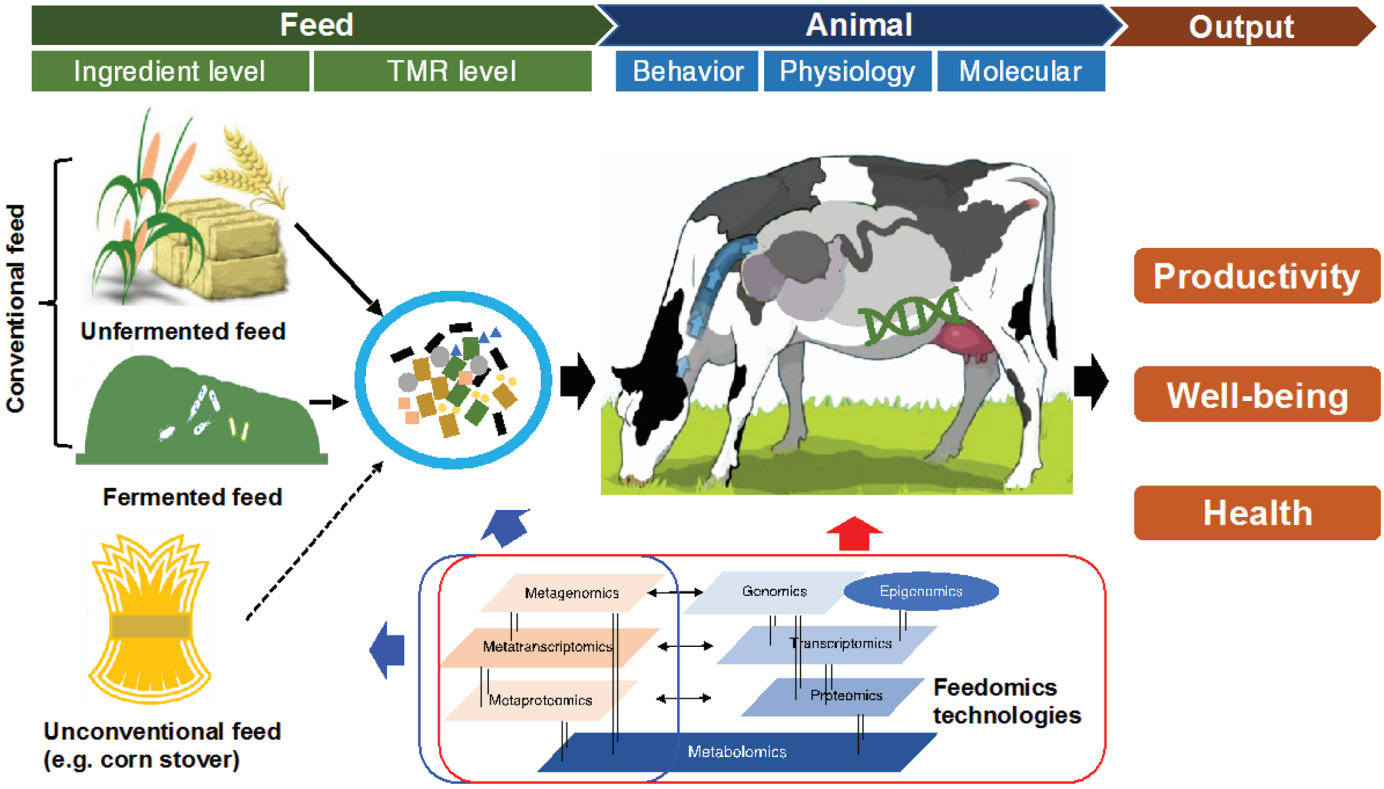

Figure 2. Proposed feedomics-based nutrition and management.

ate specific transcriptional outcomes; (3) to combine feed metabolomics (and microbiomics for fermented ingredients) with animal genomics, transcriptomics, proteomics, and metabolomics under different nutritional conditions to construct nutriomics applications; and (4) to develop robust bioinformatics methods and integrated/interaction analysis pipelines specialized for dairy cow feedomics research to present the entire molecular and biological landscape of all available omics levels.

Feed generally accounts for the largest cost in dairy farms and greatly affects subsequent biological reactions in the animal (Miller, 2012); it should therefore be considered a focus for future feedomics research. Here, we propose that feedomics research include feed at the ingredient level (including unfermented and fermented conventional feed, and unconventional feed) and the TMR level, as well as at the animal level (molecular, physiological, and behavior), to lead to greater understanding and improved outputs (productivity, well-being and health; Figure 2). Integrated feedomics technologies can be applied in feed quality assessment. For example, metabolomics combined with gene sequencing, metagenomics, and metatranscriptomics will provide novel insights into the functional components, fermentation process, and quality of fermented feed. The holistic analysis of feed and animal omics data will help identify the flow of information, from the original input to subsequent changes and functional interactions, which may break down the "black box" of regulatory mechanism and provide complete clues linked to outputs. Further, comprehensive findings identified using feedomics should be combined with traditional nutrition and feed science knowledge to translate and develop intervention strategies such as precision feeding, well-being detection, and early diagnosis of metabolic disorders and disease.

The systematic collection of large data sets from different biological layers will help generate a more holistic understanding of the biological factors affecting the current challenges for dairy. Furthermore, this improved understanding will contribute to the development of more accurate and effective management strategies. Feedomics places emphasis on the combination of multi-omics with other "big data"; for example, that detected by advanced management technologies (e.g., using remote sensors communicating with the Internet of Things to measure physiological and behavioral data, which can then be applied to monitor estrus, lameness, or rumination). Indeed, this will be the basis

of delivering precision dairy production management for the future, with new insights into understanding and improving animal production and welfare.

CONCLUSIONS

The current applications of different omics technologies in dairy cows are generally classified into 2 main themes: biomarker screening and biological mechanism discovery. To date, omics-based research has revealed biological patterns for milk yield and milk quality, diseases, and metabolic functional changes of transition dairy cows at the genomic, transcriptomic, proteomic, metabolomic, and microbiomic levels. The current omics results have laid the foundation for the precision dairy production management of the future, with new insights into animal production and welfare. However, the major limitation of current omics studies in the area of dairy cow research is that most studies only targeted one type of internal molecular data using a single omics technology. This only captures information within a certain biological layer and largely omits important information from other biological layers as well as the interaction among them. As such, these data may not contribute sufficiently to our understanding of biological or pathological phenomena to be converted into valuable knowledge and new applications. Feedomics, which aims to discover coherent biological signatures through collection and integrated analysis of multiple omics data, should be applied in the future dairy research to address this weakness. However, data interpretation will present a significant challenge in its interpretation. We encourage the research community to perform more accurate and comprehensive feedomics to better solve current and future problems for the industry. It is expected that with the right inputs (funding, deep learning, collaboration), this type of investigation will have real advantages in converting research to application and helping to achieve sustainable dairy production in the future.

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