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Review Article

Feedomics provides bidirectional omics strategies between genetics and nutrition for improved production in cattle



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ABSTRACT

Increasing the efficiency and sustainability of cattle production is an effective way to produce valuable animal proteins for a growing human population. Genetics and nutrition are the 2 major research topics in selecting cattle with beneficial phenotypes and developing genetic potentials for improved performance. There is an inextricable link between genetics and nutrition, which urgently requires researchers to uncover the underlying molecular mechanisms to optimize cattle production. Feedomics integrates a range of omic techniques to reveal the mechanisms at different molecular levels related to animal production and health, which can provide novel insights into the relationships of genes and nutrition/nutrients. In this review, we summarized the applications of feedomics techniques to reveal the effect of genetic elements on the response to nutrition and investigate how nutrients affect the functional genome of cattle from the perspective of both nutrigenetics and nutrigenomics. We highlighted the roles of rumen microbiome in the interactions between host genes and nutrition. Herein, we discuss the importance of feedomics in cattle nutrition research, with a view to ensure that cattle exhibit the best production traits for human consumption from both genetic and nutritional aspects.

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1. Introduction

As one of the most important livestock species, cattle can convert human inedible plant biomass into nutritional foods such as milk and meat. Meanwhile, cattle are one of the major contributors of annual methane emissions (Scholtz et al., 2012). Thus, with the increasing human population and the growing demand for high-quality protein, there is an urgent need for sustainable strategies to improve cattle production efficiency and reduce environmental pollution of cattle (Cisneros-Saguilán et al., 2015; Thornton, 2010). With the advancement of technologies in animal nutrition and feed science fields, researchers have made some

progress in improving cattle productivity and reducing methane emissions (Baumgard et al., 2017), however, the underlying molecular mechanisms and fundamental knowledge remain largely unknown. Owing to the development of high-throughput techniques, omics approaches are gradually being used in cattle nutrition manipulation. Such omics techniques include, but are not limited to genomics, epigenomics, transcriptomics, metabolomics, proteomics, meta-omics (metagenomics, metatranscriptomics, metaproteomics), and single-cell omics (i.e., single-cell transcriptomics). In addition, the integration of multiple omics techniques (known as multi-omics) has recently been applied to reveal the holistic mechanisms related to economic phenotypes at different molecular levels.

Phenotypes are determined by the interactions between the environmental factors (especially nutrients in feed) and internal molecular reactions (Ferguson, 2014). With the completion of the Human Genome Project in 2003 (Collins et al., 2003) and the development of the 1000 Bull Genomes Project (Hayes and Daetwyler, 2019), the focus of human and cattle nutrition research has gradually shifted from epidemiology and physiology to molecular aspects and genetics, resulting in the emergence of nutrigenetics and nutrigenomics (Mutch et al., 2005). On the one

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hand, nutrigenetics focuses on exploring the response of gene variants to the environment (diet/nutrients, lifestyle choices, and exposures) and the phenotypic consequences of their interactions (Archibald and Joffe, 2021; Sales et al., 2014). For example, once individuals undergo a C→T substitution in the gene encoding methylenetetrahydrofolate reductase, they need more folic acid to maintain requirements than those without substitution (Bailey and Gregory, 1999). On the other hand, nutrigenomics attempts to understand the mechanisms of which diet/nutrients affect phenotypes by changing molecules at different post-genomic levels (Sales et al., 2014). For instance, by inhibiting the expression and activity of the sterol regulatory element binding protein 1 (SREBP1), lipopolysaccharide can induce the decrease of triglyceride synthesis and secretion in mammary epithelial cells of dairy cows, resulting in milk fat depression (Wang et al., 2018).

Clearly, nutrigenetics and nutrigenomics provide novel insights into nutrition research supported by omics. However, in research practice, they are like two sides of a coin, and researchers usually focus on one aspect. On the one hand, geneticists are more inclined to identify specific genes or genetic markers that determine nutritional absorption/metabolism. On the other hand, nutritionists care more about how nutrients affect production/health by altering the biological and molecular mechanisms (Gous, 2010; Whitehead, 2000). However, nutritional questions are usually very complex and need to be elucidated using both nutrigenetics and nutrigenomics. From a cross-disciplinary context, Sun and Guan (2018) proposed the concept of “feedomics”, which applies omics techniques to the research of food animals, such as dairy cattle, to reveal certain physiological processes, with the goal of improving the productivity and sustainability of food animals. Unlike the broad scope of nutritional system biology (Panagiotou and Nielsen, 2009; Vailati-Riboni et al., 2016), feedomics mainly focused on livestock and especially target animal nutrition and feed science area. Therefore, some generated principles, concepts, and techniques provide more specific, suitable and precise solutions in livestock research. Feedomics techniques are tools to achieve these goals, which covers the high-throughput omics techniques mentioned above. Importantly, feedomics highlight the integration of nutrigenetics and nutrigenomics, which provide bidirectional insights into genetics and nutrition for a comprehensive understanding of livestock production improvement. With the development of sequencing techniques, data processing protocols, and analysis algorithms, feedomics is also constantly developing. Comparing with previous papers (Sun and Guan, 2018; Sun et al., 2019), the current feedomics include latest omics techniques and their application/progress in cattle research, such as the single-cell transcriptomics as well as its application in discovering novel cell subtypes with strong ability of nutrient absorption and metabolism in dairy cows. Moreover, the current feedomics considered the increasing attentions of microbial roles (especially for heritable microbes) in cattle production traits.

In this review, we discuss the application of feedomics techniques in cattle nutrition research from the perspective of both nutrigenetics and nutrigenomics aspects and highlight the roles of rumen microbiota in genetics and nutrition. This review provides novel insights into understanding the combined roles of genes and nutrition in cattle production, which will be helpful in developing precise dietary interventions for improved cattle performance in the future.

2. Application of feedomics techniques in the nutrigenetics view

Feedomics plays an important role in revealing the influence and regulation of genetic factors (including DNA coding sequence changes and epigenetics inheritance) on cattle production traits associated

with nutrition. Gene is the basic genetic unit that controls biological traits, detection of genome-wide variations associated with phenotypes helps us to dig out the full potential of bovine genome (Matukumalli et al., 2009). Bovine whole genome sequence was first completed in 2009 (Elsik et al., 2009), ushering in a new era of research into the composition and function of the bovine genetic elements. With the development of techniques like gene identification, gene mapping, single nucleotide polymorphism (SNP) chips, SNP genotyping assays, quantitative trait locus (QTL) identification and genome-wide association studies (GWAS) (Kappes, 1999; Khatkar et al., 2004; Gurgul et al., 2014; Tam et al., 2019), genetic variation loci associated with nutrition-related production traits have been continuously discovered. For example, Bolormaa et al. (2011) used 10K Affymetrix (Santa Clara, CA, USA) and 50K Illumina (San Diego, CA, USA) SNP chips to conduct a GWAS on 3 breeds of cattle (*Bos indicus*, *Bos taurus*, and *B. indicus* × *B. taurus*), and found that 111 SNP were significantly correlated with residual feed intake (RFI). In beef cattle, Abo-Ismael et al. (2013) found that SNP rs41256901 in protease, serine, 2 (*trypsin 2*; *PRSS2*) was associated with feed conversion ratio (FCR) and RFI, the rs42670351 and rs42670352 in the cholecystokinin B receptor (*CCKBR*) were also related to RFI. RFI and FCR are important economic traits (Nkrumah et al., 2004) that highly related to the nutritional process. The discovery of genetic variation loci can provide marker-assisted selection for cattle and lay a certain foundation for breeding. “The 1000 Bull Genomes Project” (<http://www.1000bullgenomes.com/>) was proposed in 2012, as of 2019, the project has collected the full genome sequences of 2,703 individuals, and identified 84 million SNP and 2.5 million small insertions of cattle (Hayes and Daetwyler, 2019), providing an extensive database for the cattle research community to estimate genetic variations in genome prediction and genome-wide association studies. Moreover, the Cattle QTL database (<https://www.animalgenome.org/cgi-bin/QTLdb/BT/index>) accommodated approximately 163 K QTL/associations related to 684 different traits and 183 cattle genes (on expression QTL), including 3,082 QTL related to feed intake and 203 QTL related to feed conversion, which exist on almost all chromosomes. The above 2 databases provide evidence of gene mutation sites and genetic markers related to production traits, and contribute to the targeted selection/breeding strategies regarding improved feed efficiency and precision nutrition.

In addition to the genetic differences caused by the above DNA sequence, epigenetic variations also exist and work for phenotypic changes (Goddard and Whitelaw, 2014), including DNA methylation, post-translational histone modifications, chromatin remodeling and small noncoding RNA regulation (Urrego et al., 2014). The influence of epigenetics on cattle production traits (such as milk production traits, meat production traits, methane emissions, etc.) has been widely studied (Goddard and Whitelaw, 2014; Ibeagha-Awemu and Zhao, 2015; Liu et al., 2015; Thompson et al., 2020), among which methylation is studied most extensively. Taking milk production traits as an example, Dechow and Liu (2018) performed genome wide methylated DNA immunoprecipitation sequencing (MeDIP-seq) on peripheral blood mononuclear cells and found 72 differential methylation regions between high-yielding and non-high-yielding cows, suggesting that epigenetic variation is an entry point for changing milk yield in dairy cows. By using whole-genome bisulfite sequencing and RNA sequencing, Dong et al. (2021) suggested that 3 important methylated genes: dedicator of cytokinesis 1 (*DOCK1*), protein tyrosine kinase 2 (*PTK2*), and phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*) were related to percentages of milk fat, protein, and kappa-casein in dairy cattle. Genome-wide DNA methylation profiles in muscle tissue (Huang et al., 2015) and milk (Del Corvo et al., 2020) have been established, which provide epigenetic clues of cattle targeting specific traits. Other epigenetic components, such as microRNAs,

have also been reported to affect cattle production (Doherty et al., 2014; Ibeagha-Awemu and Zhao, 2015; Thompson et al., 2020), especially for the potential roles in crop by-products utilization and milk protein improvement in dairy cows (Wang et al., 2016).

The use of genomics technology to investigate the mutation sites in gene sequences is promising to identify more accurate and comprehensive genetic factors determining production traits. In addition, epigenetic inheritance should also be considered as important factors affecting non-genomics variations in cattle. Combining both of the 2 aspects will be able to establish the linkage between (epi)genetic markers and performance, thus, accelerating genetic gains for desired production traits. As preferred in the feedomics, using the advantage of nutrigenetics to benefit nutrition related traits, will have a long-term role in selection and breeding of cattle and ensuring their improvement to achieve targeted and precise regulation.

3. Application of feedomics techniques in the nutrigenomics view

In addition to the genetic factors, dietary/nutritional factors can also greatly affect the production traits of cattle. The development of feedomics and related technologies play a vital role in high-throughput exploring nutrition-driven changes of post-genome molecules (such as mRNA, proteins, metabolites, etc.) and revealing the behind mechanism for targeted nutritional interventions.

Post-genomic omics (also called functional genomics) approach is nowadays widely applied in cattle research (Sun et al., 2019). Integrating and analyzing multiple functional genomics data, a new trend in omics development, is more beneficial to systematically reveal nutritional mechanisms (Huang et al., 2017). For example, multi-omics techniques are increasingly being used to reveal the mechanism of how different quality forage affect milk production and quality. By combining RNA sequencing (RNA-Seq) based transcriptomics and isobaric tags for relative and absolute quantitation (iTRAQ) based proteomics, Dai et al. (2017) found that 554 transcripts and 517 proteins were differentially expressed in the mammary glands between cows fed rice straw- and alfalfa hay-based diets. The significantly up-regulated molecules of the rice straw diet were associated with increased protein degradation, decreased protein synthesis and amino acid metabolism, suggesting that the rice straw diet may inhibit milk protein synthesis in the mammary gland. Furthermore, using the same multi-omics method, Dai et al. (2018) reported the differentially expressed genes in the mammary glands of cattle fed with corn stover- and alfalfa hay-based diets and found that both of protein synthesis and energy metabolism pathways were down-regulated in the corn stover group. However, milk synthesis is mediated by different metabolic tissues, mechanism after feed consuming but prior to the mammary gland metabolism are not able to identify in the above studies. Cross tissues multi-omics should also be considered in a systematic view. Sun et al. (2020) combined metabolomics, metagenomics, and transcriptomics to conduct the high-throughput sequencing of the rumen, liver, mammary gland tissues, as well as rumen fluid and blood of cattle fed corn stover- and alfalfa hay-based diets. The results showed that the microbiome had changed at the levels of composition and function, as well as microbial metabolites in the rumen. Down-regulated genes and functions in the liver (Sun et al., 2018) and mammary gland (Sun et al., 2017, 2020) caused the alteration of 3 key metabolic nodes (propionic acid, glucose, and amino acids), thus reducing the yield and quality of milk. In addition, hippuric acid was elevated along with the decrease of milk production in the cattle fed with corn stover (Sun et al., 2016), which could be used as a metabolic biomarker to assess the utilization of low-quality forage in dairy cows. Combining the results of the above

studies, it is not difficult to find that obtaining more comprehensive omics data facilitate in a deeper understanding of nutritional mechanisms. Feedomics provide holistic and systematic insights into investigating a series of post-genomic mechanisms of nutritional questions.

Functional genomics grow fast, this review emphasizes the application of single-cell omics which is highest-resolution technique in omics studies to date. The bulk omics (i.e., transcriptomics) can only provide the global average molecular features of certain tissues, which lack the information of cell heterogeneity (Macosko et al., 2015). The recent development of high-throughput single-cell transcriptomics has allowed us to assess the gene transcriptional features of complex organs/tissues with single-cell resolution, and discover the specific information about cell types/subtypes, cellular functional heterogeneity, cell trajectory (Lin et al., 2021). The complex process of converting plant fibers into milk/meat in cattle is orchestrated by various cell types, and the under-studied cellular composition, metabolic features, and cell–cell interactions prevents the improvement of cattle production. Recent studies of single-cell transcriptomics on cattle are trying to fill this gap. Gao et al. (2021) reported the first rumen single-cell transcriptome analysis of cattle using the 10 × Genomics Chromium. Different from the previous cognition that rumen epithelial cells consist of 4 types (stratum basale, stratum spinosum, stratum granulosum, and stratum corneum) (Graham and Simmons, 2005), 6 different cell types were identified in rumen epithelial tissue of dairy calves in that study (Gao et al., 2021), which may be related to the rumen epithelium's underlying layers, structures, and functions. Furthermore, Wu et al. (2022) conducted the single-cell RNA sequencing of 10 tissues/organs covering rumen, reticulum, omasum, abomasum, ileum, rectum, liver, salivary gland, mammary gland, and peripheral blood of lactating dairy cattle, constructed a single-cell landscape composed of 88,013 single cells and identified 55 major cell types (Wu et al., 2022). In the most comprehensive cattle cell atlas to date, several novel cell types were identified and validated, for example, channel-gap-like spinous cells (cg-like SC) were found in the forestomach tissues; hairy and enhancer of split 1⁺ (HES1⁺) progenitors were discovered in the abomasum. Wu et al. (2022) also studied the role of cells involved in the uptake of short chain fatty acids (SCFA), one of the main findings was T helper type 17 (Th17) cells with highly expressed genes cluster of differentiation 4 (CD4) and interleukin 17A (IL17A) had high potential uptake capacities of SCFA through IL-17 signaling in all 3 forestomach tissues. Single-cell RNA sequencing offers a new granularity of cell composition and their transcriptional dynamics, on this basis, integrating single-cell transcriptomics and other omics data will definitely open the door for new discoveries the molecular mechanism of the nutrition affecting host phenotype. For instance, Xue et al. (2022) used metagenomic binning to determine the fiber digestion and fermentation capabilities of 186 bacterial genomes, and identified specific bacterial genomes which are highly correlated with the biosynthesis of volatile fatty acids (VFA). Meanwhile, by using single-cell transcriptome and systematic investigation of the expression profiles of candidate genes encoding VFA transporters, Xue et al. (2022) showed that insulin like growth factor binding protein 5⁺ (IGFBP5⁺) cg-like SC were uniquely highly expressed in solute carrier family 16 member 1 (SLC16A1) and solute carrier family 4 member 9 (SLC4A9), suggesting that this cell type may play a crucial part in VFA absorption. The integration of these data is more able to link microbial genomes and epithelial single cells to nutritional systems. Currently, only single-cell RNA sequencing were applied in cattle research, other single-cell omics techniques, such as single-cell epigenetics and single-cell proteomics (Stuart and Satija, 2019), should also be highly expected in the future to decipher more accurate nutritional mechanisms.

4. The roles of gastrointestinal microbiota in cattle production through interacting with nutrition and host genetics

Feedomics highlight the important contributions of gastrointestinal (GIT) microbiome to animal production in both genetics and nutrition aspects. For ruminants, GIT (especially for the rumen) microbes can utilize human inedible plant fibers to produce VFA, providing up to 70% of the host's energy requirement (Bergman, 1990). Dietary effects on cattle GIT microbial community structure and function have been widely reported (Henderson et al., 2015; Belanche et al., 2021). In addition, GIT microbes are implicated in host immunity and health (Kim et al., 2017). Thus, the roles of these symbiotic microbes in cattle production and health cannot be ignored. Traditional methods of microbial culture have limited the researchers' understanding and development of microbial resources (Deng et al., 2008; Seshadri et al., 2018). In recent years, with the application of genomics, modern molecular technology, advanced instruments and bioinformatics analysis in microbiology fields, the meta-omics has emerged, which provides us with more comprehensive and accurate information of the composition and functions of GIT microbiota (Jansson and Baker, 2016). It has been shown that some production traits of cattle are associated with specific rumen microbes. For example, methane emissions (Difford et al., 2018; Mizrahi and Jami, 2018), meat quality (Matthews et al., 2019; Scollan et al., 2017), and feed efficiency (Li and Guan, 2017; Lopes et al., 2021), have been reported to be associated with the divergences in the rumen microbial communities. In dairy cows, Xue et al. (2020) found that *Clostridium*, *Succinivibrio*, unclassified Succinivibrionaceae and *Sharpea* were related to milk protein yield. Corn stover-based diet can significantly reduce milk protein contents through altering rumen microbiome, such as *Fibrobacter*, *Succinimonas*, and *Treponema* genera, as well as *Succinimonas amylolytica*, *Treponema succinifaciens* and *Treponema saccharophilum* species when compared with alfalfa hay-based diet (a common practice in the commercial dairy farms) (Sun et al., 2020).

Additional supplied non-fiber carbohydrate contents in the corn stover-based diet increased the populations of *Treponema*, *Ruminobacter*, *Selenomonas*, and *Succinimonas* and amino acid biosynthesis function in rumen microbiota in dairy cattle, thus resulted in better milk production efficiency (Wei et al., 2021). The supplementation of rumen-protected methionine (ruminal insoluble rate: 65%) can significantly increase the relative abundance of *Thermoactinomyces*, *Asteroleplasma*, and *Saccharofermentan* in the rumen, which contributed the higher concentration of the milk functional component α -ketoglutaric acid (Gu et al., 2021). Therefore, it's feasible to improve cattle production traits through conducting nutritional regulated strategies targeting related rumen microbes.

Although the focus of the regulation of GIT microbes are still largely on diet/nutrients, it is undeniable that the regulation mechanism of host genetic factors on GIT microbes will enable far-reaching impacts. Evidences have shown that rumen microbiome is closely related to the cattle genome. Weimer et al. (2010) reported that even when the rumen contents of dairy cattle were artificially exchanged from cattle with completely different rumen microbial compositions, after a period of time (62 d), the rumen microbiome was similar to that before the exchange. Similar results have also been confirmed in more recently studies in dairy cows (Cox et al., 2021) and beef cattle (Zhou et al., 2018), indicating that the rumen bacteria are host specific and the host may have a regulatory role in the rumen microbiome. Using the integration of host genotyping and microbiomics, different heritable rumen microbes and their linked host genetic elements have been reported in recent years (Sasson et al., 2017; Difford et al., 2018; Li et al., 2019; Wallace et al., 2019). For example, Abbas et al. (2020) found that *Prevotella* was related to several loci on cattle chromosomes 2, 6, 9, 19, 23, and 27. Heritable microbes in cattle have also been found to be associated with host traits like energy capture (Sasson et al., 2017), methane emissions (Difford et al., 2018), feed efficiency (Li et al., 2019). More recently, Grieneisen et al. (2021) revealed that almost all gut microbes (97%, including both prevalent and rare

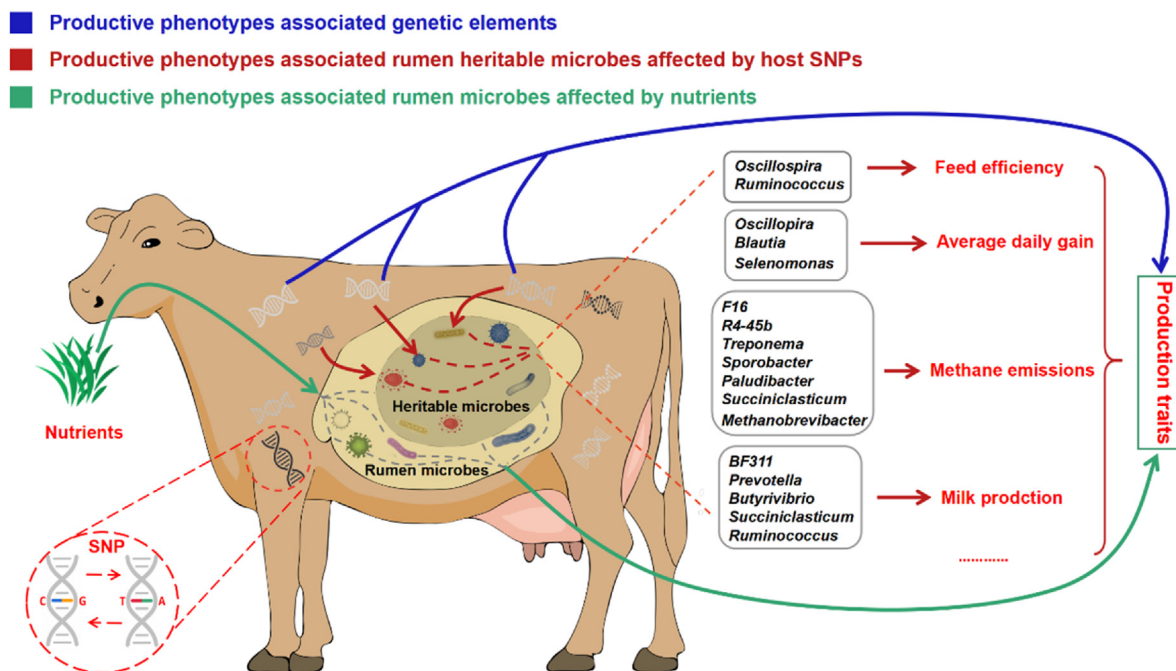


Fig. 1. Three potential pathways to improve cattle production from the feedomics view. SNP = single nucleotide polymorphism. *Prevotella*, *BF311*, *Roseburia faecis*, *Ruminococcus flavefaciens*, *Anaeroplasm*, *Fibrobacter succinogenes*, *Butyrivibrio* (Wallace et al., 2019); *Succiniclasticum*, *Prevotella*, *R. flavefaciens* (Sasson et al., 2017); *BS11*, *Ruminococcus*, *Oscillospira*, *Blautia*, *Selenomonas*, *Streptococcus*, *Anaeroplasm*, *Treponema* (Li et al., 2019); *Paludibacter*, *R4-45b*, *F16*, *Sporobacter*, *Methanobrevibacter* (Difford et al., 2018).

microbial taxa) in baboons are heritable, suggesting that the influence of host genetic factors on GIT microbiota is universal. Therefore, by using genetic selection and breeding methods, we may be able to manipulate the rumen heritable microbiota to obtain desired phenotypes; at the same time, it also provides us with the potential to identify host genetic variation through microbial composition.

In addition to the rumen microbes, hindgut microbes are also controlled by host genetics. Based on a longitudinal study of multibreed cattle, Fan et al. (2021) revealed that host genetic composition explained 52.2%, 40.0%, and 37.3% of core bacterial genera in the preweaning, postweaning, and fattening cattle, respectively and found 9 SNP located in the host metabolism genes were associated with *Roseburia* and *Oscillospira* to control butyrate production and further affect host immunity and growth. “Hologenome” considers the genomes of the host and microbes as a whole (Rosenberg and Zilber-Rosenberg, 2018), which not only helps in better understanding of genetic variations, but also assists in exploring the mode of co-evolution of GIT microbiota and host. Furthermore, the current research on GIT microbes mainly focuses on bacteria and archaea, however, the role of other microbes cannot be ignored, for example, protozoa are involved in methanogenesis (Guyader et al., 2014), virus have a great contribution to microbial horizontal gene transfer as mobile genetic elements (Brown Kav et al., 2020). This suggests that we should also use feedomics techniques for other microbial kingdom to enhance our understanding of GIT microbes and their roles in cattle production.

5. Conclusions

In the past decades, the focus of nutrition research has shifted from physiological effects to molecular mechanisms, resulting in the birth of nutrigenetics and nutrigenomics. The development of high-throughput sequencing and omics techniques has made an indispensable contribution to this field. Feedomics can be thought of as an integration of nutrigenetics and nutrigenomics to reveal the bidirectional mechanisms between genetics and nutrition. Cattle with favorable genetic merit have the premise of good traits, and nutrition as a cofactor promotes the expression of their genetic potential. However, current farm animals are generally intensively farmed and show large variations in production performance, even with similar genetic backgrounds or diets. Therefore, in the future, we should use feedomics to ensure that the cattle herd is genetically similar in nutrient utilization, as well as to choose appropriate feeds on that basis. In addition to the host genetic effects on productive performance, rumen microbes also play a vital role in various physiological activities in cattle, in which the metabolites produced by nutrient decomposition are closely related to cattle production performance. There is increasing evidence that rumen microbes can be controlled to some extent by host genetics. Some of the heritable microbes also show significant contributions to different traits, suggesting that manipulating heritable microbes may be a breakthrough in giving a host the desired phenotype. Finally, three pathways to improve cattle production from the feedomics view are summarized in Fig. 1: 1) SNP (nutrition utilization highly related) - production traits; 2) Nutrients - rumen microbiota - production traits; 3) SNP - rumen heritable microbiota - production traits. It is believed that using feedomics, the combination of genetics and nutrition can be fully investigated to achieve high efficiency and sustainable development in cattle production.

Author contributions

X. Liu: Conceptualization, Writing - Original Draft, Visualization.
Y. Tang: Conceptualization, Visualization. **J. Wu:** Writing - Original

Draft. **J. Liu:** Conceptualization, Writing - Review & Editing, Supervision. **H. Sun:** Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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