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Genome-wise engineering of ruminant nutrition- nutrigenomics: applications, challenges, and future perspectives – a review

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Abstract

Use of genomic information in ruminant production systems can help relieve concerns related to food security and sustainability of production. Nutritional genomics (i.e., Nutrigenomics) is a field of research that is interested in all types of reciprocal interactions between nutrients and genomes of organisms, i.e., variable patterns of gene expression and effect of genetic variations on the nutritional environment. Devising a revolutionizing analytical approach to traditional ruminant nutrition research, the relatively novel area of ruminant nutrigenomics has several studies concerning different aspects of animal production systems. This paper aims to review the current nutrigenomics research in the frame of how nutrition of ruminants can be modified accounting for individual genetic backgrounds and gene/diet relationships behind productivity, quality, efficiency, disease resistance, fertility, and GHG emissions. Furthermore, current challenges facing ruminant nutrigenomics are evaluated and future directions for the novel area are strongly argued by this review.

Key words: nutrigenomics, ruminants, diet-gene interactions, traits, nutrigenetics

Nutrition research in ruminants is traditionally focused on qualifying and quantifying the need for specific nutrients, formulating rations for the production purposes of certain breeds, and investigating effects of specific feeds on animal performance. However, it is widely known

that profound effects of dietary components are not fully understood without having information on its temporary or permanent interactions with the 'blueprint of life', DNA. Nutritional genomics (i.e. Nutrigenomics), is the field of research that is interested in all types of reciprocal interactions between nutrients and genomes of organisms, i.e., variable patterns of gene expression and the effect of genetic variations on the nutritional environment (Mathers, 2017; Müller and Kersten, 2003; Sales et al., 2014). Understanding these specific bilateral interactions between genomes and nutrients will ultimately enable customizing diets for traits to be improved in individuals of populations. With this purpose, the relatively novel scientific area of nutrigenomics makes use of information retrieved from various number of well-defined disciplines that are summarized in Figure 1 (den Hartog and Sijtsma, 2013; Remely et al., 2015).

(Figure 1)

Discovering the underlying molecular mechanisms behind gene-diet interactions will easily enable researchers to manipulate those in the direction of improved productivity, feed efficiency, fertility, and health with the overall aim of highly profitable and sustainable animal production. Emerging from the state of art techniques and technologies, the primary aim of nutrigenomics in ruminants is to formulate feeds that perfectly match the genomic background of animals for the targeted traits to be improved (Ghormade et al., 2011; Asmelash et al., 2018; Nowacka-Woszuk, 2019). Among the scientific disciplines that nutrigenomics utilizes, nutrigenetics provides crucial information of optimal diet for a specific genotype, whereas nutrigenomics discovers the optimal diet within a selection of various diets regarding gene expression patterns of animals (Ghormade et al., 2011). On the other hand, epigenomics is the systematic research area of the identification of epigenetic modifications or the regulation of gene expression of individuals. The interplay between nutrient bio-molecules and epigenetic mechanisms are among the main mediators of diet-genome-phenotype interaction in ruminants (Asmelash et al., 2018; Banerjee et al., 2015; Osorio and Moisa, 2019). For instance, it is

currently accepted that the nutrition of parents widely affects the epigenetic modifications in progeny and therefore the expression of phenotypic characteristics in livestock (Murdoch et al. 2016). Finally, transcriptomics is a well-integrated 'omics' area that comprises most of the research of nutrigenomics regarding ruminants (Osorio et al., 2017; Osorio et al., 2019; Sohel et al., 2020). Additional to the aforementioned three main areas, nutrigenomics also makes use of proteomics and metabolomics to create a total systems biology environment for a better understanding of nutrient-genome-phenotype interactions (Asmelash et al., 2018; Mondal and Ghosh, 2018; Müller and Kersten, 2003; Sales et al., 2014).

However, the lack of a comprehensive review regarding the techniques and technologies behind nutrigenomics, their practical/in-field applications, and nutrigenomics research on traits of interest in ruminants are hampering the uptake of the new approach in ruminant nutrition. Therefore, this paper aims to give an insight into the current nutrigenomics research in the frame of how nutrition of ruminants can be modified, by accounting for animal genetic backgrounds and gene/diet relationships, to improve economically important traits.

Techniques and technologies used for nutrigenomics research

Rapid advances in functional genomic technologies as well as bioinformatics in the past decades have resulted in several tools for studies concerning nutrigenomics in ruminant research. Availability of these novel tools has evolved nutrition research to understand the molecular effects of dietary components comprehensively on economically important traits. Hence, a great potential to increase profitability and sustainability has been achieved for ruminant production systems. Those techniques and technologies cover a great deal of 'how' questions when designing an experimental procedure to respond to common scale problems in ruminant production. Therefore, in this section, we will cover these tools for their specific utility in ruminant nutrigenomics.

To begin, microarray technology is a robust tool that is mainly used for the quantification of differential expression of genes under different circumstances for transcriptomics research, identification of mutations, and high-throughput genotyping for genome-wide single nucleotide polymorphisms for nutrigenetics research. Its efficiency, cost-effectiveness, and robustness help researchers to understand the complex interactions between nutrients, regulatory metabolic processes, and gene functions. A nutrigenomic study is one of the commonly used methods for determining food-related expression patterns and revealing individual nutritional strategies (Masotti et al., 2010).

Although microarray technology provides a large amount of genome- and transcriptome-wise representative data, it has some technical limitations and drawbacks, like its dependence on prior knowledge of reference genomic sequences. Additionally, microarray analysis does not allow the identification of transcripts from repeated sequences as well as de novo mRNA and non-coding RNA discovery. However, in expression studies, a different technology, named RNA-Seq, an approach of next generation sequencing, offers more effective analytical potential in comparison with microarray technology. RNA-Seq is used as a powerful approach for the identification of differential expression in response to specific nutrients and diets, compelling physiological conditions, such as disease, energy restriction, and vitamin and mineral deficiency in an organism. Recovering such an exclusively big data from RNA-Seq analysis provides robust and accurate information for animal nutritionists and eventually allows rations to be modified or personalized in order to improve objective traits of ruminants (Hasan et al., 2019).

Quantitative Polymerase Chain Reaction (i.e., Real-Time PCR/qPCR) is a PCR-based technology that allows the validation of a small set of differentially expressed genes, usually recovered from large microarray or RNA-Seq studies. Lower costs of analysis and robust

detection of subtle differences resulted in researchers using this technology as a gold standard for decades of validation studies.

Regarding nutritional epigenetic/epigenomic studies, there are a wide range of techniques and technologies, which are core technologies still being used, such as PCR, microarray, and NGS, as well as the Mass Spectrometry, that allow researchers to observe genome-wide/local methylation pattern changes, histone re-modifications, and non-coding RNA activities (Zheng, 2015; Turunen et al., 2018). Among these, chromatin immunoprecipitation on microarray chip (ChIP-on-chip) and currently ChIP-Seq, an NGS approach, are widely used for epigenomic studies. Epigenome-wide Association Studies, which are similar to the Genome-wide association studies, are a trending set of techniques allowing researchers to identify non-random associations between a wide range of phenotypic measurements, including nutrition-related responses and genome-wide methylation patterns (Liu et al., 2019). Moreover, nowadays, epigenome editing is possible with a set of robust techniques (Liu et al. 2016; McDonald et al., 2016; Vojta et al., 2016). However, the use of all these technologies and therefore nutritional epigenomic studies are still in its infancy in terms of ruminant research.

Nutrigenomics of growth, productivity, quality, and feed efficiency in ruminants

Studies show that the heritability of growth traits in farm animals is considerable and that effective results can be obtained in nutrigenomic studies (Behrem 2021; Osorio et al., 2017). Nutrigenomics research regarding growth, meat/dairy/fibre productivity, and quality as well as feed efficiency of ruminants has had a number of awe-inspiring discoveries in recent years. These may eventually play a key role for exploiting diet-gene interactions with the aim of efficient production of better quality and healthy food for farmers and consumers.

Dietary modifications in ruminant rations alter gene expression patterns and improve body growth performance and product quality of animals (da Costa et al., 2013; Elolimy et al., 2018; Wang et al., 2016). High silage content in cattle rations was proposed to mitigate

polyunsaturated fatty acid (PUFA) production by decreasing the expression and activity of lipoprotein lipase, fatty acid binding protein 4, and stearoyl CoA desaturase genes (da Costa et al., 2013). Furthermore, addition of vitamin A to the diet of beef cattle in the finishing period was suggested to lead to reduced marbling and adipocyte hypertrophy by changing the expression levels of fatty acid binding protein 5 and Peroxisome Proliferator-activated Receptor (Wang et al. 2016). On the other hand, alpha-amylase is a frequently used supplement in beef cattle feeding to enhance the fermentation of starch. Intensive use of this enzyme adversely affects daily body weight gains and feed efficiency by suppressing the expression levels of genes (PPARGC1A, ABRA, FOXO1) responsible for adipogenesis in muscle tissue and the genes (FAB1, BDH1) responsible for lipid catabolism in liver tissue (Elolimy et al., 2018).

Another nutrigenomic approach used to increase yield and product quality in livestock is to manipulate epigenetic patterns with diet. The muscle growth of cattle showed differential expression of certain miRNA's, an epigenetic control mechanism, between grazing and indoor animals (Horikawa et al. 2015). Accordingly, miR-208b regulating muscle fibre type, is expressed less in the Biceps femoris of grazing cattle compared to those in feedlots. The findings of the study also suggest that indoor animals show lower expression of miR-206, which is specifically recognized as skeletal muscle associated miRNA, whereas the trends were higher in those grazing animals during the adaptation period of grazing. Additionally, regarding the nutrigenetics-epigenomics perspective, variations in DNA-methyltransferases were found to be significantly associated with carcass beef quality (Liu et al., 2015).

Considering milk composition of dairy cows, one of the first nutrigenomic studies was conducted to reveal the effect of dietary conjugated linolenic acid (CLA) treatment on the expression of milk fat synthesis genes (Harvatine and Bauman, 2006). The study suggested that the addition of CLA down-regulates the expression of the mammary tissue SREBF1 gene, leading to the down-regulation of the genes involved in milk fat synthesis, namely lipoprotein

lipase (LPL), fatty acid synthase (FASN), and insulin-induced gene 1 (INSIG1). Another study found that addition of lipids (i.e. rapeseed (RS) and sunflower oil (SO) to the ration of cows substantially changed the fatty acid composition of milk. The study suggested that supplementation of SO with low forage diet regulates genes involving in lipid metabolism, mammary remodelling, and the replication, transcription, and translation processes, as well as epigenetics processes, whereas no differentially expressed genes were observed between RS + high forage diet and high forage diet (Leroux et al., 2016).

Scottish Blackface ewes were studied to measure the extent of growth effects of dietary betaine, folic acid, and methionine deficiency (Sinclair et al., 2007). They observed that 22 months-old male offspring of the ewes with a deficient diet had overall 25% more body fat and a great proportion of un-methylated or hypo-methylated CpG islands in comparison with the control diet offspring. The study also validates the previously suggested epigenetic effects of lack of these substances on the methylation mechanism (Van den Veyver, 2002). Finally, a study on the growth and metabolism of goats showed that transcription levels of PPARG substantially increased the adipose tissue of male goats fed on an enriched diet with linolenic acid. Furthermore research showed a linear upper trend between PPARG and PPARA gene expression in the muscle tissue of male goats fed with flaxseed oil, an α-linolenic acid rich nutrient (Ebrahimi et al., 2013, 2014).

Nutrigenomics of welfare, health, and disease resistance

A great deal of nutrition related diseases in ruminants are known to be partially under the control of a polygenic background and their interactions (Neeha and Kinth, 2013; Osorio and Moisa, 2019; Simopoulos and Milner, 2010). For example, heritability for ketosis and hypocalcaemia in cattle were found to be varying between 0.01 and 0.24 in different studies (Berry et al. 2011; Vosman et al., 2015). Furthermore, it is widely known that diet creates a strong predisposition to many other complex disorders in ruminants (Osorio and Moisa, 2019).

Therefore, nutrigenomic research focusing on animal wellness, health, and disease resistance has a great potential to contribute to the overall profitability and sustainability of ruminant production systems by ameliorating the welfare of animals. Several studies concerning the well-being of animals in the frame of gene-diet interactions have been conducted recently. For instance, transcriptomic research implemented on dietary effects of Selenium supplementation resulted in the profound knowledge of its regulatory effects on the immune system (Elgendy et al., 2016). Discovered differential expression patterns were mainly of the genes involved in immune system-related molecular pathways, such as leukocyte activation, T-cell differentiation, cytokine binding, B-cell, and lymphocyte activation. Further research conducted recently proved the effect of excessive dietary Zn (Zinc) on the expression patterns of sheep (Elgendy et al., 2017). Microarray-based transcriptome profiling suggested that increased Zn in the diet specifically up-regulates genes involving in arrhythmogenic cardiomyopathy as well as T-cell, Toll-like receptor, and the adipocytokine signalling pathways, suggesting potential roles of dietary excessive Zn on both cardiomyopathy and induced immune response. Differently, another study conducted on Shropshire ewes investigated the effects of under-nutrition during late gestation and over-nutrition during the early-postnatal life on Thyroid Hormone axis function (Johnsen et al., 2013). The results of the study suggested that, under-nutrition during the late gestation -fed with 50% less of the energy and protein required- leads to adult hyperthyroidism by increasing the expression of regulatory genes involving in thyroid hormone synthesis as well as de-iodination. In addition, the findings also suggested that early-postnatal over-nutrition raised overall TH levels in juvenile lambs, whereas the effect was reversible with dietary adjustments.

Combining nutritional transcriptomics with epigenomics by using qPCR and ChIP techniques, a study conducted in multiparous Romney ewes led to the discovery of under-nutrition regulatory effects on hypothalamic pathways (Begum et al., 2012). Researchers

identified the epigenetic and transcriptional effects of twinning and under-nutrition on energy balance-regulating pathways of the hypothalamus during gestation. Their conclusion suggested that inadequate nutrition during the peri-conceptional term and twinning might potentially lead to increased tendency for obesity and diabetes (Type II) in progeny, due to their discovered regulatory transcriptional and epigenetic effects on energy balance.

One of the most important terms considering beef cattle production is the adaptation of animals to the transition from forage to concentrated feeds. Regarding this adaptation period, a recent study investigated differential expression patterns of certain genes in the rumen papillae cells of Jersey steers (Novak et al., 2019). Findings of the study suggested that the expression of the ACADSB gene, which is involved in fatty acid metabolism, in steers passing from forage to grain showed a rising trend with the length of adaptation period. Furthermore, expression of the PFKL gene involved in glycolysis, ACAT1 gene in ketogenesis -LDHA in pyruvate/lactate metabolism-, and the AKT3, EGFR, IGFBP5, and IRS1 genes, in tissue growth and development, were found to be affected. The authors concluded that these expression patterns might highlight the pathways of rumen epithelial metabolism adaptation to the dietary changes.

It is currently known that nutrition can be utilized for foetal reprogramming, mainly altering epigenetic patterns, of the future progeny during gestation (Bionaz et al., 2015; Jacometo et al., 2016). Researchers supplementing cows during approximately the last four weeks of gestation with rumen-protected methionine, which is a methyl donor amino acid, discovered that the hepatic expression patterns of metabolically prominent genes such as PCK1, ACOX1, and CPT1A as well as neutrophil genes involved in the innate immune system altered significantly (Jacometo et al., 2016). However, another study focused on the immunometabolic effects of maternal over-nutrition during the last 3 weeks of gestation in Holstein cows (Osorio et al., 2013). Considerable amounts of differential expression were observed for the genes related to immune response. The findings proposed the lingering effects of maternal over-nutrition on

calves before and after colostrum feeding. Therefore, the researchers suggested that it might be beneficial to fortify colostrum with supplements promoting the immunologic capabilities of calves.

Finally, a notably interesting study was conducted by (Golder et al., 2018). These researchers aimed to discover the interactions between certain feed additives, Holstein heifer's genotype, and their enteric microbiome under acidosis challenging conditions. Utilizing genomics, metabolomics, and microbiota characterization, they discovered non-random associations between dietary ingredients, rumen microbiota contents, genotypes of animals, and acidosis manifestation. They suggested several putative quantitative trait loci for the inter-correlations between these key players of the ruminant digestion system.

Improving fertility using Nutrigenomic Research

Reduced reproductive performance and fertility problems have long been a major culling reason for ruminant farmers all around the world. Especially in the dairy industry, the elevated rate of fertility loss is now a major problem compromising longevity of animals and hence the profitability and the sustainability of the businesses. It has long been known that fertility is a complex trait influenced by factors such as stress, hygiene, nutrition, genetic background of the animals, and the interactions between genome and those factors.

Nutrigenomic studies focusing on the reproductive capacity of ruminants are still rare, yet there are a couple of exceptionally illuminating studies conducted recently. For example, an early form of nutrient-genome interaction study was conducted on Booroola Merino sheep suggesting that ewes carrying the FEC^B allele show higher rates of ovulation than non-carriers with an increased amount of starch-based diet for the three weeks preceding ovulation (Landau et al., 1995). Furthermore, another study demonstrated that expression levels of the genes involved in oocyte metabolic activity are significantly affected by reducing the diet of ewes to half of the metabolic maintenance requirements (Pisani et al., 2008). According to the findings,

expression levels of Na^+/K^+ ATPase, SLC2A3, which is involved in glucose transportation, in post-implantation embryonic development (Schmidt et al., 2009), and SLC5A1, involved in sodium/glucose co-transportation, are significantly reduced. Contrarily, the expression of HAS2 in hyaluronan synthase activity, PTGS2 in embryo implantation and positive regulation of the prostaglandin biosynthetic process, and leptin receptors in granulosa cells of the leptin mediated signalling pathway, reproduction, and ovulation (Dupuis et al., 2014), was significantly up-regulated. Finally, a quite recent study conducted by researchers working on regulatory mechanisms of spermatogenesis in Hu sheep, unveiled the effect of vitamin E supplementation on testicular expression patterns leading to improved ram fertility (Qu et al., 2019). In the study, testicular expression patterns were identified via the RNA-Seq approach and it was found that the addition of α-tocopherol considerably increased the amount of germ cells in the epididymis and testes of those lambs with a lower improvement in the maximum receiving group. It was further discovered that the CYP26B1, FSCN3, and NDRG1 genes involved in spermatogenesis are differentially expressed among different vitamin E levels. Furthermore, in the highest receiving group, lower expression of TUBB, different types of collagen, and VIM genes has led researchers to speculate that this might be the main reason behind a lower improvement in this specific group.

Cattle fertility nutrigenomics is mainly focused on the effects of under-nutrition during pre- and postnatal periods, with a few studies on the effects of various diets. In an interesting study, researchers revealed the relationship between pre-partum and post-partum underfeeding and the global gene expression profiles of reproductive system components in multiparous high genetic merit Holstein cows (Valour et al., 2013). Four cows (control group) were fed with 100% of the requirements and the other four with 80% preceding an application of oestrous synchronisation on day 80 post-partum. They observed 283 differentially expressed genes in the oviduct, 3 in the endometrium, and none in the corpus luteum, with the 10K bovine

expression array. However, the researchers discovered correlations among post-partum plasma IGF-1, b-hydroxybutyrate, insulin levels, and the oviduct expression profiles of the genes involved in connective tissue disorders, reproductive system, and metabolic diseases. Among the differentially expressed genes in the endometrium, FABP5 is known to be associated with abnormal functioning of tissue repair mechanisms. Therefore, the researcher's findings can be utilized to explain the effects of under-nutrition on repeat breeding and early embryonic mortality in high yielding post-partum dairy cows.

Positive effects of the long-chain fatty acid supplementation on different parts of the bovine reproductive system were extensively reviewed by (Santos et al. 2008; Leroy et al. 2014). Accordingly, it was found that supplementation of cows with polyunsaturated fatty acid (PUFA) sources, such as fish oil, may suppress endometrial prostaglandin biosynthesis, which in turn prolongs the corpus luteum life span and hence is expected to be highly beneficial for the survival of embryos (Bilby et al., 2006; Thatcher et al., 2006).

It is now widely accepted that some nutrients, feed additives, and dietary restrictions have enhancing or deteriorating effects on the reproductive parameters of ruminants by modifying epigenetic patterns of their genome (Ibeagha-Awemu and Zhao, 2015). It is important to keep in mind that some of these changes are hereditary and will affect trans-generational merit of certain animals and their progeny. For instance, a study conducted on Holstein cows supplemented with two levels of rumen protected methionine (1.89% vs. 2.43% of total metabolizable protein) showed that even a very small change in the diet of cows triggers a trans-generational response in gene expression profiles, associated with the regulation of methylated-DNA patterns (Peñagaricano et al., 2013). Some of the differentially expressed genes in this study were found to be involved in key biological processes, such as immune response and embryonic development. Observations of the authors remarkably proved the importance of

ration protein levels for fertility of cattle as well as its trans-generational legacy on the lifetime of progeny.

(Table 1)

The potential of nutrigenomics for the reduction of greenhouse gas emissions in ruminants

Greenhouse gas (GHG) emissions, as a result of livestock production, are significantly responsible for global warming. Supply chains of ruminants account for approximately 80% of the total livestock emissions with 5.7 Giga tonnes (Opio et al., 2013). Emissions from beef and dairy production represent approximately 44% and 37% of the total ruminant-sourced GHGs, respectively, whereas buffalo and small ruminants account nearly for 11% and 8% of these GHG emissions, respectively. Various effective mitigation strategies have been proposed to date for GHG emissions of livestock production systems (Montes et al., 2013; Kadzere 2018). Nutrigenomics holds a great potential for promising strategies such as increasing feed efficiency, reducing feed intake, utilising an animal's genetic background, rumen microbiota manipulation, and precision feeding strategies regarding an animal's genome to reduce ecological footprints of ruminant production. It is strongly expected that the applications of nutrigenomics will lower GHG emissions, both in terms of CH_4 and N_2O, bring about state of the art opportunities to relieve the effects of ruminant nutrition on global warming, and provide a means for 'climate-smart animal nutrition' (Kadzere, 2018). However, nutrigenomics studies conducted with the aim of unravelling interactions between diet, genome, and ruminant GHG emissions are quite uncommon in the literature. In fact, no study observing the direct effects of diet-genome interactions on GHG phenotypes in ruminants were encountered by our literature

search. However, a few studies indicated the potential of using nutrigenomics indirectly to mitigate the contribution of ruminants to GHGs sourced from livestock production.

A considerable amount of variation in CH_4 emissions of ruminants was suggested to be accounted for by an animal's genetic background (Pinares-Patiño et al. 2013; Lassen and Løvendahl 2016). In many studies, the ruminant genome has been investigated and several putative QTL were found to be associated with CH_4 traits (Pinares-Patiño et al., 2013; Manzanilla-Pech et al., 2016). In a genome-wide association study, five candidate genes were found to be significantly associated with CH_4 production on BTA 4, 13, and 25 in cattle. The pathway analyses of these genes showed that some of them were actively involved in metabolic processes that are responsible for CH_4 production. One of these genes (PKD1) is highly effective on CH_4 production by being involved in the development of the digestion system and nitrogen compound metabolism (Pszczola et al., 2018).

It is well known that not only the animal's genomic background is effective on CH_4 production in ruminants, but also the interaction between diet and the animal's genome (Shi et al. 2014). In a study conducted by van Gastelen et al. (2017), the effect of linseed oil addition to the diet of Holstein cows, which had DGAT1 polymorphism was investigated. The general results of the study suggested that diet, DGAT1 genotypes, and the interaction between diet and DGAT1 genotypes does not affect methane production. However, rather interestingly, linseed oil addition to diet was found to reduce CH_4 emission by interacting with the rumen microbiota and its fermentation capacity (van Gastelen et al., 2017). Nevertheless, no further study was implemented to understand the interaction between microbiota genome and linseed oil supplementation. In ruminants, methane is known to be produced by methanogenic microorganisms residing in the rumen. Therefore, it is affected by the composition of these microorganisms as well as their genetic background, host genome, and the complex interactions among these (den Hartog and Sijtsma, 2013; de Haas et al., 2016). In a study conducted on

sheep, researchers investigated whether microbiota gene expressions were associated with methane production. Meta-transcriptomic data was obtained and 349 differentially expressed genes were examined. Three of the most up-regulated genes, which encode the regulatory enzymes for methane production pathways, were found to be significantly associated with higher methane emissions in sheep (Shi et al. 2014). These genes are known to be encoded for the subunits of methyl coenzyme M reductase (MCR), an enzyme that catalyses the final and rate-limiting step during CH4 biogenesis (Cedervall et al., 2010).

As a result, the emission of CH_4 and N_2O from ruminants are controlled by diet, animal's genetic background, rumen microbiome, and the complex interaction among these factors. Understanding the nature of these interactions is highly important to apply successful mitigation strategies for GHG emissions of ruminants. For this purpose, many more nutrigenomic studies are required in the near future.

Immediate use of the emerging information

All these studies are delicate examples for the implementation of nutrigenomic research and its potential for the field. The shared outcome of all this is the perceptive power of nutrigenomics to revolutionize our approach to nutrient-organism interactions. More specifically, a set of immediate deliverables from research appear to be just around the corner (Mariman, 2006). For instance, using the outcomes of nutrigenomics research, it is now possible to develop a set of novel biological markers to manipulate gene expression via nutrients to improve overall animal performance and potential, such as productivity, welfare, health, fertility etc., as well as to reduce the environmental impact of ruminants. Some of these biomarkers can also be utilised to implement disease-specific nutrient interventions as well as being used as markers for prognosis. Additionally, pathways and discovered genomic regions will be potential candidates for molecular manipulation, which includes genome and epigenome editing, which is aimed at better health, productivity, and welfare for ruminants. Furthermore,

it is currently also possible to develop functional foods for ruminant rations. The above mentioned various nutrigenomics research conceptually suggest that pathogenic levels of gene expression profiles can be adjusted by mixtures of functional nutritional elements. Therefore, in a broad perspective, the destiny of ruminant nutrition research seems to be heavily dependent on the advances in nutrigenomics research. However, to utilize the outcomes of the research more efficiently and precisely, it is of crucial importance to overcome the challenges imposed by the limitations of the scientific area.

Current challenges

Currently, the biggest challenge facing the nutrigenomic revolution is originated from the lack of critical thinking for genome-nutrient interactions in a systems biology perspective. Therefore, tackling the complexity in a more holistic approach is the essential solution for the major challenge. A systems approach broadly requires gathering valuable information from nutrients, animals, and rumen microbiome by considering the integrated research fields in Figure 1, statistically modelling the obtained data with the available phenomics, and finally analysing all the information together via bioinformatics tools for a comprehensive answer to the quests of the research field. Using a systems approach in ruminant nutrigenomics will eventually allow researchers and farmers to "fine-tune" the metabolism of the animals towards better health and fertility as well as higher efficiency and quality of production (Bionaz, 2014; Bionaz et al., 2015). However, such an approach is currently hampered by the burdens and systematic challenges of molecular nutritional research. To our perspective, the three major limitations are the costs of such elaborated studies, technical complexity, including the need for accurately quantifying traits of interest, and the interpretation and application of the research outcomes in ruminant production systems.

Starting with the budget required a systems approach like the above-mentioned would tremendously quickly increase the costs of research to an unaffordable level. Additionally, most of these techniques and technologies involved in nutrigenomics research are already exclusively expensive on their own. For instance, genome-wide methylation pattern mapping will be a major contributor to our current ability of explaining phenotypic variation in ruminant traits (Rolf et al., 2014; Murdoch et al., 2016). However, costs of conducting such analyses (i.e. Epigenome-wide Association Studies) are currently at a high level, which partially hampers their use in ruminants. Nevertheless, considering the extreme drop in the costs of producing high-throughput genomic data during the last two decades (Wetterstrand, 2020), it is quite promising for the future of nutrigenomics research to evolve into a systems approach with a highly affordable level of data generating costs.

At the present, bioinformatics holds a central position for the purposeful integration and interpretation of the various -omics data in statistical modelling. In the era of the big data processing and systems biology approach, the analyses will quickly reach the limitations imposed by computational burden. Therefore, another issue to be focused on while encouraging the systems biology approach is to improve robust statistical models and analysis methods that will lower the computational burden of systems research. Another issue relating to the technical considerations is the evaluation of the current phenotypes and the need for precise, accurately measured, representative, and easy/cheap-to-measure phenotypes. It is long known that the variation in response to the dietary intervention has some noise that is not arising from the intervention itself but from the way of measurement (van Ommen et al., 2008). This problem directly and profoundly affects the utility of the outcomes of such studies. Therefore, success of ruminant nutrigenomics, in the long run, depends on the emerging molecular approaches to better quantify the effects of the nutritional interventions on the traits of interest. Moreover, even though it is an essential component of the ruminant digestion process, the rumen

microbiota is generally overlooked while designing nutrigenomic studies. It is currently known that the rumen microbiome may be responsible for at least part of the interaction between diet and the host genome and therefore for the variation of almost all economically important ruminant traits (Auffret et al., 2017; Schären et al., 2018). Thus, to our belief, the lack of nutrigenomics research modelling interrelations between rumen microbiome, host genome, and dietary interventions is hampering global solutions to the macro-scale questions of the area. An example for such a study conducted on cattle acidosis can be given by (Golder et al., 2018).

Currently, the outcomes of nutrigenomics studies are quite limited in terms of widespread usage in ruminant production systems. Nutrigenomics research offers precise feeding strategies for individuals of certain genomic, transcriptomic, and epigenomic background. However, individual feeding strategies concerning genome-diet interactions are not quite applicable among ruminant farmers due to resource limitations and the lower uptake of technological advancements, such as automation of individual feeding. Nevertheless, globally increased healthcare, fertility, and production costs, farmer awareness towards preventative methodologies, and reduced costs of mass production of technologies (i.e. Moore's Law), brings about a great potential for the widespread utilization of nutrigenomics in ruminant production systems in the near future.

Overall, nutrigenomics research currently has its own burdens/limitations and pitfalls. However, dealing with them is going to bring about an everlasting opportunity for engineering safe and optimal diets that are 'fortified' with nutrigenomics research and therefore matches both to the genome and to production purposes of animals. This will eminently bring returns of increased profitability and sustainability for farmers and advanced welfare for animals.

Conclusions and future perspectives

At the present, there is a consensus that the current techniques and technologies as well as their relevant costs are limiting factors for their widespread usage in the nutrigenomics research of ruminants. However, considering the incredible reduction of costs and the massive increase in technical capability in the past decade provides a more optimistic view in terms of future studies. Therefore, we propose numerous future perspectives for nutrigenomics research to improve health, welfare, productivity, and ecological footprints to ensure sustainability and relieve food security concerns regarding ruminant production systems.

It is well known that one of the focus areas of classical animal nutrition research is to improve the welfare and health of farm animals. Therefore, in our vision, it is of crucial importance to combine immune system parameters, using molecular immunity-related phenotypes with nutrigenomic data in a statistical manner for further research in the studies of ruminants. On the other hand, since almost a decade, researchers of various disciplines have focused widely on a unifying approach in the welfare of human and livestock, namely the "one biology, one health, one medicine" concept (WHO, 2020). Regarding this point of view, our suggestion is to handle nutrigenomic research of ruminants not only in terms of animals but also in terms of the final consumers. Therefore, conducting nutrigenomic research on animals and consumers of their products simultaneously, by designing research accordingly, is highly recommended for further studies. Findings, conclusions, and guidance of this type of unifying research appear to be more comprehensive and fruitful for agricultural and medical field applications. Furthermore, we believe that, advanced nutrigenomic research holds a great potential for personalised nutrition in terms of animals and the consumers regarded from this perspective.

There are already targeted gene knockout studies that have contributed to our understanding of diet-genome interactions in terms of the role of differential expression patterns of certain genes. However, the revolutionary advances in genome-editing techniques have great potential to

deepen the knowledge of diet-genome interactions to the most profound ever level. TALEN's, zinc finger nucleases and especially more recently, the CRISPR-Cas9 method has revolutionized genomic research regarding genome-phenotype interactions (Maeder and Gersbach, 2016). Using these techniques by targeting genes and therefore metabolic pathways can potentially be used for elucidating mechanisms underlying gene-nutrient interactions. Therefore, it is expected, in the near future, to promote the use of genome-editing techniques more involved in nutrigenomics research (Mathers, 2017).

Currently there are selection indices proposed for gene expression divergence between species accounting for differential expression patterns among individuals of different species (Warnefors and Eyre-Walker, 2012). Furthermore, there are studies using gene expression profiles as phenotypes of interest in statistical modelling, to discover and account for differential expression patterns of certain human cell types, reflecting both genetic ancestry and individual environments (Mathers, 2017). Therefore, our suggestion is to improve the mathematical, statistical, and biological background theory behind the estimation of selection indices, also accounting for gene expression profiles and epigenomic patterns. We believe that this methodology will somehow contribute to the problem of "missing heritability" in traits of economic interest and improve the genetic gain per annum in the breeding schemes of ruminants.

Finally, it is of crucial importance to keep nutrigenomics research of ruminants improving in the systems biology track. We are fully aware that costs and expenditures of the systems biology approach is currently at a quite high rate. However, costs of the techniques and technologies relevant to the area are decreasing at an incredible level. A well-known example to that would be the Human Genome Project, in which the partially completed human genome sequence cost 2.7 billion dollars by 2003. However, at the present day, the cost of a whole genome sequence

reduces to less than 1000 dollars per sample (Wetterstrand, 2020). In other words, conducting a systems biology approach, not only in terms of animals but also integrating consumers is expected to be surpassing this novel research field for more valuable, practically applicable, and treasury worth information for animal production systems in the near future.

Conflict of interest

The authors declare no conflict of interest.

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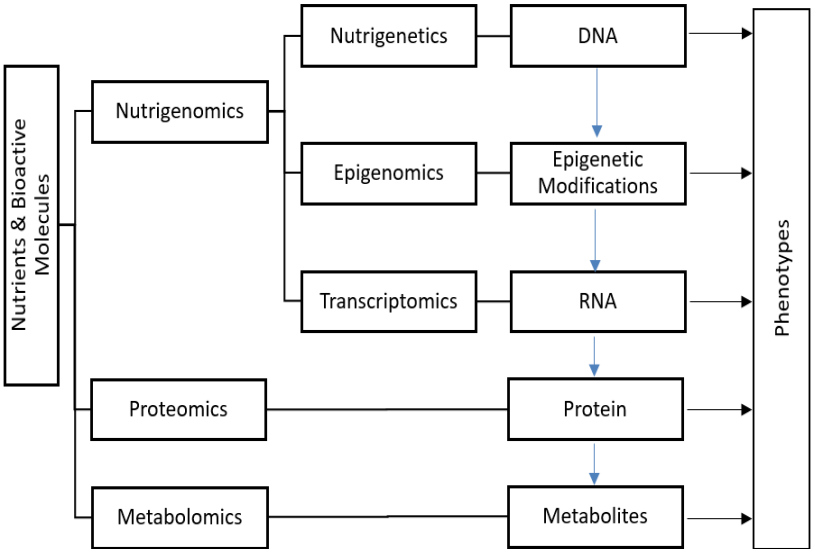


Figure 1. Interactions between nutrigenomics and various other life sciences observing phenotypes

Table 1. Summary of the selected nutrigenomic studies implemented in ruminants

Reference	Nutrient Factor	Effects on gene expression	Biological process	Trait
da Costa et al. (2013)	High silage content	Downregulated *LPL, FABP4* and *SCD*	Reduced PUFA production	Meat quality
Wang et al. (2016)	Vitamin A	Upregulated *FABP5* and *PPAR*s	Reduced marbling and adipocyte hypertrophy	Meat quality
Elolimy et al. (2018)	Alpha-amylase (enzyme)	Downregulated *PPARGC1A, ABRA, FOXO1, FAB1* and *BDH1*	Adipogenesis in skeletal muscle and lipid catabolism in liver	Growth and feed efficiency
Horikawa et al. (2015)	Grazing vs. Feedlot (Beef Cattle)	Downregulated miR-208b and upregulated miR-206 in grazing cattle	Muscle growth	Growth and Meat quality
Harvatine & Bauman (2006)	Conjugated Linoleic Acid (Dairy Cattle)	Downregulated *SREBF1*	Milk fat synthesis	Milk production and quality
Leroux et al. (2016)	Low Forage + Sunflower oil (Dairy Cattle)	49 DEGs involving in lipid metabolism, cell proliferation and differentiation etc.	Changes in fatty acid composition of milk	Milk production and quality
Sinclair et al. (2007)	Betaine, folic acid and methionine deficiency (Sheep)	Globally reduced methylation in CpG islands	Higher body fat of male offspring	Growth and meat quality
Ebrahimi et al. (2013; 2014)	Linoleic Acid (Goats)	Upregulated *PPARG* and *PPARA*	Increased adipose tissue	Growth and meat quality

Elgendy et al. (2016)	Selenium (Sheep)	Upregulated selenoproteins such as *SELENBP1*, *SEPW1*, *GPX3* and *SEPT8*	Leukocyte activation, T-cell differentiation, cytokine binding, B-cell and lymphocyte activation	Health & Welfare
Sohel et al. (2020)	Maternal high-protein diet vs. low-protein diet (Sheep)	Upregulated myogenic genes such as *MYOD1, MYH2* and *MYH1* Downregulated immune system related genes such as *CXCL11*, *HLA-E, CXCL10, CXCL9* and *TLRs*	Myogenesis, the formation and survival of myoblasts, the terminal differentiation of myotubes and activation of proinfammatory chemokines	Growth and Health
Elgendy et al. (2017)	Zinc (Sheep)	45 DEGs involving in signal transduction, zinc ion binding, Notch signalling pathway etc.	Arrhythmogenic cardiomyopathy and induced immune response	Health & Welfare
Novak et al. (2019)	Transition from forage to concentrate feed (Beef Cattle)	Upregulated *ACADSB, AKT3* and *IGFBP5*	Regulated fatty acid metabolism, tissue growth and development	Health & Welfare
Jacometo et al. (2016)	Maternal supplementation of rumen-protected methionine (Cattle)	Upregulated *FBP1, PCK1, SLC2A2, INSR* and *AKT2*	Fetal glycogenesis, glucose uptake and release, insulin signalling	Health & Welfare
Osorio et al. (2013)	Maternal over-nutrition (cattle)	Various DEGs including those downregulated genes such as *TLR4, ALOX5, ALOX5AP, PLA2G4* and IL1R2	Regulation of Immune system	Health & Welfare
Pisani et al. (2008)	Reduce diet (half of the metabolic maintenance requirements) (Sheep)	Downregulated *Na^+/K^+ ATPase, SLC2A3* and *SLC5A1*	Glucose transportation, post-implantation embryonic development and	Fertility

			sodium/glucose co-transportation	
Qu et al. (2019)	Vitamin E (Sheep)	Upregulated *FSCN3* Downregulated *CYP26B1*, *NDRG1, TUBB*, different types of collagen and *VIM* genes	Spermatogenesis and increased the amount of germ cells in epididymis	Fertility

Notes: For the description of the genes, please refer to Gene Ontology with the relevant gene names. PUFA=Polyunsaturated fatty acid, DEGs= Differentially expressed genes.