Chapter

Gene Regulation in Ruminants: A Nutritional Perspective

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Abstract

This chapter will focus on cellular regulatory programs implemented by the ruminant physiology in order to respond to external stimuli such as nutrition as well as important physiological events such as parturition. The increasing adoption of "omics" technologies and bioinformatics in nutrition and physiology in ruminant research have allowed us to delineate a clearer picture on what regulates major biological process at a molecular level such as milk synthesis and meat quality and fatty acid composition as well as pathological conditions such as ketosis, mastitis, and heat stress. The assembly of such plethora of information in a blend among nutritional research, molecular biology, and novel tools to study the response of the genome to nutrition has led to emerging disciplines such as nutritional genomics or "nutrigenomics."

Keywords: nutrigenomics, transcription factors, ruminants

1. Introduction

The increasing adoption of molecular biology techniques and bioinformatics in nutrition and physiology in ruminant research has provided a wealth of knowledge on regulatory mechanisms of major biological processes related to milk synthesis and meat quality and marbling at a cellular level. This body of knowledge has prompted a compelling case for a change in the paradigm in ruminant nutrition, where nutrients in ruminant diets can act as bioactive molecules and exert alterations in molecular mechanisms depending on the animal physiological state. Such alterations can be carried out through gene regulation mechanisms, also known as nutrigenomics. The continuous accumulation of nutrient-gene interactions in ruminant research will eventually lead to practical applications where nutritional interventions may be made in order to improve performance and efficiency in milk yield or skeletal muscle.

1.1 Ruminant model for nutrient-gene interactions

The adoption of advanced molecular technologies in basic nutritional research in ruminants has led to a more robust notion of how nutrients can affect the animal at the cellular level. Then, this body of knowledge has led toward a general notion in ruminant nutrition, where nutrients in the diet can no longer be considered only as: (1) the building blocks for cells, tissue, and organs or (2) energy source for cell metabolism and basic cell function, but rather a new alternative concept for nutrient is that they (3) act as bioactive molecules that can regulate fundamental molecular mechanisms depending on the animal physiological stage.

Because of the inherited gastrointestinal differences between ruminants and monogastrics, the final effect of a nutrient at the molecular level will differ primarily based on how susceptible such a nutrient is to rumen fermentation. Therefore, rumen fermentation and kinetics play an important role in the context of nutrient-gene interaction in ruminants (**Figure 1**). Then, from a nutrigenomic standpoint, a given nutrient in a ruminant diet will likely be fermented or bypass the rumen. If fermented in the rumen, this nutrient will become either part of the microbial biomass or an intermediate metabolite such as volatile fatty acids (VFA) which can be absorbed through the rumen wall and enter the metabolism of ruminants. In the case of nutrients bypassing the rumen, these can be converted to intermediate metabolites [1], produce a signal transduction cascade [2, 3], or directly bind and activate specialized cellular proteins called transcription factors (or nuclear receptors) [4, 5] which are responsible for carrying out the final change in gene expression by binding to specific sections in the DNA upstream of the target gene. Some transcription factors can create a secondary wave of change in gene expression by upregulating the transcription of subsequent transcription factor [6], and previously, it has been proposed that transcription factors may work in an orchestrated fashion creating a network of transcription factors that respond to dietary effects [7]. An alternative effect from intermediate metabolites is the production of DNA or histone modifications by changing the available information in the DNA [8], also known as epigenetic effects. A potential epigenetic mechanism mediated by transcription factors is the increased transcription of noncoding RNAs such as microRNAs [9], which upon transcription these small RNAs will target coding RNA prior to their translation into proteins.

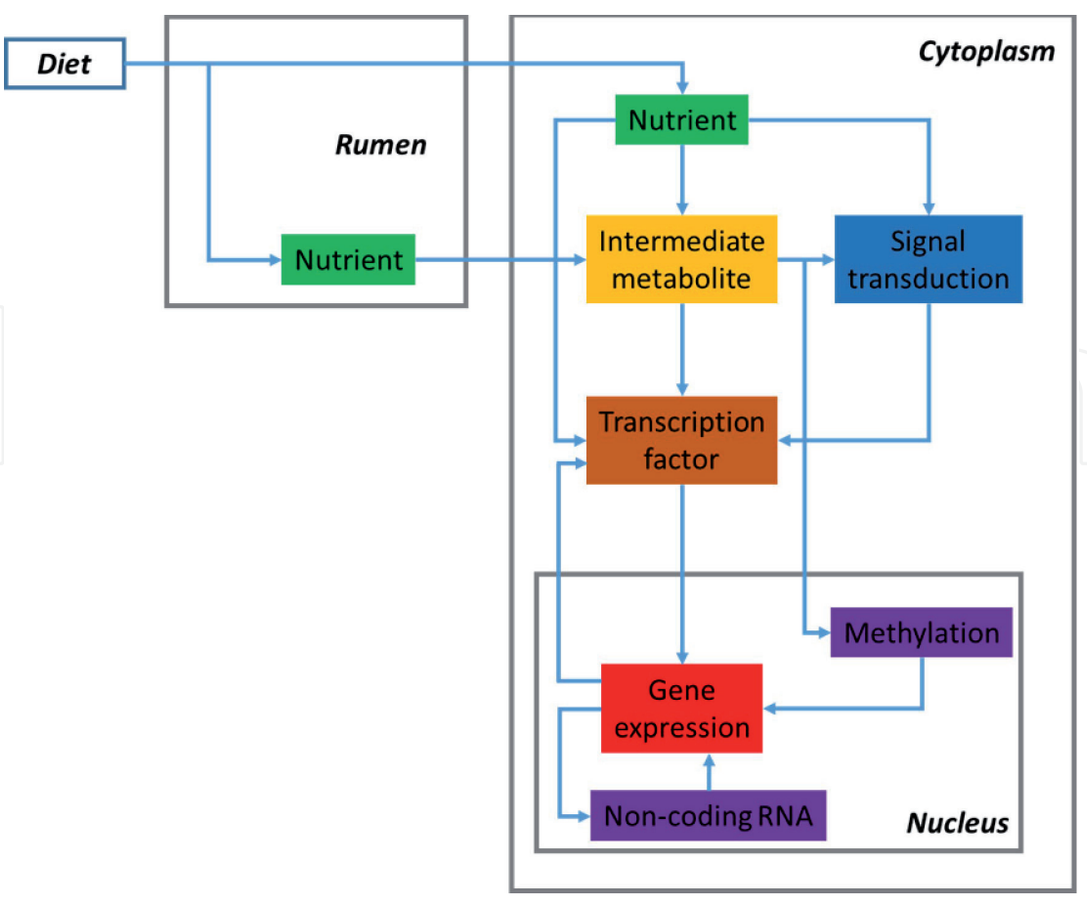

Figure 1.
Proposed ruminant model for gene expression regulation of dietary nutrients through transcription factor activation and epigenetic mechanism (i.e., DNA or histone methylation and noncoding RNA).

1.2 Mediators of nutrient-gene interactions in ruminants

Nutrients and bioactive compounds in regular ruminant diets will mainly interact indirectly with the genome through mediators in the form of specialized molecular proteins such as transcription factors, DNA methyltransferases, histone methyltransferases, among others. Here, we provide a brief overview of the major mediators of nutrient-gene interactions in ruminants known to date. Based on the ruminant model for nutrient-gene interactions (**Figure 1**), the specific transcription factors, enzymes, or cellular mechanisms with *in vivo* or *in vitro* data in ruminants are presented in **Table 1**. Among the known transcription factors with nutrigenomic potential, the peroxisome proliferator-activated receptors (PPARs) have been well studied in ruminants [10]. These transcription factors belong to the ligand-dependent nuclear receptors (LdNR) family [11], and their importance for nutrigenomic interventions in ruminants relies on their ability to bind and be activated by long-chained fatty acids (LCFA) commonly present in ruminant diets. The PPAR isotypes (e.g., α, γ, and δ) play multiple roles across several tissues in mammals, for instance, PPARγ has been observed to regulate adipogenesis and insulin sensitivity [12, 13], while PPARα has a crucial role in hepatic fatty acid catabolism [14]. In contrast to PPARγ and PPARα, PPARδ has been studied to a lesser extent; however, it is known for its role in fatty acid catabolism in skeletal muscle [15] and regulation of glucose uptake [7]. Additionally, Bionaz and collaborators [10] proposed a model for the concomitant and orchestrated regulation of major physiological adaptations by the three isotypes of PPARs in dairy cows going from late pregnancy into lactation. These effects are exerted across several tissues (e.g., liver, skeletal muscle, mammary gland, adipose, immune cells, etc.) where PPARs have a strong effect, and their ability to be activated by dietary fatty acids makes them a strong candidate for nutrigenomic effects in ruminants. The PPARs exert similar effects as observed in dairy cows in other ruminants, for instance, PPARγ has been associated with adipogenic effects in beef, cows [16, 17], and goats [18] as well as fatty acid oxidation by PPARα in transition dairy goats [19].

Similar to the PPARs, the liver X receptor (LXR) belongs to the LdNR family and has a prominent role in controlling cholesterol synthesis [15]. The LXR is known to be activated by oxysterols and derivatives from cholesterol metabolism, and fatty acids [15]. From the two known isoforms of LXR (e.g., α and β), the LXRα presents interesting characteristics including the potential control of sterol regulatory element-binding transcription factor 1 (*SREBF1*) gene expression [20], which is a major transcription factor associated with the regulation of milk fat synthesis [21]. The ability of LXRα to regulate *SRBEF1* expression confers this TF a strong potential to enhance milk fat synthesis in ruminants; however, most of the current data on LXRα activity have been conducted with synthetic agonist [20, 22]. Therefore, a stronger case for the nutrigenomic potential of this TF could be made by future research including its activation by common fatty acids present in ruminant diets.

Retinoids are metabolites derived from vitamin A, and they can regulate gene expression through two classes of receptors: retinoic acid receptors and retinoid X receptors (RXR). The latter can form homodimers and be activated in the presence of the retinoid 9-cis-retinoic acid and consequently activating specific target genes [23]. From the two isoforms (i.e., α and β) of RXR, the RXRα has been the most evaluated in ruminants, primarily because it can form heterodimers with most LdNR including PPAR, LXR, and VDR [24]. Although the latter confers RXRα a tremendous biological significance, there are limited data in ruminants on the potential nutrigenomic effects of vitamin A and derivative retinoids such as 9-cis-retinoic acid through RXRα.

Common name	Protein symbol	Gene symbol	Agonist	Main function	Ruminant[1]	Reference
Transcription factors						
Peroxisome proliferator-activated receptor α	PPARα	*PPARA*	Fatty acids	Fatty acid metabolism, inflammation, and tissue regeneration	B, D, G, and S	[10, 24], [126, 127]
Peroxisome proliferator-activated receptor γ	PPARγ	*PPARG*	Fatty acids	Adipogenesis, insulin sensitivity, and lipogenesis	B, D, G, and S	[10, 16–18, 24], [126]
Peroxisome proliferator-activated receptor β	PPARβ	*PPARD*	Fatty acids	Fatty acid metabolism, tissue regeneration, and glucose uptake in mammary tissue	B, D, G, and S	[10], [127–130]
Liver X receptor α	LXRα	*NR1H3*	Oxysterols/fatty acids	Cholesterol homeostasis, macrophage functions, and inflammation	B, D, and G	[22, 62], [131]
Retinoic X receptor α	RXRα	*RXRA*	9-cis-retinoic acid	Forming heterodimers with other LdNR and neutrophil differentiation	B and D	[132–134]
Sterol regulatory element-binding protein 1	SREBP1	*SREBF1*	N/A	Cholesterol and fatty acid synthesis	B, D, G, and S	[25, 26], [135]
DNA methyltransferases						
DNA methyltransferase 1	DNMT1	*DNMT1*	N/A	Maintenance of methylation patterns	B and D	[72, 105]
DNA methyltransferase 3 α	DNMT3a	*DNMT3A*	N/A	Creates de novo methylation patterns. Present in cytoplasm and nucleus	B and D	[72], [136]
DNA methyltransferase 3 β	DNMT3b	*DNMT3B*	N/A	Creates de novo methylation patterns restricted to nucleus	B and D	[137, 138]
Noncoding RNA						
MicroRNA 33		miR33b		Regulates lipogenesis	D	[30]
MicroRNA 192		miR192		Regulates myogenesis	S	[139]

[1]*Ruminant as B = beef cows, D = dairy cows, G = goats, and S = sheep.*

Table 1.
Important mediators associated with nutrient-gene interactions in ruminants via transcriptional regulatory factors (transcription factors) and epigenetic factors (DNA methyltransferases and noncoding RNAs).

The study of milk fat depression revealed the importance of SREBP1 in milk fat synthesis [25], which resulted in a deep understanding how *t*10,*c*12 CLA, and a milk fat-depressing diet consistently downregulate *SREBF1* in bovine mammary tissue [21]. Consequently, this effect downregulates the expression of genes associated with milk fat synthesis such as fatty acid synthase (*FASN*), lipoprotein lipase (*LPL*), and insulin-induced gene 1 (*INSIG1*) [21]. The importance of this TF for nutrigenomics in ruminants cannot be overstated since this was the first nutrigenomic effect documented. And the importance of this TF in the regulation of fat synthesis has also been observed in beef cattle and translated in marbling and meat quality [26]. A section on this commonality between dairy and beef cattle is dedicated at the end of this chapter.

Epigenetic mechanisms play a significant role as mediators of nutrient-gene interactions in ruminants and the ramifications of these effects in ruminant nutrition and physiology are only beginning to be uncovered, and they add another layer of complexity to our model (**Figure 1**). From a nutrigenomic standpoint, methyl donors present in common diets fed to ruminants such as folate, vitamin B (e.g., 2, 6, 12), choline, and methionine can regulate epigenetic modifications through the one-carbon metabolism where the intermediate s-adenosylmethionine (SAM) is produced and subsequently used as the universal methyl donor for DNA and histone methylations [27]. These effects are carried out through specialized enzymes such as DNA and histone methyltransferases. While the effect of dietary methyl donors on DNA methyltransferases has been evaluated in ruminants, the effect of methyl donors on histone methyltransferases in ruminants remains unknown. Similarly, other histone modifications such as acetylation and phosphorylation have not been investigated within the context of nutrigenomics in ruminants.

Among the various epigenetic mechanisms, noncoding RNA and specifically microRNAs have received a lot of notoriety in recent years [28], and, in contrast, long noncoding RNAs (LncRNAs) are only beginning to be evaluated in ruminants [29]. Examples of microRNAs with a potential application to improving milk and meat quality are the miR33b and miR192 (**Table 1**). The former has been previously associated with lipogenesis in the mammary gland of dairy cows as well as having the greatest upregulation from pregnancy into lactation [30]. In the case of miR192, it has been observed to influence muscle development through myogenesis in sheep. Since the interactions between microRNAs and coding mRNAs are one-to-many, meaning that a single microRNA can regulate the translation of several coding mRNAs, special caution should be applied when interpreting this type of data. The LncRNAs are relatively new in the context of ruminant nutrition and physiology and are commonly characterized by containing >200 nt that are not translated into proteins [31]. This work provided nuances on the role of LncRNAs in the mammary gland in terms of mastitis and milk quality and production.

The importance of understanding these multiple mediators of nutrient-gene interactions cannot be overstated. The authors envision that the continuous accumulation of this wealth of knowledge will lead to accurate and consistent manipulation of the ruminant genome to access or unlock the full genetic potential with the aim to produce ruminant products more efficiently, with a targeted effect on human health, and with a lesser cost for the environment.

2. Gene regulation in dairy cattle

Milk is one of the most nutritious foods known to man, and milk from dairy cattle has been part of the human diet from approximately 9000 years ago [32]. And, currently, the consumption of milk and milk-derived products around the world is expected to

increase, primarily due to an increase in world population and increased consumption in countries where milk has not traditionally been considered popular [33]. Until now, the demand of milk worldwide has been supplied by a large increase in milk yield per cow, which has been a product primarily from the selection and enhancement of management practices, including improved nutrition. However, because of the ever-increasing demand for milk and milk-derived products as stated above, there is a need to continue increasing milk production efficiency.

Milk and milk products are an excellent source of macronutrients such as fat, protein, and carbohydrates, and contain a variety of bioactive molecules associated with health benefits, for instance, conjugated linolenic acid (CLA). The CLA has been associated with reductions in cancer development [25]. Because of its ability to contain bioactive molecules, milk has been considered a functional food. However, our ability to understand and yet manipulate the cow genome through nutrigenomic approaches to enrich specific bioactive molecules in milk is in its infancy. This calls for a continuous development of a wealth of knowledge around the various complex nutrient-gene interactions in dairy cows as well as development of nutritional models that can account for both traditional aspects of ruminant nutrition and more novel molecular regulation of nutrient metabolism.

2.1 Gene regulation and milk biosynthesis

During the lactation, the mammary gland is in charge of the final biosynthesis of milk using preformed elements from other organs (e.g., glucose synthesized in the liver) or compounds synthesized within the mammary epithelial cells (e.g., *de novo* fatty acids). The biosynthesis of milk in the mammary gland is highly regulated for several factors including nutrient supply (e.g., glucose, AA, and fatty acids) and hormones primarily related to hormonal changes during the onset and at the decline of the lactation.

2.1.1 Lactogenesis and the mammary gland transcriptome

Lactogenesis is the hallmark of mammalians, and as such, this biological process conveys a tremendous impact in gene regulation with the objective to induce the mammary gland to lactate and coincides with the formation of colostrum and occurs in coordination with parturition. The strong effects of lactogenesis on the mammary gland at the cellular level have been consistently recorded through transcriptomic analysis (i.e., microarray or RNA sequencing) across several mammals including mouse [34–36], rats [37, 38], bovine [39–41], sheep [42], goat [43], human [44–46], pig [47], kangaroo [48], and seal [49]. The extreme changes in the transcriptome from pregnancy to lactation underscore the importance of such change in the transcriptome in the mammary gland to initiate and maintain milk synthesis. In the case of bovine, a closer look at such transcriptional changes due to the onset and throughout the lactation was reported previously in terms of fat [50] and protein [51] synthesis. During the lactation, the milk fat biosynthesis in the bovine mammary gland had a marked upregulation in the expression of genes associated with FA uptake from blood, intracellular transport/channeling, and key transcription factors associated with lipogenesis (i.e., PPARG and SREBF2) [50]. Then, in terms of milk protein synthesis, it was observed that cell membrane transporters, especially for AA and glucose, played an essential role along with insulin signaling through mTOR for the regulation of protein synthesis in the bovine mammary gland [51]. At a greater scale, the impact of lactogenesis in the mammary gland transcriptome has been associated with epigenetic changes that result in alterations in the DNA structure and consequently the available genetic information

for transcription [39]. Bionaz [39] observed chromatin changes (i.e., euchromatin or active transcribed chromatin and heterochromatin or tightly packed and transcriptionally unavailable chromatin) associated with lactogenesis, where a decrease of euchromatin status was observed as lactation begins and followed by an increase in euchromatin status as milk yield decreases during late lactation. The latter could be associated with natural response to lactation in the mammary gland to inhibit further epigenetic effects during the onset of lactation and to maintain a consistent transcriptome until milk synthesis declines in late lactation.

2.1.2 Milk biosynthesis in the dairy cattle from a nutrigenomic approach

Nutrigenomics is a coined term to refer to the interactions between nutrients and the genome. However, the term nutrigenomics does not refer to the effect of nutrients on the sequence of DNA, but rather the nutrient-gene interactions through the intermediate action of transcription factors (TFs) in the short to medium term and epigenetic factors in the medium to long term. Bioactive compounds with potential nutrigenomic effects can be found in regular diets of dairy cattle, and such compounds can directly or indirectly activate or repress the activity of TF.

Nutrigenomics is a product of the postgenome era and its impact on human, companion animals, and livestock species has gained more attention in recent years [52–55]. In dairy cattle, and overall in ruminants, the field can be considered in its infancy but, as argued by Coffey [56], holds great potential to improve health and productivity.

2.1.3 Transcription factors with nutrigenomic potential in dairy cattle

The TFs are fundamental to the study of nutrigenomics; they can act as intermediaries between dietary nutrients and the final alteration in gene expression. TFs that respond to nutrient effects can be activated directly or indirectly by nutrients, and upon activation, they translocate from the cytoplasm to the nucleus where they alter the transcription of specific target genes. Transcription factors can bind specific short DNA sequences (i.e., 6–12 nucleotides) called response elements located in the enhancer regions upstream of the actual gene sequence [57]. The ability of TF to modulate gene expression upon activation by nutrients confers these proteins a central stage in the field of nutrigenomics. Therefore, accurate identification and characterization of TF responding to specific nutrients and to what extent these TF can be manipulated through dietary effects should be the focus of future research in nutrigenomics in dairy cattle.

Although between 2000 and 3000 TFs with sequence-specific DNA-binding domains in the human genome were estimated, only ~100 have been experimentally verified for their DNA-binding and regulatory functions [58]. The AnimalTFDB website had collected information for almost 1300 TF and almost 400 transcription cofactors for *Bos taurus* [59]. Rather than TF working independently, a regulatory network of TF has been suggested, which is essential to coordinate the response to external stimuli and translate this into changes in gene expression [60].

Among the known TF, the nuclear receptor superfamily of TF, with 48 members in the human genome, is the most important group of nutrient sensors [61]. From this superfamily, a short list of TFs has been identified as ligand-dependent nuclear receptors (LdNR), which can bind and be activated by macro- and micronutrients [55]. Recently, the main LdNR with a potential role in nutrigenomics with an emphasis in large [62] and small [24] ruminants has been reviewed. Among the LdNR associated with macronutrients such as fatty acids are the peroxisome proliferator-activated receptors (PPAR), liver X receptors (LXR), and hepatic

nuclear factor 4 (HNF4) [63]. The LdNR associated with micronutrients are primarily vitamin-specific and include retinoid X receptors (RXR) and retinoic acid receptors (RAR) activated by retinoic acids or metabolites of vitamin A [64], vitamin D receptor (VDR), and pregnane X receptor activated by vitamin E [65].

The PPAR belongs to the LdNR group of TF and requires to form heterodimers with RXR in order to be functional. The main characteristic of PPAR is to have a prominent role in controlling expression of genes involved in lipid metabolism and inflammation. The potential nutrigenomic role of PPAR in ruminants has been reviewed at length previously [10]. This review discussed the role of PPARα in controlling lipid metabolism and inflammation in liver, the potential role of PPARβ/δ in controlling glucose uptake in mammary tissue, and the potential role of PPARγ in controlling milk fat synthesis and mastitis [10]. An interesting feature of PPAR is their capacity for binding and be activated by LCFA in both monogastrics and ruminants [10, 66]. However, in the case of ruminants, data indicate that activation of the PPAR isotypes PPARα and PPARγ is more consistent with saturated LCFA, primarily palmitate and stearate, than unsaturated LCFA [10].

2.1.4 Nutriepigenomics in dairy cattle

Environment factors such as diet and ambient conditions can not only affect the short- and medium-term gene expression, but there is also a medium- to long-term regulation of genes. The latter is primarily carried out through changes in the availability of gene sequences to be transcribed into mRNA. This concept is referred to epigenetics, where "epi" is a Greek-derived term meaning "over" then, epigenetics is commonly referred as "on-top-of genetics." The implications of epigenetics indicate that there could be a set of inherited characteristics, phenotypes, and chemical entities that are superimposed on the DNA and do not follow basic Mendelian laws. Every individual will have a set of epigenetic marks throughout the genome, which is also known as the epigenome.

Epigenetic modifications are carried out through several biological processes including DNA methylation, histone modifications (e.g., methylation and acetylation), noncoding RNA (e.g., micro- and long-RNA). And, when these biological processes respond to nutrients and compounds in the diet, it is associated with nutriepigenomic effects. In ruminants, such effects could serve important physiological adaptations during the onset of lactation including increasing the availability of gene sequences through alterations in DNA methylation for the transcription of essential proteins such as caseins in the mammary gland of dairy cows [67]. This new spinoff of nutrigenomics (i.e., nutriepigenomics) will provide essential information to our understanding of how nutrients can affect the biology of ruminants at a molecular level. However, at the same time, nutriepigenomics will add another layer of complexity to our field, where such interactions have to be fully understood, and in time, manipulated through dietary interventions.

Methylation is a major route for epigenetic modifications, through DNA and histone methylation. Therefore, methyl donors (e.g., choline, methionine, folic acid, etc.) found in the diets of dairy cattle can have a nutriepigenomic effect. These dietary methyl donors will likely increase the synthesis of SAM, which is the major biological methyl donor in the body [68]. The essential role of SAM within the context of the transition cow relies on the multiple biological processes that require this methyl donor, including transsulfuration, polyamine biosynthesis, DNA methylation [69], and histone methylation [70]. Among these, the epigenetic modifications caused by DNA and histone methylation are particularly important in order to understand the potential nutriepigenomic alterations caused by dietary methyl donor (e.g., methionine) supplementation.

DNA methylation occurs through specialized enzymes called DNA methyltransferases, which utilized the methyl group provided by SAM to methylate cytosines within a Cyt-phosphate-Gua (CpG) region ("island") in the DNA and eventually creating methylated CpG patterns in the mammalian genome [71]. In ruminants, supplementation of rumen-protected to dairy cows resulted in a prepartal upregulation of *DNMT3A*, a gene that encodes for a DNA methyltransferase in charge of the de novo methylation of the DNA [72]. And, more recently, the significance of these findings was confirmed by observing alterations due to methionine supplementation in the liver of transition dairy cows in terms of global DNA methylation and specific region methylation of an important TF, the peroxisome proliferator-activated receptor alpha PPARα [8]. The characteristics and uniqueness of this TF within the context of the transition dairy cow were initially presented by Drackley [73], and since then, this nuclear receptor has become an exciting area of research in dairy cattle nutrigenomics (i.e., nutrient-gene interaction) [10]. Therefore, the connection between Met and PPARα upregulation through DNA methylation during the transition period is another suitable mechanism to explain the consistent improvements in performance (e.g., milk yield and DMI) observed in transition dairy cows supplemented with Met [74].

In the cellular nuclei, the DNA is normally packed in condensed structures called chromatins, consisting primarily of histone proteins, which serve as spools where the DNA winds around. Then, the genetic information contained in the DNA exists in two states: unavailable or wind around histone proteins, and available or unwound. Chromatin remodeling is the main mechanism by which DNA is wind or unwound from histones and these dynamic modifications occur by enzymatic modifications including acetylation, phosphorylation, ubiquitination, and methylation [75]. The latter being a potential mechanism through which Met can alter gene expression in dairy cows. Currently, the limited amount of data on histone methylation in dairy cows has been conducted in immune cells [76] primarily related to subclinical mastitis [77]. This work has provided nuances on the interactions between mastitis-related pathogens and histone methylation; however, dietary effects on histone methylation have not been investigated.

3. Gene regulation in beef cattle

3.1 Mutations

In order to understand how changes in a single gene could significantly alter the body structure and physiology of beef cattle, we need to focus in mutations that occur in specific areas in the bovine genome. For example, a 11-nucleotide deletion in the Myostatin gene (MSTN) determines double muscling in Belgian Blue cattle, and a single nucleotide change produces the same effect on Piedmontese cattle [78]. Furthermore, the leptin gene (LEP) presents several single nucleotide polymorphisms (SNP), like AJ236854:c.73 T > C, which induces a cysteine-to-arginine amino acid substitution that could affect protein functionality [79]. The c.73C allele of LEP is associated with higher average daily gain (ADG), lower dressing percentage, and higher marbling scores [79], which are desirable characteristics in a beef carcass. Finally, intramuscular fat deposition could also be affected by a mutation in the fatty acid synthase gene (FASN), contributing to the characteristic fatty acid composition of Japanese Black beef [80]. However, not all mutations have beneficial effects on the productivity of meat-producing animals. There are also mutations that are considered lethal, affecting, for example, the reproductive performance of females through early embryonic loss [81], or mutations that produce genetic

disorders in beef cattle [82]. The Arachnomelia syndrome in Simmental cattle [83] that produce malformations of the skeleton mainly affecting the legs, the spinal column, and the skull is an example of these genetic disorders. These types of inborn errors can be prevented nowadays with techniques like genome editing [83]. Although the implementation of this technique in the animal production industry might generate controversy, it will offer tremendous potential for breeding animals with desirable traits.

Undesired mutations present in the bovine genome are difficult to avoid when they occur. Through the implementation of selection plans and genotyping the herds in order to avoid the reproduction of carrying individuals is the most commonly utilized strategy. Similarly, selection of animals that carry biomarkers in their genomes that will make them improve their meat production and marbling efficiency is the general goal of researchers passionate about beef production. Currently, identification of relevant genetic and genomic markers is ongoing, especially for tenderness—a top priority quality attribute [84].

3.2 Nutrigenomics in beef cattle

In spite of the emergence of new alternatives to beef production (e.g., cultivated meat) in order to meet the growing world population's food demand, researchers in beef production are also focusing on techniques to regulate the bovine genome with a more natural approach (i.e., nutrigenomics). Nutrigenomics study the interactions between nutrients and genes [85], that is how the nutrients present in the diet can affect gene expression. In beef animals, nutrigenomics was widely studied [26]; following, a more detailed description of how specific nutrients regulate the expression of genes related to muscle growth and intramuscular fat deposition will be addressed.

The composition of adipose tissue produced in a meat-producing animal can be "manipulated" by diet, with some variability between breeds. For example, high silage-based diets produce less proportion of the fatty acid 18:2 n-6, with the consequent decrease in the amount of total polyunsaturated fatty acids (PUFA), as compared to low silage-based diets in subcutaneous adipose tissue [86]. This variability in fatty acids composition was attributed to greater activity of fatty acid binding protein 4 (FABP4), lipoprotein lipase (LPL), and stearoyl CoA desaturase (SCD) genes in subcutaneous adipose tissue of animals fed a low silage-based diet [86].

In the same way, we are able to regulate the fatty acid profile composition of a specific fat depot by dietary changes, researchers are trying to prioritize the growth and development of the intramuscular fat that will lead to greater marbling. Intramuscular fat starts to accumulate in the late stages of growth, as compared to other adipose tissue depots that normally develop first (i.e., visceral, intermuscular, and subcutaneous fat). The ultimate goal is to improve marbling scores that will lead to premium prices for the carcasses that classify as prime or choice according to the USDA carcass grading scale [87].

When comparing dairy and beef cattle breeds, subcutaneous fatty acid profile presents several differences in terms of fatty acids profile, probably due to the difference in the degree of fatness, which is always lower for dairy cattle [88]. The important variability in fat composition between breeds could be explained by the variability in relative SCD1 expression in subcutaneous fat [88]. SCD1 seems to have a role in a depot-specific fashion.

3.3 How management decisions can affect gene expression

The combination of early weaning and high dietary starch leads to a strong programming effect in skeletal muscle tissue, with PPARγ and CCAAT

enhancer-binding protein alpha (CEBPA) as the central coordinators of this response. The implementation of early weaning (e.g., 2 months of age) in beef calves provides a different type of diet as compared to a calf weaned normally at 6–7 months of age. Therefore, the early administration of starch in a beef producing animal produces a precocious and sustained activation of the PPARG and its target genes, leading to greater intramuscular fat deposition and consequently more carcasses grading as "Choice" [89].

Castration increases intramuscular fat (IMF) deposition, improving beef quality in cattle. In a transcriptome analysis performed in longissimus muscle (LM) samples, when comparing bulls and steers, castration showed to upregulate transcription of genes for lipogenesis, fatty acid oxidation, and also genes coding for enzymes associated with the tricarboxylic acid cycle and oxidative phosphorylation [90]. Therefore, castration shifts the transcriptome of lipid/energy metabolism to favor intramuscular fat deposition in the LM following castration.

Another beef producer decision that can affect the expression of genes is the selected calving season (i.e., different temperature/humidity index = THI). For example, two groups of pregnant cows that calved during thermoneutral temperature conditions (THI = 67.3) and cows that calved in summer season (THI = 79.9) were bleed during their transition period (i.e., cows between 3 weeks before and 3 weeks after calving) for RNA extraction of white blood cells [91]. Results showed that expression of CASP-3, BCL-2, BAK, P53, and ratio of BAX/BCL-2 in white blood cells increased during summer as compared to thermoneutral conditions, suggesting the susceptibility of these cells to apoptosis or cell death [91]. Consequently, cows calving in two different calving seasons will present differences in their inflammatory response, affecting the maternal recognition of the fetus during early pregnancy [92] or also will have a negative impact in the cow's milking ability postcalving [93].

3.4 Feedlot versus pasture

The beef industry has two main ways to produce beef: pasture-base, and grain-based or feedlot. Consuming energy above requirements helps to increase the intramuscular fat deposition in beef cattle. Feeding high concentration of cereal grains is the way to reach surplus energy that can be utilized in the rumen and the small intestine to produce volatile fatty acids for glucose and energy production. The starch present in the grain is fermented by microbes in the rumen, producing propionate (a glucose precursor), which will be the signal received by the membrane receptors present in the cell activating a cascade of events that will end up with the activation of genes related to the process of adipogenesis. This type of diet is more commonly administered during the so-called finishing or fattening phase.

When the diet is mainly based on the forage available, the rumen population consists of microbes that produce a greater proportion of acetic acid which increases the activation of 5′-prime-AMP-activated protein kinase alpha (AMPK) phosphorylation, reducing the transcriptional activity of the sterol regulatory element-binding protein 1c (SREBP1C) and the carbohydrate responsive element-binding protein (MLXIPL), which decreased the expression of lipogenic genes [94]. In beef cattle finished under a forage-based diet, the fatty acid profile varies considerably as compared to animals finished under feedlot diets. Beef finished under forage-based diets presents greater concentration of polyunsaturated fatty acids (PUFAs), especially the fatty acids with nutraceutical value (20:5 or EPA and 22:6 or DHA). These types of beef products are in the eye of consumers who care about eating healthy foods. These PUFAs mentioned above are upstream regulators of genes related to fatty acid synthesis and transport. FABP4, FASN, and PPARG are particularly activated by these additional PUFAs

generated due to the administration of forage-based diets [95]. Even though we could expect a greater proportion of IMF due to the mentioned additional PUFAs, there is an overall lower fat content in a grass-fed beef product. Furthermore, grass-fed beef is known to have a different flavor and aroma as compared to grain-fed beef when cook on the grill [96].

3.5 Fetal programming in beef cattle

The fetal programming concept is related to the important physiological changes that can occur due to environmental/nutritional events during prenatal development. For example, nutrient restriction of 85% as compared to 140% of total metabolizable energy requirements during the second half of gestation can alter in fetal muscle the expression of both, myogenic and adipogenic genes, without apparent differences in fetal phenotype [97].

The canonical Wnt pathway, a β-catenin-dependent signaling pathway called the Wnt/β-catenin signaling pathway is key in establishing the fate of the undifferentiated stem cells; hence, β-catenin plays an essential role in the regulation of embryonic, postnatal, and oncogenic growth of many tissues. If the β-catenin pathway is blocked, the total number of myocytes will be reduced, and the differentiation of mesenchymal stem cells into mature adipocytes will be potentiated [98]. In the same way, adipogenesis is initiated around mid-gestation in ruminant animals; therefore, a strategic maternal nutritional plan in order to enhance the number of mesenchymal cells committed to adipogenesis will increase the number of intramuscular adipocytes in a process known as hyperplasia; therefore, this outcome will be translated as more marbling in the offspring postnatally. PPARG alone can stimulate adipocyte differentiation [99], although the continuation of this process is regulated by many PPARG target genes [100].

Bioinformatics analysis revealed a pseudoinflammatory process in early-weaned beef calves during their growing phase [101], which it is associated with the activation of the innate immune system presumably due to macrophage infiltration of intramuscular fat [101], which is a typical obesity symptom. These results could be considered as a biological sign of a precocious beginning of the adipogenic metabolic machinery in young beef calves.

3.6 Epigenetics regulations in beef cattle

Changes caused by chromatin (the complex of DNA and histone proteins that forms chromosomes within the nucleus) modification due to environmental factors is called epigenetics [102]. Another epigenetics regulation approach is through microRNAs, which are endogenous noncoding small RNA molecules (20–24 base pairs) that prevent the production of a particular protein by binding to and destroying the messenger RNA that would have produced the protein [103].

Epigenetics regulation is based on chromatin remodeling rather than alteration of the DNA code. With the aim to identify methylated genes affecting bovine growth, an elegant study provides a genome-wide landscape of DNA methylomes and their relationship with mRNA and miRNA for fetal and adult muscle of Chinese Qinchuan beef cattle [104]. Presence of SNPs in epigenetic-related genes was analyzed in different beef breeds. Interestingly, three DNA (cytosine-5)-methyltransferases (DNMTs), DNMT1, DNMT3a, and DNMT3b were found significantly associated with beef quality parameters on the carcass. In particular, DNMT3b presented five SNPs related to carcass traits, becoming a potential candidate gene for beef quality improvement [105].

In the bovine genome, no microRNAs were identified on chromosome Y, while microRNA related to adipose tissue are expressed in chromosome X [106]. This

could be a reason that explains the sexual differences in fat metabolism in mammals. Furthermore, there are highly expressed microRNAs for beef adipose tissue, miR-378 which was found upregulated in steers with high levels of subcutaneous fat [107] and miR-2478 [108] which potentially targets ELOVL fatty acid elongase 6 (ELOVL6) and stearoyl CoA desaturase (SCD), is bovine specific and had higher expression in grass-fed as compared to grain-fed cattle.

A study in bovine skeletal muscle development used next-generation small RNA sequencing, a total of 512 miRNAs were identified [109]. Thirty-six miRNAs were differentially expressed between prenatal and postnatal stages of muscle development including several myomiRs (miR-1, miR-206, and let-7 families). Compared to miRNA expression between different muscle tissues, 14 miRNAs were upregulated and 22 miRNAs were downregulated in the muscle of postnatal stage [109]. Furthermore, a genome-wide landscape of DNA methylomes and their relationship with mRNA and miRNA for bovine fetal and adult muscle recently discovered will provide a solid basis for exploring the epigenetic mechanisms of muscle growth and development [104].

Muscling in cattle influenced by genetic background, ultimately affecting beef yield is of major interest to the beef industry. The best alternative to promote muscle development is through satellite cell proliferation [110]. In fact, myoblast or satellite cells are utilized for the proliferation and differentiation of cultured meat [111]. The transcription factor Sp1, an activator of myosin D (MyoD) and a suppressor of cyclin-dependent kinase inhibitor 1A (CDKN1A), plays an important role in bovine muscle cell proliferation and differentiation. This transcription factor is a target of miR-128 and, if this microRNA is overexpressed, it inhibits muscle satellite cell proliferation and differentiation [112]. Furthermore, miR-1 and miR-206 facilitate bovine skeletal muscle satellite cell myogenic differentiation by restricting the expression of their target genes, and that inhibition of miR-1 and miR-206 increased the paired box 7 (Pax7) and histone deacetylase 4 (HDAC4) protein levels enhancing satellite cell proliferation [113].

In Biceps femoris muscle of Japanese Shorthorn cattle, a grazing period up to 4 months increased the expression of miR-208b, which has a muscle fiber type-associated role. Furthermore, a target for miR-208b, MyoD, a myogenic regulatory factor associated with the shifting of muscle property to the fast type, had lower expression in the grazed cattle after 4 months of grazing, as compared to feedlot cattle. During skeletal muscle adaptation to grazing, miR-206 expression remained higher as compared to housed animals in which it decreases [114]. MiR-206 is known as the skeletal muscle-specific myomiRNA [115].

Offspring's health depends on the maternal body condition at mid-gestation, which will make them be more predisposed to develop obesity at an early age, which in beef production is desirable. Fetal intramuscular adipogenesis was enhanced at mid-gestation due to alteration of microRNA expression; downregulation of let-7g was the main cause for this outcome [116]. This microRNA inhibits the mRNA expression of PPARG and CEBPA, both important regulators of adipogenesis [117]. Furthermore, cow plane of nutrition during the last third of gestation showed epigenetic effects on the offspring's skeletal muscle through the downregulation of miR-34a that has a role on the activation of cell cycle arrest by suppressing SIRT1 expression, which promotes adipocyte differentiation [118].

4. Molecular nutrition in ruminants

The importance of ruminants to the world food security is reflected in their contribution to the demand for animal protein around the world and particularly

in developing countries, and such demand is expected to increase in the future [119]. To face this demand, advancements in ruminant nutrition and physiology will require improvements on feed efficiency and development of novel functional foods from ruminants by enriching specific compounds associated with health benefits in humans. The latter will need a deep understanding and wealth of knowledge of molecular regulatory mechanisms in response to physiological conditions and nutrition. In this context, this vast amount of multilayered data in terms of mRNA, proteins, metabolites, and phenotypes can only be undertaken with powerful tools such as omics technologies and bioinformatics. In fact, these are the foundations of modern system biology, a field of study with the aim to enhance the understanding of complex biological models and interactions occurring within cells and tissues. Understanding this complexity and the outcomes of nutritional interventions and physiological conditions will allow the formulation of novel theories and ideas to enhance feed efficiency, development of new functional foods derived from ruminant products, and reduce carbon footprint.

Even though the outcome is different, there are similarities in dairy and beef cattle from a nutrigenomic perspective. For instance, both the synthesis of milk fat in dairy cows and the synthesis of intramuscular fat in beef steers are regulated by a similar network of TF. Nutrients or stimulus received with the diet (PUFAs, insulin, etc.), activates PPARα in the liver of the dairy cow and PPARγ in the intramuscular preadipocyte of a beef steer. The activated PPARs form a heterodimer with retinoic X receptor alpha (RXRA), leading to the upregulation of their lipogenesis-related target genes (**Figure 2**). Furthermore, in the same way, the activation of the PI3K/Akt/mTOR signaling pathway will lead to the synthesis of milk protein in dairy cows [120], the activation of the same metabolic pathway might lead to muscle hypertrophy in beef cattle, but this is a concept that has not been completely elucidated [121]. It is also worth to mention the importance of fatty acid binding proteins (FABPs) in ruminants, which bind and transport LCFA. FABP4 affects milk yield and milk protein content, both economically important traits in the dairy industry [122], and FABP4 also presents gene polymorphisms that have been associated with meat quality traits in beef cattle [123].

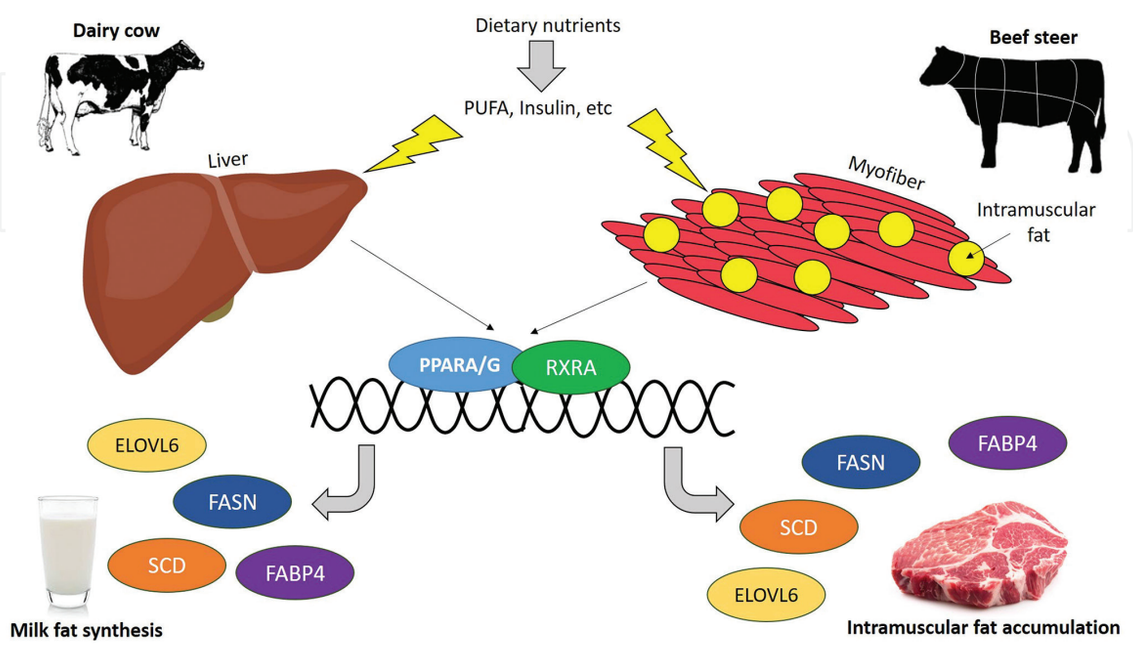

Figure 2.
Example of nutrigenomics linkage between beef and dairy cattle.

In a study aiming to use the fibroblast model to explore differences between a dairy breed (Holstein) and a beef breed (Angus) in their innate responses to LPS exposure, several immune-associated differentially expressed genes between breeds were found [124]. Within them, TLR4, which is the extracellular receptor responsible for recognition of LPS presented higher level of expression in Holstein cows as compared to Angus, suggests the Holstein animals will detect and respond to Gram-negative bacteria more vigorously than Angus animals.

Finally, epigenetic differences between beef and dairy cattle could also be observed mainly because of the different environments the offspring are exposed after birth. While a beef calf usually stays with the dam approximately until 6–7 months old, a dairy calf is separated from its mother as soon as it finishes consuming colostrum or earlier. Although there are studies that started to analyze the epigenetic differences between breeds [124], this is a promising area that needs to be studied in deep.

5. Conclusions

The general nutrigenomic model for ruminants needs to be updated based on emerging nuance information with the ever-growing pace in ruminant nutrition research with "omics" technologies. The dissection of what intermediate components or processes such as intermediate metabolites, signal transduction, TF, etc., are utilized by specific nutrients will allow for accurate predictions of the nutrigenomic outcomes of such nutrients in a practical setting. However, the multilayered and multifactorial nature of the nutrigenomic model will require the implementation of additional tools such as system biology and network theory in order to have a more holistic approach to understand how nutrients regulate milk synthesis or skeletal muscle gain and marbling.

One of the greatest challenges in ruminant nutrigenomics is to account for the final products from rumen fermentation, where several factors such as rate of passage, intake, particle size of the diet can affect rumen fermentation and kinetics. The latter can be avoided by feeding nutrients encapsulated or protected from ruminal degradation; however, this does not eliminate the need to account for the substantial impact the rumen fermentation and its products may have on the overall nutrigenomic effect from a particular diet. Because of this reason, the resurgence of the field of the microbiome in ruminant nutrition research promise to add valuable information on rumen microbes response to nutrients in the diet and correlate this with final nutrigenomic responses at the whole animal level.

Our understanding of the impact of nutrition on regulatory mechanisms at the cellular level in the ruminant animal has grown an accelerated pace over the last decades. As pointed out by Drackley 12 year ago [125], the marriage between "omics" technologies with measurements of tissue metabolism and the final performance (e.g., milk yield and skeletal muscle gain) has been enlightening and essential to identify key responses to nutritional changes and physiology. However, there is still too much to learn in the complex nutrient-gene interactions in the context of the ruminant animal. The future of nutrigenomics in ruminants is to develop technologies and algorithms to predict the final molecular outcomes of nutrients and diets fed to ruminants in a practical setting. This monumental task can only be accomplished by generating a wealth of knowledge in several orders of magnitude of what we currently have on nutrigenomics in ruminants.

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