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Nutrigenomics in livestock: potential role in physiological regulation and practical applications

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ABSTRACT

The relationship among nutrition, health, and productivity of livestock is a continuously changing interaction between environment and physiology. As such, understanding how the physiological system is able to adapt to the type and amount of nutrients consumed is central to our ability to care for and manage livestock. Recognition that cells possess proteins with the ability to 'sense' and trigger a cascade of biological events in response to nutrient availability is at the core of nutritional genomics (or nutrigenomics) as a field of science. Nutrigenomics is generally defined as the study of the genome-wide influence of nutrition. Certain transcriptional regulators can interact with nutrients and cause large-scale alterations in gene expression, metabolic and signaling pathways, and ultimately tissue function. The advent of high-throughput technologies to study an animal's microbiome, genome, transcriptome, proteome, and metabolome (i.e. 'omics' tools) has been instrumental in moving the field of nutrigenomics forward. Available data from studies with livestock species using targeted or untargeted molecular methods underscore the existence of networks of multiple transcriptional regulators at play in controlling nutrigenomics responses. Fatty acids, amino acids, trace nutrients, and level of feed and energy intake have the strongest reported nutrigenomics potential. An important goal for applying nutrigenomics at the animal level is to uncover key molecular players involved in the physiological adaptations to changes in nutrient supply and environmental conditions.

Keywords: cattle, digestion, gene, growth, lactation, microbiota, nutrients, systems biology.

Introduction

The advent of methods to study large-scale molecular adaptations in tissues of livestock in response to specific nutrients, environmental changes, and their interactions has in the past 10 years resulted in a remarkable output of biological information. Reviews as far back as 2005 (Everts *et al.* 2005) on the role of 'functional genomics' as a discrete field of study within the broader animal sciences underscored the value of molecular information in livestock species as a way to better manage growth and production performance of the animal (Cogburn *et al.* 2007; Tuggle *et al.* 2007; Loor 2010). Recognition that metabolic regulation in livestock, as in model organisms (Papin *et al.* 2005), relies partly on transcriptional control of gene networks (i.e. a set or sets of genes controlling specific cellular functions) that are under the control of transcription factor(s) or nuclear receptor(s) led to proposals for broader application of the 'systems biology approach' (Bionaz and Loor 2012; Loor *et al.* 2013, 2015; McNamara 2015). Conceptually, such an approach would allow for integrating information from an animal at the gene (DNA), mRNA, protein, and metabolite level with measures of performance. Thus, from a 'nutrigenomics' standpoint, the systems biology approach is a means to understand better how nutrients (or diet composition, e.g. energy density) can alter phenotypes such as marbling, milk composition, growth rate, and health.

The systems approach to livestock biology research has been dramatically enhanced by the development of 'high-throughput' technologies (also known as 'omics') and the completion and functional annotation of livestock genomes, i.e. 'the process of identifying functional

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elements along the sequence of a genome, thus, giving biological meaning to it' (The FAANG Consortium *et al.* 2015). A central aspect of the systems approach is the use of tools to infer biological meaning from the vast amount of data that can be generated (Huang *et al.* 2009*a*). For example, a number of 'gene enrichment' tools that use biological knowledge accumulated in public databases such as the 'Gene Ontology Resource' (Ashburner *et al.* 2000; The Gene Ontology Consortium 2021) or 'Kyoto Encyclopedia of Genes and Genomes (KEGG)' (Kanehisa *et al.* 2021) have been developed since at least 2000 (Huang *et al.* 2009*a*). Publicly accessible tools such as the 'Database for Annotation, Visualization and Integrated Discovery (DAVID)' (Huang *et al.* 2009*a*, 2009*b*) allow users to upload large gene lists and perform analyses to identify biological themes that are 'enriched' or 'over-represented' within the gene list, and also to visualise genes on the KEGG pathways. Other tools such as STRING (Szklarczyk *et al.* 2021) contain databases of known and predicted protein–protein interactions for a large number of organisms, including livestock (Szklarczyk *et al.* 2021). The user can input a list of proteins and after the tool identifies the proteins, it will display a 'network' encompassing all the mapped proteins and their interconnections. A similar tool for building networks with gene expression data is Ingenuity Pathway Analysis (IPA), which allows users to build causal networks constructed from individual relationships curated from the scientific literature (Krämer *et al.* 2014). International efforts such as the Functional Annotation of ANimal Genomes (FAANG) project have generated foundational data regarding regulatory genomic regions in farmed animal genomes (Clark *et al.* 2020). Although key goals of FAANG in the long-term are to link genotypes, phenotypes, and genetic merit for application in the field, knowledge on the role of specific macro- and micronutrients in contributing to a specific phenotypic outcome is still in its infancy.

The main objective of this short review is to provide a general overview of the recent advances on 'nutrient-sensing' transcriptional networks that affect livestock performance and health. A number of 'nutrient-sensing' proteins exist in cells and have a potential nutrigenomics role (non-exhaustive list in Table 1). Similarly, there has been progress in identifying compounds that can induce a nutrigenomics effect in tissues of livestock (Table 2). Additional nutrient-sensing proteins may yet be identified.

Methods for nutrigenomics

In-depth understanding of the role of a given nutrient, mixtures of nutrients, or even feed additives and diet composition on gene transcription ideally requires the application of 'high-throughput' techniques such as RNA sequencing, often called 'next-generation sequencing' (NGS; Loor *et al.* 2015). Application of genome-enabled NGS also requires use of bioinformatics and proper statistical analysis methods so as to generate meaningful biological data. Because the use of NGS allows for evaluating the entire genome landscape in a given tissue or cell, application of 'omics' generates a holistic view of the overall physiology and molecular adaptations of an organism (Loor *et al.* 2015). Such a view can encompass genes and genome (transcriptomics), proteins and proteome (proteomics) and metabolites and biological pathways (metabolomics). Detailed explanation of these methods, along with some historical background, in the context of livestock are available and will not be discussed in this review (Bionaz *et al.* 2015; Loor *et al.* 2015; Osorio *et al.* 2017). Suffice it to emphasise that transcriptomics allows for exploring changes in the profiles of mRNA, proteomics deals with evaluating changes in protein profiles, and metabolomics allows evaluation of changes in metabolite profiles. As a result, besides their application in nutrigenomics, these approaches are routinely used in studies aimed at understanding complex phenotypes such as feed efficiency, ability for fat or lean deposition, and the role of maternal nutrition on development of the offspring ('programming effect'; Table 2).

Due to complexity and cost, most published nutrigenomics studies have relied on one of these approaches to infer how nutrients, diets, or climate impact the physiology of livestock. There are few published attempts integrating two or more technologies. One study that merits specific mention is that of Jastrebski *et al.* (2017), dealing with the hepatic response at the transcriptome and metabolome to a chronic heat stress challenge. That work underscored changes in cell-cycle regulation, DNA replication, and DNA repair along with immune function. When metabolomics data were integrated, it revealed important biological effects on pathways including glucose, amino acid, and lipid metabolism, along with glutathione production and β-oxidation (Jastrebski *et al.* 2017). Another example of the complementary use of transcriptomics and metabolomics is the study of Shahzad *et al.* (2019) in which these techniques were used to establish biological associations between the prepartal transcriptome/metabolome profiles in the liver and the susceptibility to clinical ketosis postpartum in Holstein cows. Among the most-salient findings, the study uncovered that a lower concentration of glucose-6-phosphate (from metabolomics) and a marked downregulation of fructose-1,6-bisphosphatase 2 and pyruvate dehydrogenase kinase 4 mRNA abundance in the liver 2 weeks prior to parturition were associated with the development of ketosis postpartum. Thus, authors inferred that impaired gluconeogenesis in the liver of cows prior to parturition could increase the risk of developing ketosis after calving. As such, practical approaches that optimise feed intake in the late prepartum period could help reduce the susceptibility to this metabolic disease. Additional examples of published studies in which various omics have been applied are listed in Table 2.

Table 1. Proteins responsive to specific nutrients, dietary manipulations, and intracellular metabolites.

Common name	Symbol	Ligand/activator condition	Main function
Retinoic acid receptor α	RARα	Retinoic acid	Development, differentiation, apoptosis
Retinoic acid receptor β	RARβ	Retinoic acid	Embryonic morphogenesis, cell growth and differentiation
Retinoic acid receptor γ	RARγ	Retinoic acid	Limb bud development, skeletal growth, and matrix homeostasis
Peroxisome proliferator-activated receptor α	PPARα	Fatty acids/polyphenols	Fatty acid metabolism, inflammation, tissue regeneration
Peroxisome proliferator-activated receptor β/δ	PPARβ/δ	Fatty acids/polyphenols	Fatty acid metabolism, tissue regeneration, epidermal proliferation
Peroxisome proliferator-activated receptor γ	PPARγ	Fatty acids/polyphenols	Adipogenesis, insulin sensitivity, lipogenesis
Liver X receptor α	LXRα	Oxysterols/fatty acids (?)	Cholesterol homeostasis, macrophage functions, inflammation
Liver X receptor β	LXRβ	Oxysterols/fatty acids (?)	
Vitamin D receptor	VDR	Vitamin D	Mineral metabolism, immune response
Pregnane X receptor	PXR	Vitamin E	Detoxification
Hepatocyte nuclear factor 4 α	HNF4α	Fatty acids (?)	Development of the liver, kidney, and intestines
Retinoid X receptor α	RXRα	9-*cis*-retinoic acid	Forming heterodimers with other LdNR, differentiation of leukocytes
Retinoid X receptor β	RXRβ	9-*cis*-retinoic acid	Embryonic morphogenesis, cell growth and differentiation
Nuclear factor, erythroid 2 like 2	NFE2L2	Electrophilic ligands, polyphenols	Control of antioxidant response, enhances utilisation of glutathione and metabolism of methionine *via* 1-carbon metabolism
Histone deacetylases	HDAC	Butyrate	Removal of acetyl groups from histone proteins, leads to suppression of gene transcription
Sterol regulatory element binding transcription factor 1	SREBF1	Glucose, carbohydrate	Lipogenesis
Sterol regulatory element binding transcription factor 2	SREBF2	Sterols	Cholesterol synthesis
Nuclear factor kappa B subunit 1	NFKB1	Electrophilic ligands, polyphenols, amino acid deprivation	Regulator of immune, stress, apoptosis, and differentiation responses; activated when one or more amino acids become limiting
CCAAT-enhancer binding protein-α	CEBPA	Amino acids	Cell-cycle regulation; activated when one or more essential amino acids becomes limiting
CCAAT-enhancer binding protein-β	CEBPB	Amino acids	Cell-cycle regulation in hepatocytes; regulation of lipid metabolism; regulation of gluconeogenesis; activated when one or more amino acids become limiting
Serine/threonine-protein kinase	GCN2	Amino acids	Sensor of amino acid deprivation; activated when one or more amino acids become limiting
MLX interacting protein like (carbohydrate-responsive element binding protein)	MLXIPL (ChREBP)	Glucose, carbohydrate	Lipogenesis (adipose)
cAMP response element binding protein 1	CREB1	Glucose, carbohydrate	Gluconeogenesis, lipogenesis (mammary), adipogenesis (adipose)
E2F transcription factor 1	E2F1	Glucose, carbohydrate	Cell cycle regulation; gluconeogenesis, lipogenesis (liver), cholesterol uptake (liver), oxidative metabolism (muscle, brown adipose)

Adapted and modified from Bionaz *et al.* (2015). Regulation of the activity of these proteins occurs mainly at the post-translational level, and in some cases *via* phosphorylation and dephosphorylation of specific amino acid residues on the protein.

Transcriptional regulators and nutrient supply

In livestock, one of the most-studied molecular regulators of transcriptional networks responsive to nutrients are the peroxisome proliferator-activated receptors (PPAR; Bionaz *et al.* 2013, 2015). A comprehensive review of PPAR in ruminants is available (Bionaz *et al.* 2013) and it is also important to highlight that other livestock species such as pigs possess a PPAR (at least in the liver) network that is responsive to changes in nutrient supply, i.e. PPARα target genes are upregulated in response to fasting (Cheon *et al.* 2005). With few exceptions, the three PPAR isotypes, α, β, and γ, are expressed preferentially in a given tissue,

Table 2. Selected examples of published papers reporting the use of various omics techniques to study livestock physiology, including the effect of nutrition.

Animal	Type of analysis	Tissue	Focus	Effect or objectives	Reference
Pig	Transcriptomics Metabolomics	Muscle	Enshi black pigs	Differentially expressed genes and metabolites revealed candidate targets that help explain intramuscular fat content and meat colour	Zhan *et al.* (2022)
Chicken	Transcriptomics	Muscle Abdominal fat	Embryonic stage through Day 180 post-hatch	Network analysis identified gene modules and hub genes associated with important traits such as intramuscular fat content and breast muscle content	Xing *et al.* (2021)
Pig	Metabolomics	Plasma	Duroc pigs	Branched-chain amino acids are associated with high intramuscular fat (IMF) content. Thus, these can be used as biomarkers for IMF content in the loin eye area	Taniguchi *et al.* (2020)
Pig	Transcriptomics	Muscle	Pigs with different residual feed intake	Differentially expressed genes revealed enhanced activity of adaptive immunity and phagocytes in feed-efficient pigs, suggesting more efficient conservation of resources, which can be utilised for other important biological processes	Horodyska *et al.* (2018)
Pig	Proteomics	Muscle	Chinese and western-type pig breeds	More than 250 differentially expressed proteins were detected between breeds. Network analysis indicated that a subset of these proteins was associated with differences in muscle growth and lipid deposition between breeds	Wang *et al.* (2017*b*)
Beef steers	Transcriptomics	Muscle Liver	SNP detection for feed efficiency	Liver and muscle tissue RNA sequencing data from beef steers with low or high residual feed intake measures were used to determine detection power, read depth, and accuracy of SNP calling by comparing three different RNA sequencing pipelines	Lam *et al.* (2020)
Dairy cows	Transcriptomics	Liver	SNP detection for feed efficiency in Holstein and Jersey	Liver tissue RNA sequencing data from lactating Holstein and Jersey cows were used to identify SNP associated with low or high residual feed intake (RFI) within each breed, and also overlapping SNP in the low or high RFI groups that are common across both breeds	Lam *et al.* (2021)
Nutrigenomics and systems biology					
Pig	Transcriptomics	Muscle	Level of dietary lysine (5-week feeding)	Dietary level of lysine can regulate various signaling patwhays associated with protein turnover and lipid metabolism. Excess supply of dietary Lysine can enhance skeletal muscle deposition at the expense of lipid synthesis	Wang *et al.* (2017*a*)
Pig	Transcriptomic	Muscle	Mulberry leaf powder fed at three levels	Feeding 6% mulberry-supplemented diets to finishing pigs led to differential expression of more than 500 genes and was associated with better average daily gain and measures of meat quality	Chen *et al.* (2019)
Sheep	Transcriptomics	Muscle Subcutaneous fat	Level of vitamin E (30-day feeding after weaning)	Supplemental vitamin E increased its concentration in muscle and decreased lipid oxidation of the meat. Those responses were asociated with differential expression of genes, especially in pathways related to lipid biosynthesis, cholesterol, and steroid biosynthesis	González-Calvo *et al.* (2017)
Dairy cow	Transcriptomics Metabolomics Proteomics Enzyme activity	Neonatal liver	Rumen-protected methionine (last 4-weeks prior to birth)	Enhanced post-ruminal supply of methionine in late-pregnancy led to greater calf development *in utero* and, although hepatic DNA methylation was increased, there were distinct alterations in the hepatic transcriptome, metabolome, and proteome profiles at birth	Palombo *et al.* (2021)

(*Continued on next page*)

Table 2. (*Continued*).

Animal	Type of analysis	Tissue	Focus	Effect or objectives	Reference
Developmental programming and nutrigenomics					
Dairy cow	Transcriptomics	Embryo (whole)	Rumen-protected methionine (from calving to 70 days postpartum)	More than 250 genes from a total of ~10 500 identified had differential expression in response to feeding RPM prior to implantation, and the majority were downregulated. A number of the differentially expressed genes are associated with development and immune function. The increased supply of methionine from feeding RPM was suggested to have increased the methylation of DNA, hence, explaining the downregulation of most genes	Peñagaricano *et al.* (2013)
Dairy cow	Transcriptomics	Mammary	Heat stress (no cooling) during a ~45-day dry period	More than 150 differentially expressed genes were detected due to heat stress from lack of cooling in the dry period. These were associated with alterations in ductal branching morphogenesis, inflammation, and cell death	Dado-Senn *et al.* (2018)
Dairy heifer	Transcriptomics DNA methylation Morphology	Mammary	Heat stress (no cooling) during a ~45-day dry period	A number of differentially methylated DNA regions (i.e. CpG sites; regions of DNA where a cytosine (C) nucleotide is followed by a guanine (G) nucleotide) and more than 100 differentially expressed genes were detected in response to heat stress during the dry period. Authors suggested these alterations *in utero* were partly responsible for morphological changes detected in the mammary gland of heifers after birth	Skibiel *et al.* (2018)
Sheep	Transcriptomics Methylomics	Fetal muscle	Corn-based diet (mid-gestation to 1-week before parturition)	Feeding a corn-based versus a hay-based diet led to differential methylation of a discrete number of DNA regions. Those changes were associared with differential gene expression. Data indicated that maternal diet from mid- to late-gestation alters the epigenome and transcriptome of fetal muscle	Namous *et al.* (2018)
Broilers	Transcriptomics	Embryo spleen	Vitamin C injection into fertile eggs at embryonic day 11	There were 141 differentially expressed genes in spleen due to *in ovo* viatmin C injection. Functional analysis *via* bioinformatics indicated that the purine nucleotide metabolism pathway is key for the regulation of spleen development in response to vitamin C	Zhu *et al.* (2021)
Beef calves	Transcriptomics	Neonatal muscle	Supranutritional selenium-yeast supplementation during the first, second, or third trimester of gestation	*Longissimus*sas muscle biopsies harvested at 12–48 h after birth were used to evaluate gene expression. More than 3000 genes were differentially expressed across all treatment comparisons. A total of 237 unique transcriptional regulators were identified and putatively regulate the differentially expressed genes. A number of genes related to muscle development were altered depending on selenium-yeast supplementation trimester	Diniz *et al.* (2021*a*)

e.g. PPARα in liver, PPARβ in muscle, and PPARγ in adipose tissue (Bionaz *et al.* 2013). It is that preferential expression that confers each PPAR a unique biological function, e.g. PPARα coordinates transcriptional regulation of fatty acid oxidation genes in liver, PPARβ controls fatty acid oxidation in muscle, and PPARγ coordinates processes related to lipogenesis both in adipose tissue and mammary gland of ruminants and swine (Bionaz and Loor 2008; Bionaz *et al.* 2013; Moisá *et al.* 2014; Palombo *et al.* 2018; Albuquerque *et al.* 2020).

Since the review of Bionaz *et al.* (2015), published data not only confirmed the potency of 16:0 and 18:0 fatty acids for activating transcriptional networks in ruminant mammary cells controlled by PPARγ, but also provided evidence for the existence of other transcriptional regulators (at least in mammary cells) that are uniquely sensitive to the supply of 16:0 (Vargas-Bello-Pérez *et al.* 2019). Thus, other transcription factors (TF) should be investigated to fully understand the transcriptomic effect of 16:0 on milk fat synthesis or

adipogenesis (Moisá *et al.* 2017; Minuti *et al.* 2020). Such an endeavor could encompass the use of RNA sequencing, which would provide data that could be mined through bioinformatics methods and help generate information regarding putative transcriptional regulators. An example of a bioinformatics analysis focused on gene networks and TF discovery is depicted in Fig. 1. In that study, a systems approach was used to understand changes in the subcutaneous adipose tissue transcriptome in dairy cows fed a typical lower-energy diet or a higher-energy diet

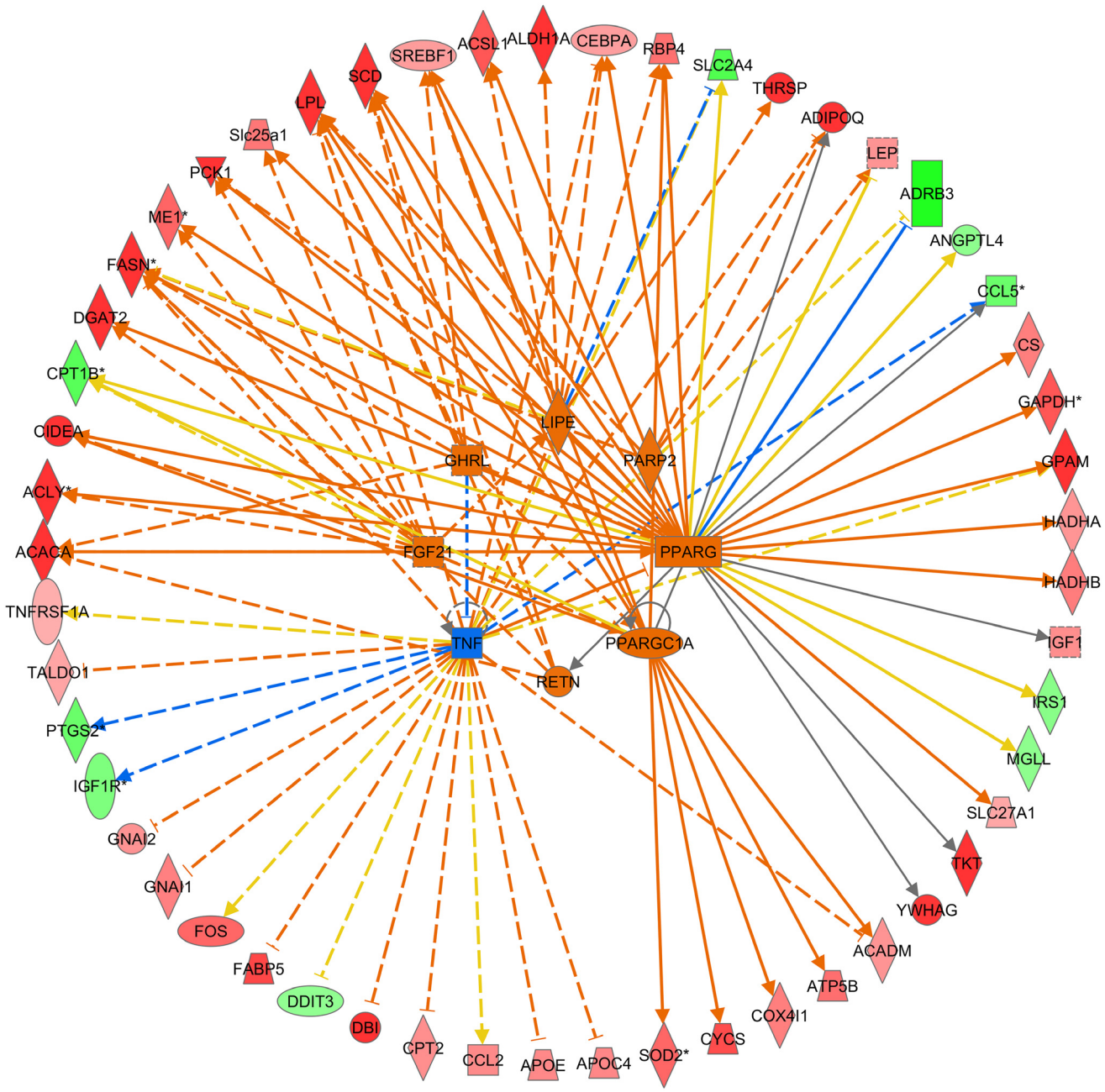

Fig. 1. Network of upregulated genes including transcriptional regulators (FGF21, GHRL, LIPE, PAPR2, PPARG, PPARGC1A, RETN) with the highest predicted impact for controlling differences in subcutaneous adipose-tissue transcriptome profiles in Holstein dairy cows fed a higher-energy versus control-energy diet during a typical 50-day dry period. Adapted from Minuti *et al.* (2020). Analysis depicts data from transcriptomics analysis in biopsy tissue harvested at −14 days relative to parturition. Orange shades denote activation and blue shades inhibition of the upregulators. Red shades denote upregulation, while green shades denote downregulation. Blue and orange dotted lines in arrows denote the predicted inhibition and activation effect respectively, of the upstream regulators on target genes. Network analysis was performed with the commercial software Ingenuity Pathway Analysis (QIAGEN Digital Insights, Hilden, Germany).

during a typical ~50-day dry period (Minuti *et al.* 2020). Transcriptome data and bioinformatics analysis along with plasma and performance data were integrated to develop a systems view of the effect of dietary plane of energy on fat deposition. Besides the fundamental scientific questions under study, the practical relevance of the systems analysis performed is underscored by the fact that dietary energy overfeeding in confinement systems for dairy cows often increases the risk of developing disorders after calving (Drackley and Cardoso 2014).

Another important consideration in the context of long-chain fatty acid supply to the animal is the fact that tissues are actually exposed to mixtures of fatty acids, the amount of which, and profiles, are likely to change in response to physiological state or level of dietary intake. To begin addressing this complexity from a nutrigenomics standpoint, Busato and Bionaz (2021) performed an *in vitro* study with bovine hepatocytes to evaluate the degree of activation of PPARα in response to a wide range of saturated and unsaturated fatty acids, both individually and in combination. Results not only highlighted that 16:0 and 18:0 alone elicit the strongest activation of PPARα, but when 12:0 was combined with each of them, PPARα activation was even greater (Busato and Bionaz 2021). Thus, an exciting outcome was the recognition that some mixtures of long-chain fatty acids display a synergistic effect leading to PPAR activation greater than the sum of their individual effects. Authors speculated that such responses are partly explained by structural dynamics within the PPAR ligand-binding pocket (Busato and Bionaz 2021). The practical context of nutrigenomics studies like this one is underscored by the consistent increases in milk fat yield, without negative effects on ruminal digestion, in dairy cows fed rumen-protected lipid supplements (at ≤3% diet dry matter) with a high 16:0 content (dos Santos Neto *et al.* 2021).

Beyond milk fat synthesis regulation, it is evident that fat depots in livestock also possess a functional PPARγ (example for bovine in Fig. 1), and it has been demonstrated that the transcription network controlled by this transcriptional factor is not only sensitive to nutrition (e.g. high dietary starch; Moisá *et al.* 2014), but also responds to endocrine changes associated with a given physiological state, e.g. the transition from pregnancy (anabolic state) into lactation (catabolic state; Minuti *et al.* 2020). More important from a practical perspective, it is now well known that manipulation of the PPAR network not only alters aspects of lipid metabolism, but can also help control oxidative stress and inflammation (Gessner *et al.* 2017; Hassan *et al.* 2020). An example of such linkages was uncovered by the TF network analysis of Minuti *et al.* (2020) in which activation of PPARγ in adipose prior to calving when a higher-energy diet was fed was negatively associated with an abundance of the proinflammatory cytokine tumor necrosis alpha (TNF) and other immune-related genes (e.g. *PTGS2*, *CCL5*; Fig. 1).

Besides the well known effect of long-chain fatty acids on the PPAR network, other nutrients such as polyphenols (flavonoids) can activate the PPAR network in tissues and antagonise inflammation and oxidative stress by blocking the activation of the proinflammatory TF nuclear factor kappa B (NFKB1; Gessner *et al.* 2017). Dairy cow liver expresses the PPARα and PPARβ isotypes, and the latter is upregulated by inflammatory challenges such as those that occur when circulating concentrations of endotoxin increase (Graugnard *et al.* 2013). It could be possible that PPAR networks in a given tissue play 'dual roles', for example, metabolic and immune. More importantly, the fact that feeding lipids or alternative feedstuffs (e.g. crop residues, agro-industrial byproducts) to livestock have or are becoming important in the management at the farm underscores the potential nutrigenomics effect of diets fed to livestock. Although agro-industrial byproducts such as grape marc and citrus leaves in ruminant diets have received special focus for their potential role in altering methane emissions (Moate *et al.* 2014; Fernández *et al.* 2021), they contain molecules such as polyphenols and essential oils, which could have a nutrigenomics effect at the tissue level.

In addition to long-chain fatty acids, short-chain fatty acids such as butyrate have strong nutrigenomics potential. *In vivo*, using NGS, it was demonstrated that a sustained ruminal infusion of sodium-butyrate (at 10% of expected daily metabolisable energy intake to support lactation) in dry Holstein cows over a 7-day period led to alterations in the abundance of more than 3000 genes relative to baseline (Baldwin *et al.* 2018). Among the most notable changes induced by butyrate were alterations in genes controlled by PPAR, underscoring the broad biological relevance of these nuclear receptors in the coordination of nutrigenomics responses (Bionaz *et al.* 2013). Although most of the published work on volatile fatty acid (VFA) metabolism, and butyrate specifically, has centered on ruminants (calf and mature animal), the continued emphasis on hindgut function as it relates to carbohydrate nutrition in non-ruminant livestock suggests that butyrate availability could have a real effect (Tiwari *et al.* 2019). It is well accepted that, of the major VFA, butyrate elicits the most potent changes at the cellular level, e.g. cell differentiation, proliferation, motility, and induction of cell cycle arrest and apoptosis (Li and Elsasser 2005). Besides a direct effect on gene expression, potentially through a TF, butyrate inhibits the function of histone deacetylases (HDAC), which are active and essential components of transcriptional regulatory complexes (Li and Li 2014).

Transcription-factor networks and nutrigenomics

A large number of transcriptional regulators are likely to be involved in nutrient sensing, and application of various

omics in studies with livestock has shown potential biological associations among transcriptional regulators that can interact with nutrients or intermediate metabolites and, subsequently, trigger a response (Table 2, Fig. 1). For instance, work with bovine mammary cells first provided evidence that PPARγ partly controls abundance of the transcriptional regulator SREBF1 (Kadegowda *et al.* 2009), but the production of natural agonists (i.e. long-chain fatty acids) *via* the SREBF1 pathway (i.e. lipogenesis) can affect the activity of PPARγ, as observed during differentiation of 3T3-L1 adipocytes (Kim *et al.* 1998). Perhaps the most concrete evidence for the high degree of interdependence among various transcriptional regulators arose from work with bovine and goat mammary cells, in which the use of techniques to overexpress or 'silence' these genes was used (Shi *et al.* 2013; Li *et al.* 2014; Cui *et al.* 2015; Zhu *et al.* 2015). It is likely that interactions among TF control biological processes such as milk fat synthesis (Bionaz and Loor 2008), intramuscular adipogenesis (Moisá *et al.* 2014), fat depot deposition (Moisá *et al.* 2017; Minuti *et al.* 2020), and immune cell function (Vieira-Neto *et al.* 2021).

The existence of networks among various TF highlights the complexity that needs to be accounted for in nutrigenomic studies and interventions. The complexity is even more evident when we consider that TF interact not only at the intracellular level, but also at the systemic level where activation of a TF in one tissue can induce the activation or repression of a TF in another tissue (i.e. tissue cross talk) by inducing expression of secreted signaling molecules. One example of this effect is the hepatokine fibroblast growth factor 21 (FGF21), a signaling molecule whose transcription is controlled by PPARα in the liver and after secretion into the circulation can affect adipose tissue metabolism (Eder *et al.* 2021). Adipokines such as adiponectin represent another example of a protein under control of TF (e.g. PPAR), which can affect metabolism in tissues such as the liver (Sauerwein and Häußler 2016). It is now more apparent that TF and target gene networks work in conjunction to alter physiological pathways, not only in the mature animal (Shahzad *et al.* 2014), but also in response to altering the nutrition of the mother during pregnancy (Namous *et al.* 2018; Palombo *et al.* 2021; Table 2).

Despite limitations in terms of availability of livestock-specific data for building networks among TF and target genes in nutrigenomics studies, 'user-friendly' tools such as the commercially available IPA suite are helpful, especially when advanced computational biology approaches are not readily accessible to nutrition researchers. The gene network in Fig. 1 is an example of how IPA can be used to search and build connections between a TF (PPARG, PPARGC1A) and its targets within a list of differentially expressed genes (Minuti *et al.* 2020). Several of these genes have been validated *via* RT-PCR in similar studies with dry/pregnant dairy cows (Ji *et al.* 2012), and together with measures of body mass, fat depot mass, and plasma biomarkers, they highlight an anabolic response in bovine adipose tissue to increased intake of dietary energy that is similar to responses in non-ruminants (Janovick *et al.* 2011; Drackley *et al.* 2014). Although not depicted in the figure, the user also has the flexibility to include molecules such as metabolites (e.g. glucose) or hormones (e.g. insulin) in the network analysis, such that changes in concentrations can be linked with a given set of TF or target genes.

There are also publicly accessible tools that allow identification of TF responsible for the observed changes in gene expression in a given nutrigenomics experiment, e.g. the ChIP-X Enrichment Analysis 3 (ChEA3) transcription-factor enrichment analysis tool (Keenan *et al.* 2019). Its use in a recent nutrigenomics experiment dealing with RNA sequencing data from liver of neonatal calves born to cows fed normal or greater amounts of methionine (a methyl donor) during the last 30 days of pregnancy led to identification of 72 TF that had statistically significant associations with 568 differentially expressed genes (Palombo *et al.* 2021). Among the TF identified were some with known nutrigenomic potential (Table 1), e.g. PPARγ, hepatocyte nuclear factor 4 α (HNF4A), or some that are responsive to changes in endocrine signals such as circulating insulin (forkhead box O1, FOXO1; E2F transcription factor 1, E2F1) and glucagon (cAMP responsive element binding protein 1, CREB1).

Clearly, generating molecular networks provides novel targets for hypothesis-driven experiments that can help better understand how nutrition of the animal may be used to achieve a given phenotype, such as e.g. alterations in marbling or milk fat composition. The application of algorithms that allow for building co-expression networks among differentially expressed genes based on correlations and information theory (e.g. PCIT) (Reverter and Chan 2008) also has allowed for identifying significant gene-to-gene associations within a tissue and among tissues. This approach has been used to study regulatory mechanisms controlling phenotypes that can be affected by nutrition, such as marbling (Cesar *et al.* 2015, 2018) or the mineral content of meat (Afonso *et al.* 2020). Besides ChEA3, identification of biologically relevant TF and target-gene networks can be conducted through implementation of regulatory impact factor (RIF) algorithms (Reverter *et al.* 2010). The metrics generated from the RIF analysis provide information on TF connected to target genes, and also help identify those TF with the potential to predict target-gene abundance (Reverter *et al.* 2010; Pérez-Montarelo *et al.* 2012). This approach was used recently in bovine fetal tissues (cerebrum, liver, and muscle) from beef cows underfed or fed to meet estimated dietary energy requirements from breeding to Day 50 of gestation (Diniz *et al.* 2021*b*). The greatest changes in target-gene and TF expression (e.g. *PPARA*, *SREBF2*; Table 2) due to underfeeding were detected in the liver (2319 unique differentially co-expressed gene pairs; Diniz *et al.* 2021*b*), an organ with a central role in fetal

metabolism (Battaglia and Meschia 1978). Analyses also identified TF that repress gene transcription in muscle tissue along with an over-representation of co-expressed genes in nutrient-signaling pathways such as the one encompassed by PI3K-AKT-mTOR. Some TF that function as transcriptional repressors were negatively correlated with genes in these nutrient-signaling pathways, suggesting that underfeeding led to an overall repression in muscle formation and differentiation (Diniz *et al.* 2021*b*). These data provided mechanistic information to explain the reduction in the number of muscle fibres and muscle mass in beef calves exposed *in utero* to underfeeding between mid- and late gestation (Paradis *et al.* 2017).

Developmental programming and nutrigenomics

A growing body of research is underscoring how specific nutrients (e.g. 'methyl donors'), nutritional management (e.g. dietary energy density), or environmental temperature (e.g. heat stress) at various stages of pregnancy can lead to alterations in cellular 'epigenetics' in the offspring of livestock (Elolimy *et al.* 2019; Caton *et al.* 2020; Dunislawska *et al.* 2022; Reynolds *et al.* 2022). Epigenetics is a key biological mechanism underlying the phenomenon of 'developmental programming' or 'fetal programming', a concept based on the idea that maternal stress, e.g. over- or under-nutrition, during critical developmental windows of the animal can have short- and long-term, positive or negative consequences for the offspring (Caton *et al.* 2020). Because the regulation of normal growth, development, and nutrient utilisation in mammals are programmed *in utero* and affect the postnatal physiology of the animal, perturbations of the maternal environment during gestation can affect fetal growth and development through epigenetic modifications (Tiffon 2018; Caton *et al.* 2020). In the case of poultry, because the embryo develops outside the mother factors such as incubation temperature, humidity, light, and *in ovo* treatments such as specific nutrients can affect normal development before hatching (Saeed *et al.* 2019; Dunislawska *et al.* 2022).

Epigenetics, the control of transcription through various chemical compounds added to the DNA or histone proteins, results in various 'epigenomic marks' that change the spatial conformation of chromatin (Tiffon 2018). As such, these marks can lead to compacting or opening of the chromatin complex and either prevent or allow TF binding to the DNA. Examples of epigenetic modifications include the following: DNA methylation, addition of methyl groups to cytosine on DNA, resulting in decreased transcription; and histone acetylation, addition of acetyl groups to lysine residues on histones resulting in increased transcription; and non-coding RNA, functional RNA molecules not translated into protein that modulate chromatin structure and function (Tiffon 2018). Work with ruminants and poultry in the past 10 years has confirmed the role of nutrition or other environmental factors (e.g. heat stress) on developmental programming of tissues such as brain, skeletal muscle, adipose, and the mammary gland, with pronounced consequences for the offspring (Table 2). With the increased pressure to develop efficient and sustainable approaches to raise livestock as a consequence of the expected increase in population growth worldwide (Caton *et al.* 2020), a greater focus on the role of nutrition and climate change before birth on efficiency of nutrient use by the offspring could prove critical.

Perspectives

As new technologies for high-throughput data generation become more affordable and user-friendly, 'open-source' statistical and bioinformatics tools are developed [Bioconductor suite; (Gentleman *et al.* 2004; Huber *et al.* 2015)], a growing number of animal scientists (especially younger generations) will undoubtedly embrace the systems approach; whether it is to address a nutrigenomics goal or to gather fundamental information regarding the physiology of the animal. Although genotype-to-phenotype research will continue to be important as we move towards greater understanding of functional elements in the genome of livestock species (Harrison *et al.* 2021), as those efforts continue to generate information, it will become more important to increase our understanding of the potential effects of management (e.g. nutrition, feed availability) and climate change on the phenome. Such a task, clearly, will be challenging; however, available data suggest that the nutrigenomics effects of dietary compounds are real and could, in the long-term, help fine-tune dietary requirements (under different environmental conditions) to optimise production and health of livestock.

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