Nutrigenomics in livestock sector and its human-animal interface-a review

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ABSTRACT

Noncommunicable diseases such as cardiovascular disease, obesity, diabetes, and cancer now outnumber all other health ailments in humans globally due to abrupt changes in lifestyle following the industrial revolution. The industrial revolution has also intensified livestock farming, resulting in an increased demand for productivity and stressed animals. The livestock industry faces significant challenges from a projected sharp increase in global food and high animal protein demand. Nutrition genomics holds great promise for the future as its advances have opened up a whole new world of disease understanding and prevention. Nutrigenomics is the study of the interactions between genes and diet. It investigates molecular relationships between nutrients and genes to identify how even minor modifications could potentially alter animal and human health/performance by using techniques like proteomics, transcriptomics, metabolomics, and lipidomics. Dietary modifications mostly studied in livestock focus mainly on health and production traits through protein, fat, mineral, and vitamin supplementation changes. Nutrigenomics meticulously selects nutrients for fine-tuning the expression of genes that match animal/human genotypes for better health, productivity, and the environment. As a step forward, nutrigenomics integrates nutrition, molecular biology, genomics, bioinformatics, molecular medicine, and epidemiology to better understand the role of food as an epigenetic factor in the occurrence of these diseases. This review aims to provide a comprehensive overview of the fundamental concepts, latest advances, and studies in the field of nutrigenomics, emphasizing the interaction of diet with gene expression, and how it relates to human and animal health along with its human-animal interface.

1. Introduction

The production of an adequate amount of nutritious animal protein for the world’s growing population is a challenge faced globally. By 2050, the world’s population is expected to reach 9.4 billion (Fukase & Martin, 2020; Molotoks et al., 2021), and the global food supply will also increase at an annual rate of 2.3% to meet the growing demand of the increasing population (Tian et al., 2021). Animal protein makes up an essential part of the human diet globally, but its demand, especially in developed countries, is expected to increase by many folds with the increase in the GDP of these countries (Sun & Guan, 2018). An 11% increase in the global population is expected to support a 14% increase in global meat consumption by 2030 (Aduli et al., 2022). Furthermore, the livestock industry has been using antibiotics indiscriminately to increase production, which has led to the emergence of antimicrobial-resistant bacteria and the spread of antimicrobial resistance genes, a global health concern (Kimura et al., 2022). Therefore, the only logical way out appears by increasing per unit plant and animal productivity, which will allow us to meet the growing nutrient demand of our population (Barros-Rodríguez et al., 2021).

Nutrigenomics is a short-term assessment of genome activity in response to dietary changes, while nutrigenetics is the study of...
microarray (transcriptomics), proteomics, metabolomics, and epigenomics (Fig. 1) (Pal, 2022).

However, this requires introducing modern production technology to improve animal husbandry, such as precision animal husbandry using molecular methods (Hasan, Feugang & Liao, 2019). As we all know, the animal kingdom is a sequence of gene expression pathways. Nutrition is the driving force behind these processes, including the fact that they are genetic. Therefore, animal nutrition study aims to thoroughly comprehend how nutrients influence animals' genetic programming throughout their lifetimes (Wu, 2022). Nutrigenomics (molecular animal nutrition) is a relatively recent topic that deals with animal nutrition on a molecular level (Pal, 2022). The goal is to use contemporary molecular biological sciences and technology to examine animal biological processes at the gene expression level or to examine the interactions between nutrients and genes (Malgwi et al., 2022). In the end, it is about studying the complex bi-directional process interactions between nutrients and genes that will clarify the fundamental molecular mechanisms that regulate the expression of nutrients in the diet of the animal genes, the biochemical reaction, as well as the physiological and phenotypic processes (Ahluwalia, 2021).

Nutrigenomics has effect on dietary ingredients that results changes in gene expression patterns and epigenetic modifications, such as histone modifications and DNA methylation (Bordoni & Gabbianelli, 2019; Mosca, Leheup & Dreumont, 2019). Like genomic imprinting, they rely on epigenetic pathways that are very sensitive to dietary changes. For example, developmental traits such as insulin-like growth factor 2 (IGF2) genes are printed on pigs which promote increased muscle mass and fat storage (Ding et al., 2022). In the past decade, the number of microRNA precursors found in miRBase of cattle has increased three times (Ibeagha-Awemu & Zhao, 2015).

Nutrigenomics studies were conducted in humans and mice to study the molecular base of diseases like obesity, cardiovascular diseases, and cancer to understand them through interactions between genes and diet (Ahluwalia, 2021; Pal, 2022). Conventionally, rodent models have been used in research to examine the effects of diet on genome function. Cross-generational studies and measurement of specific life stages (such as pregnancy) have also been performed on mice and rodents. The hypothesis that the mother’s diet will affect the genome structure of the offspring has recently been studied in mice (Chmurzynska et al., 2018). Although similar farm animal methods are still in their infancy, nutrigenomics research is booming, especially in the meat industry, due to health reasons as meat products directly impact human health (Nowacka-Woszuk, 2020).

Nutrigenomics is not a new subject, but a technology with such a promise for the future warrants periodic reviews and updates to inspire thinking and novel approaches. This review aims to provide a comprehensive overview of the fundamental concepts, latest advances, studies in the field of nutrigenomics, emphasizing the interaction of diet with gene expression, how nutritional intervention can change the tissue composition of animals, as well as how it relates to human health along with its human-animal interphase.

2. Nutrigenomics in the livestock sector

The livestock industry is one of the primary sources of livelihood for the farmers in India. Around 60–70% of the total inputs for livestock production are in the form of animal feed. Thus, the livestock industry economics largely depends upon the feed utilization efficiency of the animals (Rauw et al., 2020). The complex and highly diversified rumen microbial ecosystem act symbiotically and synergistically for efficient bio-fermentation within the rumen. In the rumen, efficient anaerobic systems exist to degrade lignocellulosic feeds. However, rumen microbes can extract only a fraction of potential energy from lignocellulosic feeds (Liang et al., 2020). Losing feed energy leads to significant economic losses for the livestock industry. Rumen microbiologists and nutritionists have been making efforts to minimize the losses and decode the complexity of the microbial ecosystem. The molecular era and advanced molecular techniques apply to resolve un-explained quarries of nutrition at the gene level. The field of nutrigenomics paves a way by which nutritional diseases/molecular disorders can be prevented or clinically managed. Differential gene expression studies will allow the identification of candidate genes and the pathways accountable for economically important traits. In the changing nutrition scenario, nutrigenomics examines the impact of nutrition on gene expression or regulatory systems that could be linked to various biological processes affecting animal health and production (Asmelash, Mahlet & Brhane, 2018).

For years, functional genomic methods like transcriptomics, proteomics, and metabolomics have been hailed as having immense potential

![Figure 1: Omic tools used in Nutrigenomic Research.](attachment:image)
for advancing nutritional science by offering a new understanding of diet-gene interactions and discovery of novel nutritional biomarkers (Akanbi, 2019). It can be said that genomics summarizes the instructions given by DNA, whereas transcriptomics is concerned with the pattern of gene expression. The study of complex protein products and their interactions is called proteomics, whereas a step toward comprehending an organism’s entire metabolism is called metabolomics (Muthubharathithi, Gowripriya & Balamurugan, 2021). Technologies available for practical genomic testing are constantly evolving and improving. The field of nutrigenomic research is continually expanding due to this development. The relationship between nutrition and genes can be assessed using DNA microarray methods, real-time quantitative polymerase chain reaction (PCR), and DNA sequencing. Chip technology now enables the sequencing of many genes and the development of an accurate understanding of changes in gene expression patterns (Zduńczyk et al., 2009).

Contrary to expensive transgenesis (Bruh et al., 2017), nutrigenomics can be successfully and cheaply used to increase animal production, growth rate, milk production, feed utilization, disease resistance, and fertility (Figure: 2). Genomics can help bridge the gap between the genetic map of animal husbandry and feeding, improving transformation efficiency and productivity. In the past, nutrigenomics studies have used approaches like Differential Display PCR and Real-Time Quantitative PCR to monitor the expression of some genes. Modern advances in genome analysis offer more effective solutions to a wide variety of biological problems. Thanks to the discovery of microarrays and massive transcriptome sequencing (RNAseq), it is now possible to analyze gene expression on a large scale (Benitez, Núñez, Ovilo & Ovilo, 2017). These innovative technologies were based on the idea of accumulating high-throughput data by automating and parallelizing protein and DNA/RNA synthesis. The most extensively utilized omics methods for gathering proteomics, transcriptomic, and metabolomic data have been created. However, scientists may now use current systemic methodologies to examine interactions occurring within living animals using developing bioinformatic tools in tandem with biological data provided by genomics and transcriptomics (Manzoni et al., 2018). Nutrigenomics investigates the effects and interactions of nutrition on gene expression using large-scale gene expression methods (Hasan et al., 2019). Researchers can learn more about the molecular basis of observed phenotypic differences within organisms by studying gene expression in animals subjected to different nutritional conditions and the metabolic pathways directly involved in regulating tissue structure, thus contributing to tissue quality.

2.1. Transcriptomics

With technical advancements in the microarrays and RNA sequences, the expression of virtually all the transcribed genes in a sample could be quantified, hence the transcriptome. A transcriptome is a snapshot of all the transcripts present in a cell at a particular point in time (Lowe, Shirley, Bleackley, Dolan & Shafee, 2017). Transcriptome research has improved our understanding of the RNA-based gene regulatory network as next-generation high-throughput sequencing technology. For the first time in small ruminants, a nutrigenomic analysis of goat mammal transcriptome responses was performed in feed-deprived goats in 2007 (Osorio, Vailati-Riboni, Palladino, Luo & Loo, 2017). This research showed the genes responsible for reductions of milk fat, lactose, and protein, genes responsible for the impediment in the proliferation and differentiation of mammalian cells, and the increase in programmed cell deaths contribute to the early mammalian involution. RNA sequencing has been in use since 2011 and has recently replaced microarray systems in omics science. This technology was used to study the transcriptome and the micro RNAome from small ruminants such as goats and sheep (Martyniuk et al., 2020).

RNA-seq with high throughput has become the method of choice for animal nutritionists to set up a framework for developing feeds or feed additives, promoting animal growth, health, and production. This method is being used to investigate global gene expression patterns in tissues linked to economically significant features like feed effectiveness (Alexandre et al., 2015) or quantitative determination of the genes or transcripts, which can be used as potential biomarkers for production traits (Han, Gao, Muegge, Zhang & Zhou, 2015). Indeed, recent advances in farm animal genome sequencing, such as swine, cattle, and sheep, have given essential reference genomes for aligning RNA-Seq
short reads to assess changes in gene expression in response to dietary nutrients (Hasan et al., 2019; Santos, Blanck & de Freitas, 2014; Wickramasinghe, Rincon, Islas-Trejo & Medrano, 2012; Wang et al., 2009). In conclusion, even though its application faces some technical challenges in both experimental and computational aspects, the novel RNA-Seq technology for transcriptomics analyses of living organisms is considered a powerful approach to better understanding molecular mechanisms in terms of nutrient–gene interactions.

2.2. Proteomics

The word “proteomics” was coined in 1995, describing it as the broad-scale characterization of cell lines, the tissue’s or organism’s entire protein complement, simply defining it as a study of proteins, chiefly their function and structure (Hossain et al., 2020). Proteomics is a crucial component of nutrigenomics, which aims to comprehend how our genome is expressed in response to nutrition on a holistic level. The main objective of proteomics is to achieve a more global and integrated view of biology by analyzing all of a cell’s proteins at a time. The application of proteomics in livestock has been limited in past due to a lack of optimized protocols and high cost (Baykalir, Baykalir & Simek, 2018). However, new computational tools and analytical methods for the analysis of proteomic data have led to an increased understanding of animal health, production, and reproduction efficiency (Kaya et al., 2022; Ye et al., 2022).

Proteomics-based approaches are used in a variety of research environments, identifying multiple diagnostic targets, vaccine candidates, pathogenicity factors, interpreting functioning protein pathways in various disorders, as well as variations in expression patterns in response to diverse signals (De Sousa et al., 2018; Katsarou et al., 2021). The proteomic scope has advanced from protein recognition and characterization to protein–protein interactions, protein structure, and function since the human genome sequencing. The technologies used in proteomic research include mass spectrometry (MALDI-MS, ESI-MS, LC-MS/MS, MALDI-TOF MS, etc.) measuring mass to charge (m/z) ratio of ionized peptides for protein identification, yeast two-hybrid screens, one-dimensional (ID) gel electrophoresis, 2-dimensional (2D) gel electrophoresis, Chromatography (gas and liquid) and computational prediction programs (Sharma, Ray & Mahapatra, 2022).

The use of proteomic approaches for studying reproductive problems has dramatically increased in the past decade (Peddinti, Memili & Burgess, 2011). Targeting robust protein markers is useful in disease monitoring, surveillance, health monitoring, and overall well-being of the animal which will help assess pharmacologic response to therapeutics (Muhanguzi et al., 2022). Proteomics is used to identify genetic variants with traits desirable for breeding and selection for various animal products post-harvest like milk, meat, cheese, etc. (Almedia et al., 2015).

Proteomic approaches to farm animals have been applied to improve animal welfare to prevent a negative effect on animal production and human health besides clinical management & treatment of human diseases (Ceciliani, Eckersall, Burchmore & Lecci, 2014). Since the animal genome has not been fully sequenced as in humans, the serum proteome analysis and characterization in most farm animals are in the preliminary phase (Di Girolamo et al., 2014). Protein and metabolites level expression measurement provides new ways and knowledge to determine and manage the nutrient balance in farm animals. Hypotheses for such studies can be translated from similar human studies which help to optimize diet composition and dietary nutrient supply in defined populations of livestock species or individual animals (Asmelash et al., 2018).

In farm animals, proteomics could help evaluate the risk of zoonosis, increase productivity and fertility, and improve the safety and quality of animal products thus, reducing financial losses as well. The proteomic investigation has been applied to veterinary and animal sciences over the last decade but it has still not reached its full potential in animal health and production. Quantitative proteomic investigation of biofluids and tissue samples from cattle, pigs, sheep, chickens, cats, and dogs has helped to identify potential novel biomarkers like in an experimental model of Strepotococcus uberis mastitis of dairy cows. Milk proteins have potential as disease biomarkers, like haptoglobin, cathelicidin, and mammary-associated serum amyloid A3. These markers can help diagnose subclinical as well as clinical mastitis. On similar lines, proteomic analysis of chicken plasma following stimulation of the inflammatory response to E. coli LPS reveals major changes in the plasma proteome (Eckersall, 2020).

Proteomics also enables the identification of candidate protein markers of fertility for molecular breeding. In a recent study on Tibetan pigs having heritable adaptation to hypoxic environments, eight fertility-related proteins were overexpressed by LC-MS/MS analysis (Zhao et al., 2021). Analysis of seminal plasma proteins by LC-MS/MS found a significant correlation between proteins with fertility (Willfors et al., 2021). The application of proteomics can help identify fertile bulls to increase productivity and reduce the non-return rate (NRR). For selective breeding, proteomic tools are utilized to identify superior genetic variants. Mullins et al. (2021) have identified protein markers by proteomics which will help in the selection of genetic variants, accelerate genetic gain and increase profitability (Mullins et al., 2021).

The last decade has marked proteomics as the main forum for interviewing plasma/serum proteomics for exploration of next-generation biomarkers in the veterinary and human sectors, with introducing standard pre-analytical sample therapies, MS-based systems, and data processing systems for data management (Castelli et al., 2021; Ghodasara, Satak, Sadowski, Kopp & Mills, 2022). Thanks to the vast number of serum proteins that can be investigated concurrently, the proteomic approach is quicker than the ELISA and PCR methods. However, the high initial cost needed to purchase the equipment is a significant barrier to the broader application of the technique. However, the costs incurred have quickly decreased, thus preferring their procurement (Nicholson et al., 2012). The discovery of next-generation biomarkers that help a range of human and farm animal disease diagnoses and new proteomic technologies can significantly improve surveillance.

2.3. Metabolomics

Metabolomics deals with screening the small molecule metabolites in biological samples like animals, plants, and microbes (Baharum et al., 2018; Bishai et al., 2021). By comparing the metabolome profiles (metabolic phenotypes or ‘metabotypes’), one can establish patterns of variation among different groups, i.e., control versus treated, healthy versus diseased. Metabolomics in livestock has made significant advancements to livestock welfare, reproduction, and development, as well as the detection of biomarkers for transformation diseases (Sun et al., 2015), production traits in dairy (Goldsans et al., 2017), and beef cattle (Migliani, Wouters, van Westen, Dubbelman & Hankemeier, 2019), all to incorporate prognostic techniques in animal health and improve prediction accuracies. In addition, many bio-fluids have been investigated for metabolomics research, including metabolic profiling of plasma, milk, urine, and serum, which has abrided animal welfare concerns (Gowda et al., 2006).

Currently, two fundamental techniques are being used in metabolomics, i.e., nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). However, mass spectrometry is often coupled together with a separation technique, such as gas chromatography (GC), liquid chromatography (LC), or capillary electrophoresis (CE). Nuclear magnetic resonance (NMR) is now more advanced than mass spectrometry (MS) for high-throughput analysis in terms of analysis time and cost per sample. The NMR spectrum usually takes 5 to 8 min, while the LC analysis takes 5 to 30 min (Wishart, Feunang and Marcu, 2018). Due to its high sensitivity, mass spectrometry (MS) has a broader range of coverage. It has potential performance advantages in terms of
Retinoic acid, vitamin D, and folate receptors regulate adipogenesis and mutations in the central regulatory genes of adipogenesis (Chen, 2021). Retinoic acid is the active metabolite of vitamin A, which can induce retinoic acid receptor (RAR) and retinoid X receptor (RXR), leading to epigenetic modification of the genome. In dairy cattle, the experiments are focused on milk yield and composition. The most formidable challenge in metabolomics research is integrating data with other omics and phenotypic data (Salkir, Kemahlioglu & Yuce, 2021). A more conscientious approach in the design and implementation of metabolome studies would be to investigate a wider variety of samples such as saliva, urine, amniotic fluid, and semen, along with expanding the types and number of animal breeds (Goldansaz et al., 2017).

2.4. Lipidomics

Meat production worldwide has recently concentrated on improving meat quality in fatty acid profile and marbling. Induced marbling requires a better understanding of the pathways that regulate fat formation (Ladeira et al., 2018). Vitamin A has recently been discovered to play an important role in adipogenesis. Retinoic acid is the active metabolite of vitamin A, which can induce retinoic acid receptor signals to change the development and differentiation of adipose tissue. Retinoic acid, vitamin D, and folate receptors regulate adipogenesis and reduce lipid accumulation. Vitamin D interacts with retinoic acid receptor signals to change the development and differentiation of adipose tissue (Szymczak-Pajor, Miazek, Selmi, Balcerczyk & Śliwińska, 2022).

Further, dietary manipulation during specific periods of pregnancy, like in the prenatal period, nutrients act not only on the developing fetus but also on the primary germ cells that give rise to the next generation (Dimofski, Meyre, Dreumont & Leininger-Muller, 2021). By using these newly developed methods, functional lipidomics can help profile and understand the unique functions of each lipid subtype (Ferguson et al., 2016). Lipidomics can be applied directly to human plasma, potentially identifying novel and predictive disease biomarkers such as coronary disease progression and responsiveness to treatment. Considering that many specific lipid species are synthesized in vivo from dietary precursors, lipidomics provides a promising method for investigating the relationship between dietary lipids and cardiometabolic risk, allowing the identification of lipid biomarkers.

3. Impact of the relationship between nutrients and genome in animal health and production

There has been a prodigious increase in facing the substantial challenges from a steep projected increase in global demand for food and high-quality animal proteins, besides adapting to environmental stresses. Nutrigenomics research aims to explain the molecular interactions between genes and diet and identify necessary molecular signatures to develop effective nutritional strategies. Most nutrigenomics studies have concentrated on human nutrition and its consequent effects on disease etiology (Reddy, Palika, Ismail, Pullakhandam & Reddy, 2018). Studies of gene expression analysis are carried out in response to dietary regimens because the biochemical parameters depend on the specific gene transcripts (Mierziak et al., 2021). In dairy cattle, the experiments are focused on milk yield and composition. In contrast, in beef cattle, experiments are focused on obtaining the fatty acid profile in muscle tissue and thus modulating specific diets. Animal health is essential in both pigs and poultry, so supplements such as amino acids, vitamins, and prebiotics are used, affecting the transcription of genes and playing a vital role in improving the immune system function (Alagawany et al., 2021).

The effects of diet on genome functioning have usually been performed on experimental models like pigs, rats, and mice. Studies of specific life periods (pregnancy) have been conducted in rats and mice (Chmurzyńska et al., 2018), and the phenomenon of fetal programming, wherein maternal nutrition affects progeny genome functioning, has also been studied in rodents (Reynolds & Vickers, 2018). Similar approaches to farm animals are still in their infancy stage. However, the nutrigenomics concepts have gained much importance, especially in the meat production industry and in improving the health of animals. A recent study by Kang, Madkour and Kuenzel (2017) demonstrated that psychological and early life nutritional stress on birds modulated vital regulators of DNA methylation. In another study, a link between nutrients and bovine genotype and the enteric biome in acidosis challenging conditions has been seen. Several putative QTL were identified for metabolites like butyrate and lactate, acidosis, and host-microbiome interactions (Golder, Thomson, Denman, McSweeney & Lean, 2018). In broilers, a diet rich in Morinda Citrifolia (Noni) was reported to alleviate heat stress by modulating hypothalamic orexin-AMPK-mTOR pathways (Rajase-Charifbadi et al., 2017). These studies suggested the ability of nutrition-genome interaction in modulating and changing the future of dietary guidelines by identifying key molecular markers for personalized nutrition approaches.

4. Epigenetic control on livestock production

The study of nutritional epigenetics relates to gene-diet interactions (Lucini et al., 2020). Nutritional epigenetics in livestock production is still in its infancy stage. However, a foundation of nutritional epigenetics research has been established and validated. Diet might play a regulatory role in the epigenetic makeup of the first-generation consumer, but it also affects progeny performance. Due to the rapid reproductive cycles of swine and poultry and the large number of offspring produced may be a landmark for the industry (Roberts et al., 2019).

There are multiple genes and environment interactions while considering the phenotypic variation. One of the critical environmental players in these phenotypes is nutrient quality and quantity. For example, nutrient-induced epigenetic events can be found in honeybees and mice (Kucharski et al., 2008). Nutritional phenotypes are primarily studied from the growth, feed intake, and efficiency perspectives. In livestock and genome-wide nutritional epigenomics studies (Shin et al., 2014), associations between epigenetic modifications and nutritional phenotypes have been well documented (Shin et al., 2014). Associations between epigenetic mechanisms, genetic variation, and subsequently economically important phenotypes have been identified in livestock. One of the overarching goals is to investigate the economically essential traits to determine the extent to which phenotypic variation can be accounted for by genetic variation in the livestock genomics community. Nevertheless, to comprehend a mechanistic link between phenotype and genotype, tools must be generated that will allow us to interrogate the epigenetic modifications. In the past, epigenetic studies in livestock animals have utilized DNA methylation-based next-generation sequencing methods to investigate the role of methylation in the phenotypic variation of their economically important trait (Boddicker et al., 2016). A high-resolution DNA methylation array has been used in humans (Bibikova et al., 2011). Using the same technology for animals will permit EWAS and ultimately enable epigenetic modifications for livestock production and breeding (Rolf et al., 2014).

4.1. Epigenetic control of Adipose tissue

Reversible inhibition of lineage-specific genes allows stem cells and progenitor cells to retain pluripotency or multipotency while promoting...
gene expression involved in stem cell self-renewal. However, lineage-specific genes are released during separation, while pluripotency and multipotency genes are inhibited (Reik et al., 2007). A transcription factor and lineage-specific gene are triggered to enable progenitor cells to commit to a particular lineage when a central development gene is activated (Aloia, Di Stefano & Di Croce, 2013).

Zfp423 is one of the leading CpG-rich genes in the development and is primarily controlled by epigenetic modifications (Yang et al., 2013). Histone modifications and DNA methylation are also examples of epigenetic modifications. Polycomb inhibition complex (PRC) is responsible for reversible gene suppression by catalyzing histone methylation. PRC1 and PRC2 are two PRCs that have been thoroughly studied. The PRC2enhancerZeste 2 (EZH2) is a crucial component (Qi et al., 2012) that mediates the trimethylation of the gene silencing marker histone 3-lysine 27 (H3K27me3) (Mendenhall, Kocher & Truong, 2010). It has not been proven that PRC2 has specific DNA binding properties, but it prefers to bind to promoters with many CpG sites to attract PRC1 binding. In the absence of PRC release stimulation, these promoters are usually methylated in DNA (Shankar et al., 2020; Shankar et al., 2020; Mackin et al., 2019).

Environmental and genetic factors influence the complexities of these epigenetic regulation in critical developing genes. Gene polymorphisms in essential developed genes modify the binding of epigenetic modulation complexes and influence the cell lineage interplay of the progenitor during development (Murdoch, Murdoch, Greenwood & McKay, 2016). In addition, environmental stimuli and indications, such as nutrients influence animal development by modifying pathologies for cellular signage or by recruiting epigenetic transcription factors, such as adipogenesis.

4.2. Role of B-complex vitamins and methyl donors

Epigenetic changes are histone and methylation of DNA, but unless methyl donors help, methylation is unlikely to happen. Using S-adenosyl methionine, DNA’s methyl methionine (SAM) adds a methyl group to DNA (SAM). Following transfer to DNA or histones, SAM is converted into S-adenosylhomocysteine (SAH). This operation is supported by folic acid, vitamin B12, choline, and concrete nutrients. Food methylation, folic acid, vitamin B12, and choline, betaine promote DNA and histone methylation of genes reliably (Bellner et al., 2015). Folic acid and Vitamin B12 therapy inhibit adipogenic development in 3T3-L1 cells via modulating Wingless and Int (Wnt) 10b (Cordero, Gomez-Uriz, Campion, Milagro & Martinez, 2013). Burton et al., 2019 suggested the influence of methyl donors on adipogenesis through epigenetic alterations in processing genes.

5. Adipogenesis and the role of vitamin A, retinoic acid, and vitamin D receptors

Various lipid signaling components, such as steroid hormones, retinoids, thyroid hormones, and Vitamin D metabolites activate intracellular nuclear receptors. Ligand-activated transcription factors bind to their corresponding DNA components to stimulate gene expression. Adipogenesis is summarized in the following section by discussing the effects of Vitamin D and retinoids. All-trans retinoic acid is produced when dietary vitamin A is absorbed and extracted. Retinoic acid acts as a ligand for retinoic acid receptors (RAR). They will bind to retinoic acid reaction elements (RAREs) on target genes via retinoid X receptors (RXR). By activating the orphan receptor PPAR, retinoic acid promotes cell proliferation, lipid breakdown, and lipid oxidation (Osz et al., 2020; Rochette-Egly 2020; Rochette-Egly et al., 2020). The partitioning of retinoic acid between RAR and PPAR will determine the biological consequences of retinoic acid. CRABP-II and fatty acid-binding protein type 5 (FABP5) are cellular retinoic acid-binding proteins that govern retinoic acid partitioning, with CRABP-II delivering retinoic acid to RAR and FABP5 supplying retinoic acid to PPAR/. A high CRABP-II/FABP5 is expressed in adipogenic progenitor cells, leading to RAR signaling dominance. CRABP-II and RAR down-regulate during adipogenic differentiation, whereas FABP5 and PPAR/ up-regulate, activating PPAR/signaling in mature adipocytes. Because of the stage-specific expression of associated transcription factors, retinoic acid has differing effects on progenitor cells and mature adipocytes (Abdelhamed, El-Dawla, Karadag, Agamia & Melnik, 2021; Ladeira et al., 2018).

Vitamin D is considered to control adipogenesis and its roles in calcium balance and bone metabolism. In obesity, vitamin D has been reported to affect insulin secretion, tissue sensitivity to insulin, and ultimately, systemic inflammation. The direct and paracrine effects of vitamin D led to VDR activation in pancreatic beta-cells, CYP27B1 expression, and local synthesis of 1,25(OH)2D (Mastro, Dávila, Carranza & Calle, 2003). Polymorphisms reduce obesity and diabetes in genes involved in Vitamin D production and signaling. In both in vivo and in vitro investigations, vitamin D has been shown to decrease adipogenesis. The active metabolite of vitamin D, 1,25-dihydroxy vitamin D, suppresses 3T3-L1 preadipocyte development and downregulates adipogenic gene expression in a dose-dependent manner (Blumberg et al., 2006). The 1,25-dihydroxy vitamin D receptor, which has been identified to be activated by 1,25-dihydroxy vitamin D, regulates adipogenesis (VDR). VDR suppresses adipogenesis by downregulating C/EBP expression in the presence of 1,25-dihydroxy vitamin D (Lu, Taylor & Körner, 2018; Miao et al., 2020).

6. Summing up the role of nutrigenomic in nutrients

Vitamin A, during the early adipocyte development, triggers adipocyte generation during the fattening phase and thus, increases marbling. Conversely, vitamin D metabolites curtail adipocyte production. Vitamin D through VDR binding, binds to the RXR, competing with PPAR ligands and their receptors, which bind to the RXR, which otherwise is required for adipogenesis (Wang et al., 2016). Adipogenesis may also be affected by methyl-donors that regulate epigenetic changes during early adiposis. On the other side, vitamin A supplementation decreases adipocyte hypertrophy and marbling by promoting lipid degradation in feedstock beef cattle. Suppose vitamin A is supplemented from birth until weaning (Peng, Smith & Lee, 2021). In that case, there may be a greater production of intramuscular adipocytes, resulting in more intramuscular pre-adipocytes capable of storing lipids (hypertrophy) throughout the fattening stage, promoting marbling without increasing carcass fatness.

The path to creating healthy meat should be paved with adequate balanced feeding, with alternative nutrients being thoroughly researched for short and long-term impacts. The gene expression studies are carried out concerning the dietary regimes because any change in the biochemical parameter will depend on the particular gene transcript. Even though transcriptome studies have been carried out in farm animals, sophisticated investigations involving protein levels should be carried out. Furthermore, in farm animals, the impact of nutrition on epigenetic mechanisms is still unknown (Nowacka-Woszuk, 2020). Therefore, a complete strategy should be used during nutrigenomic investigations, including genome functioning, breeding aims, and physical characteristics. Innovative technology is already being used extensively in rodent and human nutrigenomic investigations and will almost definitely be employed more often in other species.

7. Nutrigenomics in poultry

In poultry, the intestinal tract (GIT) expands allometrically compared to the rest of the body during the first week after hatching. Because of this rapid expansion rate, supplemental feeding during the first 96 h of hatching has a long-term impact on the animal (Van Every, 2021). For these animals to reach their genetic potential, they must have a stable digestive system. Intensive poultry rearing causes stress in birds,
resulting in a lowered immune response that enhances intestinal colo-
nization of pathogens and gastrointestinal disturbances (Arif et al.,
2021). Scientists have used modern nutrigenomic approaches to inves-
tigate how the diet interacts with the gut immune system to further
understand the processes and efficacy of various food therapy strategies.
Cinnamaldehyde, carvacrol, oleoresin from Capsicum spp., and turmeric
(Abd El-Hack et al., 2022; Khodadadi, Sheikh, Nazarpak & Brujeni,
2021; Pirgozliev, 2019), according to studies, are all effective on the GIT
immune response. Plant-derived phytochemicals have been shown to
control the gene expression involved in physiology and immunity (e.g.,
protein and energy metabolism), implying that they can help chickens
become more immune. Eimeria acervulina induces intestinal damage in
commercial poultry production. It has been tested for its efficacy against
anethole, turmeric, and garlic metabolites (Nahed et al., 2022; Abdelli,
Sola-Oriol & Perez, 2021).

The expression of oxidative phosphorylation genes and other cellular
stress response genes in the jejunum was improved by prebiotics, such as
yeast cell walls. Gene expression profiles in yeast cell-wall supplemented
broilers demonstrated that biological processes and pathways connected
to enhanced health and metabolism were activated compared to a
common antibiotic (bacitracin) (Jha & Mishra, 2021). According to the
findings of this microarray study, birds that were provided yeast cell
walls underwent genomic changes that corresponded to slower gut cell
turnover and, as a result, improved energy utilization for growth (Khan
et al., 2018). Probiotics have also been studied with the use of omics
techniques. Among the enterocyte proteome of broilers fed Enterococcus
caecium, some differentially expressed proteins were associated with
antioxidant and immune processes, suggesting that the chickens used
fewer nutrients and energy to cope with antioxidant and immune stress
(Khan et al., 2018). In addition, trace minerals like chromium have been
utilized for weight gain to improve feed conversion ratio and muscle
development and modify the immune response in broilers (Haq et al.,
2016; Wang et al., 2022). The latest nutrigenomics findings explicitly
open up new opportunities for developing effective drug-free disease
prevention strategies for poultry infectious diseases.

The effect of micronutrient supplementation on transcriptional pro-
files of chicks was also studied including vitamins and minerals in the
diet of hens. Supplementation increased the gene mRNA level of intes-
tinal cells and proliferation, which corresponded to the number of villi
proliferating cells and the transitional area of the supplemented popu-
lation. As a result, gene expression has been modified and could affect
feed absorption, metabolism, and the gut immune system (Gilani et al.,
2021). Chromium is a mineral needed to metabolize the body’s nucleic
acids, lipids, and carbohydrates. Complete chromium supplementation
of serum proteins and sugar triglycerides has affected the action of in-
sulin. Out of the 57 skeletal muscle development and growth micro-
RNAs, 16 have been shown to have modified muscle tissue expression
(Vilar et al., 2020).

The recent increase in mycotoxin content in feedstuffs due to shifting
climatic conditions has sparked curiosity about their effect on the liver
of animals. At concentrations as low as 2 to 2.5 mg/kg of feed, aflatoxin B1
and deoxynivalenol may affect this organ. In addition, these toxins can
induce intestinal damage in the jejunum (Bhatti et al., 2018). Implementing a single mycotoxins
decontamination/control technique rarely warrants protection against a
chemically diverse range of mycotoxins. The presence of multi-mycotoxins and a range of fungi in food and feed needs the
application of several decontamination techniques at the same time for
effective management. On the other hand, decontamination of poultry
feeds can be accomplished using chemical, physical, and biological
means. Some bacteria that detoxify mycotoxins in the gut have been put
into feeds to avoid their absorption (Adebo, Njobeh, Gbashi, Nwinyi &
Mavumengwana, 2017).

8. Nutrigenomics of meat and its human perspective

Marbling is an essential characteristic of ruminant meat consistency
because it affects juiciness and flavor. Adding together, since the fatty
acid content of lipids in meat is critical for human health, this issue has
gotten much attention in recent decades. Nutrigenomic research has
aided researchers in better understanding the cellular pathways that
affect fatty acid profile and meat marbling in this way. This information
could benefit the livestock industry by encouraging it to produce sub-
stances or chemical compounds that can modulate the expression of
genes, resulting in better meat quality (Aiken & Ozanne, 2014). Nutri-
tionists will now be able to use feedstuffs and other foods due to this
experience. Adipogenesis and marbling are programmed in the womb.
Adipogenesis occurs in the womb and has long-term implications for
meat quality and fat deposition (Desoysa & Herrera, 2021). It’s necessary
to look into the effect of dam nutrition on offspring adipogenesis
through nutrients influencing gene expression in the fetus until we can
look into the direct impact of nutrients on genes during the finishing
phase. This influence is related to the idea of fetal programming. It’s
difficult to say how the dam’s diet affects the offspring. It has been
suggested that dams may affect progeny phenotypes by providing half of
the fetal genes in addition to epigenetic marks via somatic epigenetic
reprogramming, through ooplasmic contribution to the fetus, and by
providing an intrauterine atmosphere (Vahmani et al., 2015).

There is a concern about manipulating the fatty acid profile of meat
due to their potential beneficial or harmful effects on human health.
Conjugated linoleic acid C9, 11-C18:2 reduces the risk of cancer,
hyperlipidemia, and diabetes, and certain saturated fatty acids (SFA)
increase high-density lipoprotein (HDL)-cholesterol (Berton, Fonseca &
Gimenez, 2016). PUFA is involved in many biological processes vital to
human health (Wood, Richardson & Nute, 2004). Because of the
observed hypercholesterolemia, lauric and palmitic fatty acids are
hypercholesterolemic. Conversely, because of the pragmatic increase in
low-density lipoprotein content in the blood, lauric and palmitic fatty
acids are hypercholesterolemic (McPherson et al., 2020).

9. Human nutrigenetics

Nutrigenetics studies how genetic factors determine an individual’s
disease risk, nutritional requirements, and metabolic response (Sure-
nadran & Vimalaswaran, 2021). The human genome is 99.9% identical in
all people. Single nucleotide polymorphisms (SNPs) account for nearly
90% of the human variation between individuals and account for the
remaining 0.1% of the variation. SNPs are DNA sequence variations
when one nucleotide in the genome sequence changes. Each gene is
thought to differ from the standard gene by about ten differences (or
polymorphisms) in its code. However, because SNPs can be found in
both coding and non-coding regions of the human genome, not all
polymerase has a functional impact (Roche, 2006). Given many potential SNPs for candidate genes, it’s critical to distinguish between functional and non-functional SNPs to include only functional genetic variants in genetic association studies.

Nutritional genomics aims to find the key candidate genes involved in the most common diet-related disorders (obesity, metabolic syndrome, T2DM, CVD, etc.). This is a complicated process due to the complex polygenic nature of many diseases, which involve disruptions in multiple metabolic pathways (Sikalidis, 2019). Metabolic syndrome symptoms include insulin resistance, abnormal lipoprotein metabolism, hypertension, and obesity. Over 50 candidate genes have been implicated in lipid metabolism, with new candidate genes emerging due to ongoing research in this field. As a result, many genes and polymorphisms are likely to play a role in the pathogenesis and progression of major dietary disorders (Laddu & Hauser, 2019).

Nutrigenetics will be a very intriguing subject of study in the future decades. To understand the impact of gene nutrient interactions, huge data-rich cohorts will be required. Well-characterized phenotypes based on extensive clinical food intake data and sensitive biomarkers of dietary intake data will be necessary to establish the impact of various nutrient exposures in the setting of common polygenic, diet-related illnesses. Robust bioinformatic techniques capable of determining the influence of many genes interacting with nutritional exposures will be necessary to tackle these prevalent but complicated diet-related disorders.

10. Impact of nutrigenomics on humans

Nutrigenomics involves studying how food affects a person’s genes and how genes affect a person’s response to food. Nutrigenomics explores how genes and diet may affect health and the risk of developing diseases like cancer, diabetes, atherosclerosis, etc. Several micronutrients (vitamins), macronutrients (protein, carbohydrate), and naturally occurring chemicals (flavonoids, coumarins, carotenoids) have been shown to influence gene regulation (Lundstrom, 2020). Tumors and coronary disorders (CVD) are the most noticeable pathologies caused by lifestyle changes (Popovic et al., 2022). Therefore, recognizing nutritional risk factors is essential, and it will undoubtedly aid in reducing their effect on the population.

10.1. Cancer treatment

The most current developments in molecular biology approaches have provided researchers with new insights into many health-related topics, including cancer. Unlike normal cells, cancer cells produce energy by glycolysis accompanied by lactic acid fermentation. Therefore, glucose plays a critical function in cancer cells, and changes in the expression of glucose-responsive genes such as pyruvate kinase type M2 and phosphofructokinase1 may treat cancer (Rodriguez-Enriquez et al., 2019). Fruits and vegetables are high in vitamins and minerals to help prevent cancer. Folic acid in fruit is transformed by several chemical pathways (Sikalidis, 2019). Metabolic syndrome symptoms include insulin resistance, abnormal lipoprotein metabolism, hypertension, and obesity. Over 50 candidate genes have been implicated in lipid metabolism, with new candidate genes emerging due to ongoing research in this field. As a result, many genes and polymorphisms are likely to play a role in the pathogenesis and progression of major dietary disorders (Laddu & Hauser, 2019).

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10.3. Cardiovascular diseases

Individual dietary patterns have changed dramatically in recent years, resulting in many health issues. Obesity, stroke, and thrombosis are signs of cardiovascular disease (CVD) which is a chronic illness caused by a combination of abnormal conditions. Apolipoprotein A-1, which is related to HDL, is present in the liver and intestine (HDL). The A-1 HDL complex takes part in cholesterol transfer and has been associated with a lower risk of heart failure (Sacks et al., 2018). The APOA1 gene, which codes for Apo A-1, is polymorphic and has been extensively studied (Sampath et al., 2005). Variation in this gene significantly affects cholesterol transfer, which contributes to CVD. Polysaturated fatty acids (PUFA) can activate the APOA1 gene. In a study on PUFA in cholesterol transport, people with the A allele in the APOA1 gene had higher HDL levels as their PUFA intake increased (Sampath et al., 2005).

11. Role of nutrigenomics in human-livestock interface

The expanding number of research on humans, animals, and cell cultures indicates that nutrients and other bioactive chemicals in the diet can affect the expression of genes in a variety of ways (Felsbino, Granzotti, Bello-Santos & Guiñoski, 2021). Thus, studying the molecular mechanisms of nutrients and other bioactive food ingredients is necessary to understand the effect of diet on health. Because of the intricacy of human behavior and the human genome, studying animals is a helpful way to understand genetic implications on food selection. As a result of the applied study of animal nutrition, the use of animals for food consumption studies was a natural development. A recent study in mice and humans has been conducted in this field to understand the molecular basis of diseases such as cardiovascular disease, obesity, and cancer due to gene/diet type interactions (Mondal & Panda, 2020). These nutrigenomic studies in domestic animals are much less common. They focus on a minimal number of genes that are specifically related to a specific treatment, which is usually associated with the energy content of the diet or the content of some of its components, such as polysaturated fatty acids (PUFA), protein, or L-carnitine (Hamill, Aslan, Mullen,
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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