

Regulation of Gene Expression in Response to Nutritional Interventions in Swine

Jianli Zhong ✉

Hainan Institute of Biotechnology, Haikou, 570206, Hainan, China

✉ Corresponding author: jianli.zhong@hibio.org

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Abstract This study explores the complex interactions between dietary components and gene expression pathways, with a focus on their effects on pig growth, development, and metabolic health. Nutritional interventions, including macronutrients, micronutrients, and feed additives, are discussed, and the main benefits of targeted nutritional strategies, including improved muscle development, enhanced immune response, and optimized energy efficiency, are summarized. The progress of nutrigenomics, such as transcriptomics research and integrated omics methods, is briefly described. A case study illustrates how specific dietary changes affect gene expression and its practical application in pig production. Despite progress, challenges such as the complexity of gene nutrient interactions and methodological limitations still exist. Future research should prioritize the integration of multiple omics and innovative technologies to improve nutrition strategies and pave the way for personalized pig feeding practices. This study emphasizes the transformative potential of nutrigenomics in optimizing gene expression for sustainable pig production.

Keywords Pig; Nutritional genomics; Gene expression; Epigenetics; Nutrient-sensing pathways

1 Introduction

Understanding gene expression in swine nutrition is crucial for optimizing health and production efficiency in the swine industry. Nutritional interventions can significantly influence gene expression, impacting various biological processes such as growth, immune response, and metabolism. For instance, dietary prebiotics and arachidonic acid have been shown to alter gene expression in piglets, affecting gastrointestinal health and reducing inflammation (He et al., 2019). Similarly, dietary lysine restriction impacts gene expression in skeletal muscle, influencing protein synthesis and metabolic pathways (Wang et al., 2019). These insights highlight the potential of nutritional strategies to modulate gene expression for improved swine health and productivity.

Gene-nutrient interactions play a pivotal role in swine health and production by modulating gene expression profiles in response to dietary components. For example, the supplementation of *Clostridium butyricum* in piglets modifies liver gene expression, enhancing immune function and metabolic processes (Qiao et al., 2020). Additionally, maternal dietary interventions, such as betaine supplementation, can epigenetically regulate gene expression in offspring, affecting lipid metabolism and stress responses (Cai et al., 2016; Cai et al., 2017). These interactions underscore the complexity of nutritional programming and its potential to enhance swine growth, reproductive performance, and overall health.

This study explores the gene expression regulation mechanisms of pigs in various nutritional interventions, elucidating the molecular pathways influenced by dietary components and their effects on pig health and production through recent research. This includes analyzing the effects of specific nutrients (such as amino acids, prebiotics, and probiotics) on gene expression, as well as their effects on different tissues (including liver, muscle, and gastrointestinal tract). This study aims to provide insights for optimizing pig nutrition to improve productivity and health outcomes.

2 Nutritional Interventions and Gene Expression

2.1 Types of nutritional interventions

Nutritional interventions in swine can be broadly categorized into macronutrients, micronutrients, and feed additives. Macronutrients such as proteins and amino acids play a crucial role in gene expression. For instance, dietary lysine, an essential amino acid, has been shown to affect the expression of genes related to muscle protein synthesis in pigs. Micronutrients, including vitamins and minerals, are also significant as they can modulate gene expression through epigenetic mechanisms, such as the regulation of microRNA (miRNA) profiles (Beckett et al., 2014). Feed additives like betaine, a methyl donor, have been used to influence gene expression by altering DNA methylation patterns, impacting pathways such as the STAT3-dependent pathway in piglets (Cai et al., 2015).

2.2 Role of dietary components in regulating gene expression pathways

Dietary components regulate gene expression pathways through various mechanisms. Amino acids like lysine can influence transcriptional regulators and pathways involved in protein synthesis and metabolism, such as the inhibition of insulin and activation of STAT3, which affects cell movement and fatty acid metabolism. Betaine supplementation during gestation has been shown to suppress the expression of lipogenic genes in piglets through epigenetic modifications, such as DNA hypermethylation and histone modifications, which are mediated by glucocorticoid receptors (Cai et al., 2016). Additionally, micronutrients can modulate miRNA expression, which in turn regulates gene expression at both transcriptional and post-transcriptional levels.

2.3 Benefits of targeted nutritional strategies for optimizing gene expression in swine

Targeted nutritional strategies can optimize gene expression in swine, leading to improved growth, health, and productivity. For example, lysine supplementation can enhance muscle protein synthesis by modulating key transcriptional regulators, thereby improving muscle growth and development (Wang et al., 2019). Maternal betaine supplementation has been shown to reduce hepatic lipogenesis in piglets, potentially leading to healthier metabolic profiles and reduced fat deposition. Furthermore, the modulation of miRNA by dietary components can provide a means to fine-tune gene expression, potentially reducing the risk of diseases associated with dietary imbalances. These strategies highlight the potential of nutritional interventions to enhance swine production through precise regulation of gene expression pathways.

3 Molecular Mechanisms of Nutritional Regulation of Gene Expression

3.1 Epigenetic modifications

Epigenetic modifications, such as DNA methylation and histone modifications, play a crucial role in the regulation of gene expression in response to nutritional interventions. Nutrients can influence these epigenetic marks, thereby altering gene expression without changing the underlying DNA sequence. For instance, dietary components like methyl donors (e.g., betaine) can lead to DNA hypermethylation, affecting the expression of lipogenic genes in swine. Additionally, nutrients such as methionine are vital for maintaining the levels of S-adenosylmethionine, a key methyl donor in epigenetic processes, which influences histone methylation and gene expression (Figure 1) (Roy et al., 2020). Other studies highlight the role of dietary polyphenols and flavonoids in modulating DNA methylation and histone acetylation, further demonstrating the impact of nutrition on epigenetic regulation (Abdul et al., 2017).

3.2 Nutrient-sensing pathways

Nutrient-sensing pathways, including mTOR and AMPK, are pivotal in mediating the effects of nutritional status on gene expression. These pathways detect the availability of nutrients and modulate metabolic processes accordingly. The mTOR pathway, for example, is activated by amino acids and regulates protein synthesis and cell growth, while AMPK acts as an energy sensor, promoting catabolic pathways when energy is low (Haro et al., 2019). These pathways are integral to maintaining metabolic homeostasis and are influenced by the availability of nutrients, thereby affecting gene expression patterns in swine.

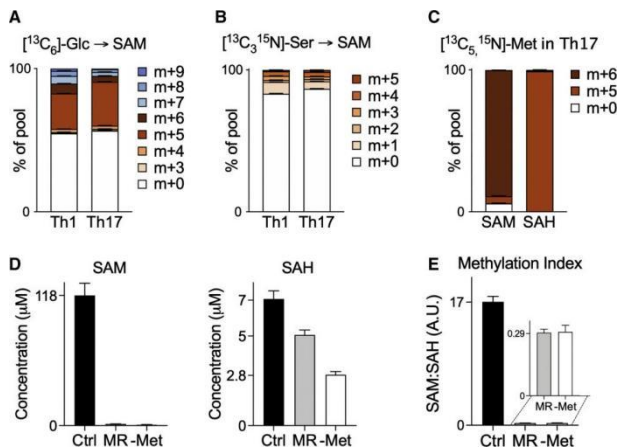


Figure 1 SAM Is derived from methionine in activated T cells (Adopted from Roy et al., 2020)

Note: (A and B) ^{13}C mass isotopomer distribution (MID) in SAM for Th1 and Th17 cells cultured with (A) $^{13}\text{C}_6$ -glucose or (B) $^{13}\text{C}_3^{15}\text{N}$ -serine for 6 h. Data represent the mean \pm SEM for biological triplicates. (C) ^{13}C MID in SAM and SAH for Th17 cells cultured with medium containing $^{13}\text{C}_3^{15}\text{N}$ -methionine for 6 h. Data represent the mean \pm SEM for biological triplicates. (D) Intracellular SAM and SAH levels in activated T cells following 6 h of culture in medium containing high (200 μM , Ctrl), low (3 μM , MR), or no (0 μM , -Met) methionine. Data represent the mean \pm SEM for biological triplicates. (E) Methylation index of T cells treated as in (D). Inset, SAM:SAH ratio for MR and -Met culture conditions (Adopted from Roy et al., 2020)

3.3 Role of transcription factors

Transcription factors such as peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs) are key regulators of gene expression in response to nutritional changes. PPARs are activated by fatty acids and play a significant role in lipid metabolism, influencing the expression of genes involved in fatty acid oxidation and storage. SREBPs, on the other hand, are crucial for cholesterol and lipid biosynthesis, and their activity is modulated by nutrient availability, particularly lipids (Cai et al., 2016). These transcription factors integrate nutritional signals to regulate metabolic pathways, ensuring that gene expression is aligned with the organism's nutritional status.

4 Impacts on Growth, Development, and Health

4.1 Regulation of genes influencing muscle growth and development

Nutritional interventions significantly impact the regulation of genes associated with muscle growth and development in swine. For instance, dietary lysine restriction has been shown to alter the expression of genes in porcine skeletal muscle, affecting protein synthesis and muscle development through transcriptional regulators such as STAT3 and HNF1A (Wang et al., 2019). Similarly, dietary tryptophan influences muscle fiber type transformation, enhancing growth performance and increasing the proportion of fast muscle fibers in weaned piglets (He et al., 2024). Additionally, L-arginine supplementation promotes muscle gain by regulating lipid metabolism genes, favoring lipogenesis in muscle tissue (Tan et al., 2011).

4.2 Effects on immune system gene expression and disease resistance

Nutritional interventions also modulate immune system gene expression, which can enhance disease resistance in swine. The balance of omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) in the diet affects genes related to immune response and inflammation, with an imbalance potentially increasing the risk of inflammatory diseases (Manaig et al., 2023). Furthermore, maternal energy restriction during gestation can alter the expression of immune-related genes in offspring, impacting their stress response and disease resistance (Sanglard et al., 2018). The plasticity of intestinal gene expression in response to nutritional interventions also highlights the potential for dietary strategies to modulate immune functions in piglets (Schokker et al., 2019).

4.3 Influence on genes associated with metabolic health and energy efficiency

Nutritional interventions play a crucial role in regulating genes linked to metabolic health and energy efficiency in swine. For example, dietary protein intake affects the expression of genes involved in lipid metabolism in a

genotype-dependent manner, influencing fat deposition and energy utilization (Liu et al., 2015). L-arginine supplementation has been shown to regulate genes involved in lipid metabolism, promoting lipolysis in adipose tissue and improving the metabolic profile. Additionally, dietary interventions during gestation, such as L-arginine supplementation, can enhance placental growth and fetal survival by modulating genes related to nutrient metabolism and energy efficiency (Li et al., 2022).

5 Advances in Nutritional Genomics for Swine

5.1 Identification of gene-nutrient interactions through transcriptomic studies

The application of RNA sequencing (RNA-Seq) technology has significantly advanced the understanding of gene-nutrient interactions in swine. RNA-Seq allows for comprehensive profiling of gene expression in response to dietary interventions, providing insights into how nutrients affect cellular processes and phenotypic outcomes (Hasan et al., 2019). This technology has been used to study the impact of various dietary components, such as fatty acids, proteins, and bioactive compounds, on gene expression in key metabolic tissues like the liver and muscle (Liao and Hasan, 2020). These studies highlight the potential of transcriptomics to uncover complex nutrient-gene interactions, which are crucial for optimizing swine nutrition and improving production efficiency (Liao et al., 2019).

5.2 Application of nutrigenomics to precision swine nutrition

Nutrigenomics, which examines the effects of nutrients on gene expression, is paving the way for precision nutrition in swine. By understanding the genome-wide influences of nutrition, researchers can tailor diets to enhance growth, health, and production performance (Osorio and Moisés, 2019; Hassan et al., 2022). This approach involves using genomic data to predict how individual animals will respond to specific nutrients, allowing for more targeted and effective feeding strategies. The integration of nutrigenomics into swine nutrition research is expected to lead to more efficient and sustainable production systems by optimizing nutrient utilization and minimizing waste (Bionaz et al., 2015; Abdelrahman et al., 2022).

5.3 Integration of omics technologies for personalized feeding strategies

The integration of various omics technologies, including genomics, transcriptomics, and metabolomics, is essential for developing personalized feeding strategies in swine. These technologies provide a comprehensive view of how nutrients interact with the genome and influence metabolic pathways (Di Renzo et al., 2019; Hashemi et al., 2020). By combining data from different omics approaches, researchers can develop more precise nutritional interventions that consider the genetic and phenotypic variability among swine populations. This holistic approach aims to enhance animal performance and health by aligning dietary formulations with the specific genetic makeup and metabolic needs of individual animals (Ramos-López et al., 2021).

6 Case Study

6.1 Background and context of the selected case study

The selected case study focuses on the impact of dietary prebiotics and arachidonic acid (ARA) on gene expression in piglets experiencing gastrointestinal disturbances. Gastrointestinal (GI) issues are a significant concern in the swine industry due to their economic impact. Nutritional interventions, such as the use of prebiotics and ARA, have been explored to manage inflammation and optimize microbial colonization in the GI tract (Figure 2). The study of He et al. (2019) specifically investigates the differential gene expression in piglets subjected to an acute colitis model induced by dextran sodium sulfate (DSS).

6.2 Nutritional intervention details and observed effects on gene expression

In this study, piglets were divided into four dietary groups: 0.5% ARA, 0.5% ARA with prebiotics (galactooligosaccharide and polydextrose), 2.5% ARA, and 2.5% ARA with prebiotics. The intervention aimed to assess the effects of these diets on gene expression in the context of DSS-induced colitis. The results showed that prebiotic supplementation significantly reduced the number of differentially expressed (DE) genes in piglets with colitis, from 83 to 33, indicating a potential protective effect against inflammation. A total of 133 DE genes were identified, with prebiotics and ARA affecting gene expression differently but without interaction effects. These DE

genes were involved in various signaling pathways, highlighting the role of nutritional interventions in modulating gene expression in response to GI disturbances (He et al., 2019).

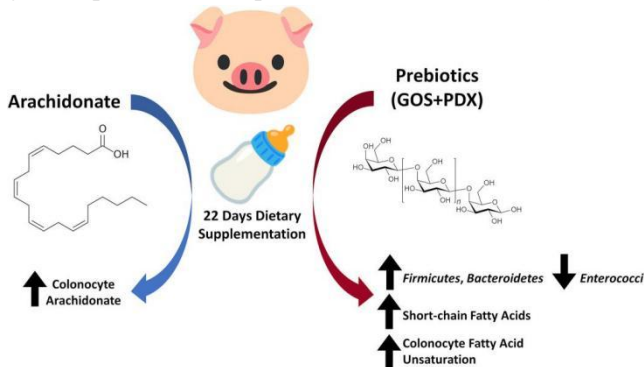


Figure 2 Summary of the effects of formula supplementation with prebiotics and ARA on suckling pigs over 22 d. GOS, galactooligosaccharides; PDX, polydextrose (Adopted from Eudy et al., 2023)

6.3 Implications for broader applications in swine production systems

The findings from this case study have significant implications for swine production systems. The ability of prebiotics and ARA to modulate gene expression and potentially reduce inflammation in piglets suggests that these nutritional interventions could be strategically used to enhance gut health and overall productivity in swine. By optimizing the gut microbiome and reducing the incidence of GI disturbances, producers can improve animal welfare and reduce economic losses associated with health issues. This approach aligns with the broader goal of using nutritional strategies to enhance the resilience and efficiency of swine production systems (Schokker et al., 2019; Qiao et al., 2020).

7 Challenges and Future Directions

7.1 Complexity of gene-nutrient interactions and environmental factors

The regulation of gene expression in response to nutritional interventions in swine is a complex process influenced by numerous factors, including the intricate interactions between genes and nutrients. These interactions are further complicated by environmental factors that can alter gene expression patterns. For instance, the interplay between chromatin structure and transcription factor-DNA interactions is crucial in regulating gene expression, and dietary factors can significantly impact these processes (Bonet and Palou, 2020). Additionally, the non-coding genome plays a vital role in regulating gene-diet interactions, highlighting the need to understand how non-coding RNAs contribute to phenotypic changes in response to dietary manipulation (Law and Holland, 2018). The complexity of these interactions necessitates a comprehensive approach to study the multifaceted nature of gene-nutrient interactions.

7.2 Limitations in current research methodologies

Current research methodologies, such as RNA sequencing (RNA-Seq), have advanced our understanding of transcriptional regulation in response to dietary nutrients. However, these methodologies come with technical challenges and limitations. RNA-Seq, while powerful, requires careful consideration of experiment design, sample collection, and data analysis to avoid inconclusive results (Liao and Hasan, 2020). Moreover, the integration of transcriptomics data from various studies can be challenging due to differences in experimental conditions and data interpretation (Schokker et al., 2019). These limitations highlight the need for standardized practices and improved methodologies to enhance the reliability and reproducibility of research findings in this field.

7.3 Emerging opportunities in technology and multi-omics integration

Emerging technologies and the integration of multi-omics approaches offer promising opportunities to overcome current challenges in studying gene expression regulation in response to nutritional interventions (Li and He, 2024; Zhu and Lin, 2024). RNA-Seq technology, for example, provides a holistic view of intracellular RNA expression and can monitor all gene expressions simultaneously in response to dietary interventions (Hasan et al., 2019; Liao et al., 2019). Additionally, the application of multi-omics technologies, such as proteomics and metabolomics, can

provide a more comprehensive understanding of the molecular mechanisms underlying gene-nutrient interactions. These technologies hold significant potential to uncover new insights and drive advancements in swine nutrition research, ultimately improving animal health and production efficiency.

8 Concluding Remarks

This study highlights the significant impact of nutritional interventions on gene expression in swine, demonstrating the potential for optimizing health and growth through dietary modifications. Various studies have shown that dietary components such as prebiotics, arachidonic acid, lysine, betaine, and probiotics can modulate gene expression in different tissues, including the gastrointestinal tract, liver, muscle, and placenta. For instance, prebiotics and arachidonic acid have been shown to alter gene expression in piglets with colitis, affecting pathways related to inflammation and microbial colonization. Similarly, lysine restriction impacts muscle protein synthesis by influencing transcriptional regulators, while betaine supplementation during gestation affects hepatic lipogenesis through epigenetic mechanisms. Probiotics like *Clostridium butyricum* also modify liver transcriptomic profiles, enhancing immune responses and nutrient metabolism.

Future research should focus on elucidating the precise molecular mechanisms by which different dietary components influence gene expression and metabolic pathways in swine. Longitudinal studies examining the effects of nutritional interventions from gestation through to adulthood could provide insights into the long-term benefits and potential trade-offs of such strategies. Additionally, exploring the interactions between multiple dietary components and their cumulative effects on gene expression could lead to more comprehensive dietary recommendations. Investigating the role of epigenetic modifications and their heritability in response to nutritional interventions could also offer valuable information for breeding programs aimed at improving swine health and productivity.

Optimizing swine nutrition through targeted gene regulation presents a promising avenue for enhancing animal health, growth, and productivity. By understanding the complex interactions between diet and gene expression, it is possible to develop tailored nutritional strategies that support optimal physiological functions. This approach not only benefits the swine industry economically but also contributes to sustainable agricultural practices by improving feed efficiency and reducing the environmental impact of livestock production. Continued research in nutritional genomics will be crucial in unlocking the full potential of dietary interventions in swine.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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