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Unraveling the genetic and epigenetic landscape governing intramuscular fat deposition in rabbits: Insights and implications

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ABSTRACT

Intramuscular fat (IMF) content is a predominant factor recognized to affect rabbit meat quality, directly impacting flavor, juiciness, and consumer preference. Despite its significance, the major interplay of genetic and epigenetic factors regulating IMF in rabbits remains largely unexplored. This review sheds light on this critical knowledge gap, offering valuable insights and future directions. We delve into the potential role of established candidate genes from other livestock (e.g. *PPARγ, FABP4,* and *SCD*) in rabbits, while exploring the identified novel genes of IMF in rabbits. Furthermore, we explored the quantitative trait loci studies in rabbit IMF and genomic selection approaches for improving IMF content in rabbits. Beyond genetics, this review unveils the exciting realm of epigenetic mechanisms modulating IMF deposition. We explored the potential of DNA methylation patterns, histone modifications, and non-coding RNA-mediation as fingerprints for selecting rabbits with desirable IMF levels. Additionally, we explored the possibility of manipulating the epigenetic landscape through nutraceuticals interventions to promote favorable IMF depositions. By comprehensively deciphering the genomic and epigenetic terrain of rabbit intramuscular fat regulation, this study aims to assess the existing knowledge regarding the genetic and epigenetic factors that control the deposition of intramuscular fat in rabbits. By doing so, we identified gaps in the current research, and suggested potential areas for further investigation that would enhance the quality of rabbit meat. This can enable breeders to develop targeted breeding strategies, optimize nutrition, and create innovative interventions to enhance the quality of rabbit meat, meet consumer demands and increase market competitiveness.

1. Introduction

An essential part of the human diet is meat products, and the consumption of meat has significantly increased in the last decade, as reported by Henchion et al. (2021) and Ursachi, Perta-Crisan, and Munteanu (2020). From a nutritional standpoint, meat is considered crucial for optimal bodily growth and the well-being of modern society (You et al., 2022). However, the quality of meat has become a critical focus of research, as it directly impacts consumer health. This poses an ongoing challenge for livestock farmers and meat producers in delivering high-quality meat that has minimal or no adverse health effects on consumers.

Marbling, the presence of fat between the muscle fibers in meat, is an important meat quality trait of major economic relevance that positively influences sensory quality aspects such as flavor, juiciness, and tenderness of meat. This fat cells (intramuscular fat) located in the spaces between muscle fibers is surrounded by connective tissue (Purslow, 2020). It is a predominant factor recognized to affect meat quality, because it enhances the flavor and tenderness of meat (Zhang et al., 2022). In addition to enhancing taste, marbling plays a crucial role in carrying lipid-soluble flavor compounds and contributes to the tenderness of meat by acting as a lubricant between muscle fibers, resulting in meat that is both tender and moist when cooked. Furthermore, it also helps retain moisture during cooking, preventing the meat from becoming dry (Matarneh et al., 2023). Higher marbling scores generally lead to better grading scores in most grading systems. The appearance of marbling can also impact the value of the meat. While most countries in the world, such as Korea, Japan, Australia, and the USA, value marbling highly, certain other countries, particularly in Europe, such as France and Germany, prefer leaner meats (Liu et al.,

2020). Therefore, it is necessary to have a thorough understanding of the factors that affect IMF (marbling) regulation and the mechanisms responsible for its deposition, to enable this balance of leanness and marbling, thereby meeting consumers preferences for meat.

The intramuscular adipocytes, or marbling fat, are typically considered a tissue that matures later. This is because as an animal grows, the rate of fat deposition is higher than the rate of lean muscle deposition (Schumacher et al., 2022). As a result, the concentration of fat within the lean muscle increases later in the animal's life. This trait of higher fat percentage is considered late maturing, but it should not be misunderstood as the actual intramuscular adipocytes or the pool of intramuscular fat maturing late. As observed by Liu et al. (2020), biologically, intramuscular fat itself is not late maturing, but the expression of marbling (percentage of fat) is late maturing. The development of adipocytes between the muscle fibers in the skeletal muscle leads to marbling. These adipocytes are likely to be of the white adipose tissue type. They originate from connective tissue stem cells, which can differentiate into pre-adipocytes when exposed to certain stimuli (Wang et al., 2023). These pre-adipocytes then proceed to adipogenesis. Therefore, the connective tissue of the muscle always has the potential to develop into marbling fat, with this development being controlled by various stimulatory or inhibitory factors. Hence, intramuscular adipogenesis, which refers to the development of fat cells within muscle tissues, plays a crucial role in meat quality and production. Studying the regulatory mechanisms of this process provides insights into improving meat quality, managing intramuscular fat content, and enhancing overall meat production.

Although most researches on improving the quality of intramuscular fat (IMF) in livestock (Li et al., 2023; Zhang et al., 2022; Kang et al., 2020; and Chen et al., 2020), focus on nutritional manipulations, which are believed to produce rapid results, particularly during fattening phases, genetic and epigenetic manipulation could have more sustainable and often irreversible effects on IMF quality. This is because genetic modifications are inherited, and epigenetic changes can be passed on to offspring under certain conditions (Burton and Greer, 2022). It is important to note that while nutritional manipulation allows for some control over IMF deposition through precise nutrient adjustments, individual animal responses can vary. Therefore, targeted genetic and epigenetic manipulation of IMF deposition would be more precise by focusing on specific genes or epigenetic markers, as observed by Li et al. (2020). Although this emerging field shows promising potential for long-term effects, careful evaluations are necessary to thoroughly assess its effects. This understanding will enable us to manipulate marbling and meet consumer requirements.

There are several aspects of rabbit production such as meat, wool and fur (Dorożyńska & Maj, 2021). breeds such as the Angora, American Fuzzy Lop, and Jersey Wooly, have always been used to produce wool. However, since the American Fuzzy Lop and Jersey Wooly are both dwarf breeds, only the much larger Angora breeds such as the English Angora, Satin Angora, giant Angora, and French Angora are used for commercial wool production. Also, a number of rabbit breeds have been developed with the fur trade in mind. Breeds such as the Rex, Satin, and Chinchilla are often raised for their fur. Recently, rabbits have been raised for meat production in a variety of settings around the world. Many local, "rustic", landrace or other heritage type breeds may be used only in a specific geographic area. In contrast to the multitude of breeds and types used in smaller operations, breeds such as the New Zealand and the Californian, along with hybrids of these breeds, are most frequently utilized for meat in commercial rabbitries. Rabbit meat has several advantages over other conventional livestock meats. For example, rabbit meat offers several nutritional advantages over beef, veal and pork. According to Jiang et al. (2020), rabbit meat has lower overall fat content and a more beneficial fatty acid profile. In comparison to pork, beef, and veal, rabbit meat has an average content of 24.1 Omega 6 fatty acids and 5.6 Omega 3 fatty acids, while pork has 14.3 Omega 6 and 6.2 Omega 3, beef has 7.55 Omega 6 and 1.43 Omega 3

and veal has 9.07 Omega 6 and 6.2 Omega 3. Additionally, rabbit meat is rich in lecithin and other unsaturated lipids (Martinez-Alvaro, Blasco, & Hernandez, 2018). The lower fat content of rabbit meat is a primary advantage for consumers who want to manage weight or reduce the risk of cardiovascular disease. It is also a suitable choice for individuals with heart conditions or those aiming to maintain healthy cholesterol levels. The favorable fatty acid profile of rabbit meat, which is high in essential fatty acids, contributes to overall well-being by supporting brain function (Horman et al., 2020), vision (Fu et al., 2021), and reducing inflammation (Yao et al., 2022). Incorporating rabbit meat into the diet can be particularly beneficial for cognitive health, especially in growing children and the elderly. Despite its lower fat content, rabbit meat is an excellent source of high-quality protein (Siddiqui et al., 2023), which is essential for tissue building and repair, immune function, and maintaining muscle mass. This makes it a valuable option for athletes, the elderly, and individuals recovering from illness. Rabbit meat can also be incorporated in weight management plans, due to its lower calorie and fat content, providing satiety without excessive caloric intake. Finally, rabbits are excellent animal models for biomedical and genetic research. While rabbit meat is known for its lean quality, it also has the potential for enhanced intramuscular fat content, a key determinant of taste and tenderness. Compared to other species, rabbit meat has relatively low intramuscular fat content, with bovine muscle at about 3.25 % (Li et al., 2021), lambs at 1.96 %, chicken at 4.92 % (Selim et al., 2021), and rabbit muscle at about 1.63 % (Jiang et al., 2020). Although there has been significant research on marbling in traditional livestock such as cattle, pig, poultry, sheep and goat (Kim et al., 2020; Nguyen et al., 2021), the understanding of marbling processes in rabbits remains relatively unexplored. To unlock this potential, further research is needed to understand the factors that regulate intramuscular fat deposition in rabbits.

This review therefore aims to analyze and assess the existing knowledge regarding the genetic and epigenetic factors that control the deposition of intramuscular fat in rabbits and unravel the genetic and epigenetic landscape governing IMF deposition in rabbits, drawing inference from other species. It explores the current knowledge and advancements in the genetic and epigenetic regulations of IMF in rabbits, providing insights that can inform breeding strategies and enhance rabbit meat quality. By doing so, we will identify any gaps in the current research and suggest potential areas for further investigation that would enhance the quality of rabbit meat. Also, we can develop targeted breeding strategies, optimize nutrition, and create innovative interventions to enhance the quality of rabbit meat. Ultimately, this will enable us to meet consumer demands and increase market competitiveness.

2. Genetic basis of IMF regulation in rabbits

The regulation of marbling is a complicated process influenced by several genetic factors which play significant roles in determining variations observed in IMF content across livestock populations. Understanding the genetic basis of IMF regulation is essential for improving meat quality through selective breeding strategies. Whereas intramuscular adipogenesis, the formation and development of intramuscular fat cells, is well-studied in other species, understanding the specific regulatory elements involved in IMF regulation of rabbits remains an underexplored area. Several genes like *PPARγ, FABP4*, and *SCD*, known for their important roles in fat metabolism and storage in other livestock (Revilla et al., 2018; Liu et al., 2021), could potentially hold similar significance in rabbits. Recently, it was discovered that the zinc-finger protein *Zfp423* plays crucial role in the commitment of progenitor cells to become adipocytes, or fat cells. Its expression causes precursor cells to commit to becoming pre-adipocytes, and this in turn causes *PPARγ* (peroxisome proliferator-activated receptor γ) to be expressed (Rauch & Mandrup, 2021). In bovine stromal vascular cells, *Zfp423* has a function in controlling adipogenic commitment (dela Cruz, Pacunla, &

Hwang, 2022). Additionally, using genome-wide association studies (GWAS) and quantitative trait loci (QTL) mapping, it was revealed that numerous genomic areas and single nucleotide polymorphisms (SNPs) are linked to IMF variation across various livestock species (Buss et al., 2023; Gao et al., 2021). This highlights the complex genetic architecture, meaning multiple genes and their interactions contribute to IMF regulation. These discoveries in other species, could possibly hold for rabbits.

2.1. Candidate genes influencing IMF regulation in rabbits

Candidate genes are genes hypothesized to be associated with a specific trait, such as a disease, physical characteristic, or behavior (Paredes-Sánchez et al., 2020). This association can be based on the gene's known biological function, its location within the genome, or its similarity to genes previously connected to the desired characteristics. As stated by David (2021), the selection of candidate genes relies heavily on existing scientific knowledge and researchers often focus on genes known to be involved in pathways that are potentially relevant to the trait being investigated. Candidate gene approach is an effective way to research how genes and phenotypes are related, and provides information that are valuable for genetic improvement using marker-assisted selection. Whereas, literature on candidate genes associated with IMF deposition in rabbits presents a unique challenge due to the limited research available in this area, studies in other species, such as pigs and mice, have identified genes like *PPARγ, FABP4, SCD,* and *FTO* as key players in IMF regulation. Liu et al. (2021) found an association between *PPARγ* gene, adipogenesis and lipid metabolism, which impact IMF content. Other genes implicated in the creation, storage, and metabolism of fat, including *FABP4* and *SCD*, also contribute to IMF deposition (Luo et al., 2022). As earlier observed by Luo et al. (2022), the intramuscular fat content of mammals increases with age, hence, the expression level of the gene that regulate IMF might also increase with age. Luo et al. (2023) confirmed this concept with Rex rabbits, where they found that the expression level of the *APMAP* gene (IMF regulatory gene) increases with age. The *APMAP* gene expression is significantly proportional (p < 0.01) with intramuscular fat, which implies that a high expression level of the *APMAP* gene amounted for a high intramuscular fat content (Luo et al., 2023). Another important gene is the *fat mass and obesity-associated* (*FTO)* gene. This gene has been confirmed as a candidate gene association with IMF and plays a crucial role in postnatal growth (Safaa et al., 2023).

Furthermore, several studies reported association between polymorphism in candidate genes and meat quality traits in rabbits (see Table 1 and Fig. 2). These polymorphisms have been linked to IMF. For example, Safaa et al. (2023) confirmed that *FTO* mutation was associated with cooking loss and intramuscular fat weight, whereas the insulin receptor substrate-1 (*IRS-1*) SNP was significantly associated with drip loss and intramuscular fat in Baladi rabbits. In addition, the pathways of *FTO* targets many other genes which have direct effect on intramuscular fat (Luo et al., 2023). Therefore, the FTO gene can be used as a candidate gene for IMF content in rabbits. Although the presence of the *FTO* gene in rabbit made them susceptible to obesity and also affected their growth, particularly postnatal growth (Safaa et al., 2023), the mechanism behind this remains unknown and requires validations. Similarly, the SNP of the *myf5* genes with GG-AA-AA genotype has been associated with redness of the longissimus dorci and intramuscular fat in biceps femoris of Ira rabbits (Bozhilova-Sakova et al., 2022). This indicates that the genotype GG-AA-AA could be used as a genetic marker to increase intramuscular fat in biceps femoris of rabbits. *POU1F1* (also named *PIT-1*), the first pituitary-specific transcription factor to be identified in the human and mouse, as a member of the POU-domain family gene*,* is a positive regulator for growth hormone (GH), prolactin (PRL) and thyroid stimulating hormone β (TSHβ), by binding to target DNA promoters as a dimer in mammalian animals (Chaker & Peeters, 2022). The mutations of *POU1F1* gene were shown to be associated with IMF in Tianfu

Table 1
Candidate genes that regulate IMF in Rabbits.

Genes	Functions	Impact on IMF	Breed	References
FTO	Regulates adipocyte proliferation, and differentiation. Its pathways target many other genes which have direct effect on intramuscular fat.	promotes adipocyte differentiation	Baladi rabbits	(Safaa et al., 2023)
APMAP	A regulatory factor related to adipocyte differentiation and causes insulin resistance.	Its content is directly proportional the intramuscular fat quantity in cells	Rex rabbits	(Luo et al., 2023)
IRS-1	The SNP regulates adipocyte proliferation, and differentiation.	significantly associated with intramuscular	Ira rabbits	(Safaa et al., 2023)
POU1F1	Positive regulator for growth hormone (GH), prolactin (PRL) and thyroid stimulating hormone β (TSHβ) by binding to target DNA promoters as a dimer in mammalian animals.	Mutations of *pouf1* regulates IMF	Tianfu black rabbits	(Helal et al., 2022)
MyF5	Could promote cell proliferation and increase in the number of mononuclear adipocytes	The SNPs; CC-TT-GG genotype could increase redness in longissimus dorsi and biceps femoris TT-AA-AA genotype could be used as a genetic marker for increasing yellowness and IMF in biceps femoris	Ira rabbits	(Bozhilova-Sakova et al., 2022)
LEP	Regulates energy balance	Presence of the SNPs, g.16081633 T>C, CC for g.16081420C>T, and GG genotype for g.16079636C>, increases IMF deposition	New Zealand White (NZW) × Belgian Giant Grey (BGG)	Luo et al., 2022

rabbits (Bozhilova-Sakova et al., 2022). Thus, *SNP of POU1F1* could be a potential genetic factor used in marker-assisted selection for intramuscular fat traits in rabbits. Again, the polymorphisms of *leptin, LEP* (a hormone synthesized and secreted primarily in adipose cells that help to regulate energy balance) are associated with several meat production traits (Picó et al., 2022), although their effects on IMF is still doubtful. However, Luo et al. (2022) found an associations between IMF value and g.16081633T>C, g.16081420C>T, and g.16079636C>G polymorphism in *LEP* gene in crossbreed rabbits, thus, presenting *LEP* gene as a candidate gene for IMF in rabbits.

Numerous studies have previously implicated some of the above candidate genes and their SNPs in IMF regulation of other species (Table 2). For instance, a study conducted in vitro found that overexpression of *FTO* induces adipogenesis in 3T3-L1 preadipocytes, porcine intramuscular preadipocytes, and mouse embryonic fibroblasts (MEFs) (Wu et al., 2019). In addition, overexpression of *FTO* in mice resulted in an obese phenotype (Huang et al., 2023), whereas removal of both exons 2 and 3 of the *FTO* gene from mice resulted in a considerable reduction in the amount of adipose tissue (Chauhdary et al., 2021). In
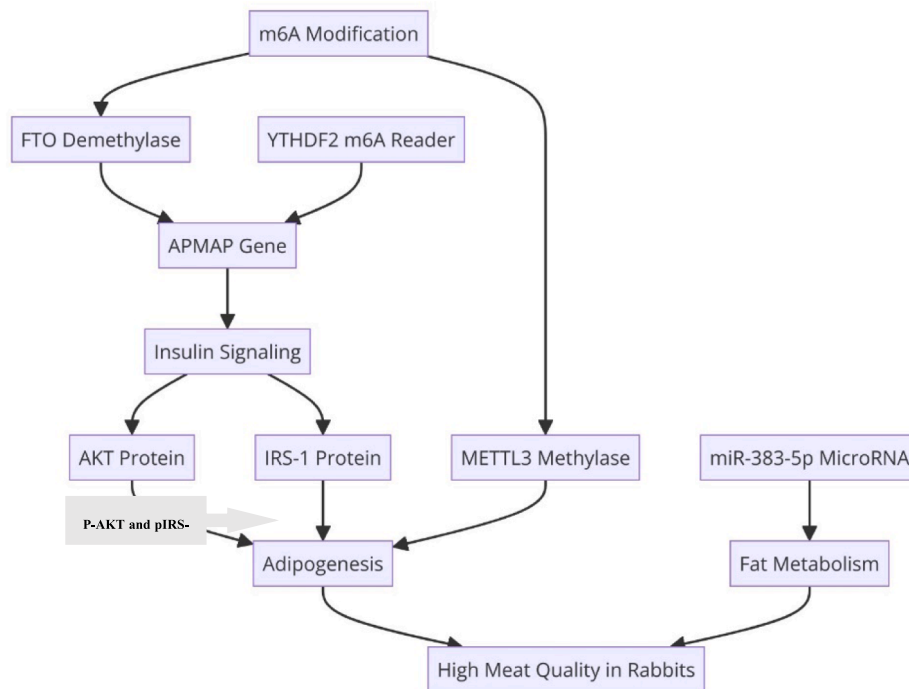
Fig. 1. Regulatory mechanism of intramuscular fat (IMF) in rabbits mediated by m6A RNA modification: The above process involves key proteins such as FTO (a demethylase), YTHDF2 (an m6A reader), and METTL3 (a methylase). The FTO protein regulates the expression of the APMAP gene, which is crucial for adipogenesis (fat cell differentiation) and is also influenced by YTHDF2. The APMAP gene impacts insulin signaling, involving AKT and IRS-1 proteins, which further drive adipogenesis. The METTL3 protein negatively regulates adipogenesis. Additionally, miR-383-5p influences fat metabolism, contributing to the overall fat content and quality of meat in rabbits. The diagram connects these elements, showing how they interact to regulate IMF, ultimately affecting meat quality.
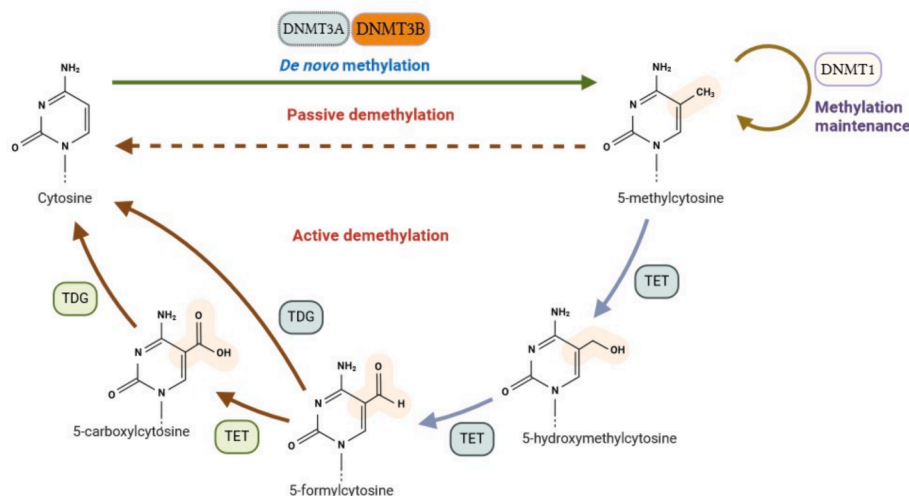

Fig. 2. DNA Methylation Pathway: This figure illustrates the main enzymes and processes involved in DNA methylation and demethylation. DNA methyltransferases (DNMTs), such as DNMT3A, DNMT3B, and DNMT1, catalyze the addition of a methyl group to cytosine, resulting in the formation of 5-methylcytosine. Demethylation can occur through passive or active mechanisms. Passive demethylation occurs when methylated cytosines are diluted during DNA replication if DNMT1 does not perform maintenance methylation. Active demethylation involves the oxidation of 5-methylcytosine to different intermediate forms (5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine) by TET enzymes, followed by base excision repair facilitated by TDG.

pigs, a study by Wang et al. (2018) revealed that the protein expression level of *FTO* in the white adipose tissue was considerably greater in obese pigs than in lean pigs. The adipocyte plasma membrane associated protein (*APMAP*) is one of the genes that is targeted by the *FTO* gene pathway, which works to regulate many other genes, and it's suggested to be the main determinant of IMF content (Table 2) (Safaa et al., 2023). *POU1F1*, linked to growth traits, weaned weight, size of litter, and milk production, in sheep and goats (Jaffar et al., 2019).The established functions of these genes in fat metabolism and adipogenesis suggest they could potentially hold similar significance in rabbits.

Table 2
Candidate genes that regulate IMF in other livestock.

Genes	Functions	Impact on IMF	Species	References
Acyl-CoA thioesterase 9 (*ACOT9),* cholesteryl ester transfer protein (*CETP), LPIN1,* diacylglycerol O-acyltrasferase 2 (*DGAT2),* retinol binding protein 7 (*RBP7),* fructose-bisphosphatase 1 (*FBP1),* phosphorylase kinase regulatory subunit α 1 (*PHKA1),* angiopoietin-like 4 (ANGPTL4), CD36, fatty acid transport proteins 1 and 4 (FATP1, FATP4), and perilipin 2 (PLIN2), *THRA, PEA15L1, SCFD1*	Associated with energy metabolism, IMF percentage, cholesterol content, Phospholipid content, and involved in the PPAR signaling pathway.	Regulate IMF deposition, although the mechanisms are not yet fully elucidated.	poultry	(Cao et al., 2023; Kang et al., 2021; Li et al., 2020)
SFRP5	Suppresses oxidative metabolism and promotes adipocyte development during adipogenesis via blocking Wnt signaling.	Increase the vulnerability to diet-induced obesity by promoting adipocyte differentiation and blocking the interaction between Wnt ligands and frizzled receptors.	Pig, Mouse, cattle, poultry	(Cao et al., 2023; Valdés-Hernández et al., 2024)
KLF9	Transcription factor regulating gene expression	Reduces the amount of IMF via inhibiting gene expression (*PPARG, CEBPA* and *AP2*) required for preadipocytes to mature into fat cells.	poultry	(Li et al., 2019; Raza et al., 2022)
PPARα & PPARγ	Regulate the development of fibroblast-like preadipocytes into mature adipocytes.	Whereas, PPARα regulates genes involved in lipid metabolism, PPARγ regulates adipogenesis and glucose homeostasis. However, both were associated with higher IMF content.	Pig	(Malgwi et al., 2022)
FABP3 (H-FABP)	Nuclear hormone receptors, plays a key role in the preAD differentiation process	Transports fatty acids within cells. Strong genetic marker for IMF deposition.	Pigs	(Jiang et al., 2022)
FABP4 (A-FABP)	Adipocyte fatty-acid-binding protein	Transports fatty acids within adipocytes, and might influence IMF content.	Sheep	(Yan et al., 2023)
SCD	Stearoyl-CoA desaturase gene	Contains an enzyme that changes saturated fats (SFAs) into monounsaturated fats (MUFAs). Increased expression linked to higher IMF content.	pigs	(El Nagar et al., 2023; Malgwi et al., 2022)
LEP (LEPR)	Leptin (hormone) and its receptor	Regulates food intake and energy homeostasis, and also increased expression associated with higher fat deposition and IMF content.	Poultry	(Gai et al., 2023)
ACACA	Marker for IMF	Regulates fatty acid synthesis. Mutations in this gene may influence IMF content in some breeds.	Yak, pig	(Wang et al., 2021)
FASN	Fatty acid synthase	Encodes an enzyme for fatty acid synthesis. May be associated with IMF content, but effects vary across breeds.	Chicken	(Cui et al., 2023)
MSTN (GDF8)	Myostatin or growth differentiation factor 8	Reduces fat metabolism. Limited evidence on its direct role in IMF, but mutations may affect muscle growth and fat deposition.	Cattle, Pigs	(Ren et al., 2020; Tan & Jiang, 2024)
SREBP-1 (SREBP-1c)	Possesses the ability to trigger the transcription of genes that code for acetyl-CoA, carboxylase (ACC) and fatty acid synthase (FAS) enzymes	Regulates gene transcription for muscle fat deposition. Effects on IMF content may vary by breed.	Pigs	(Tan et al., 2022)

Finally, it is worthy of note that several genes that regulate fatty acid compositions have also been shown to affect intramuscular fat deposition. For instance, the expression of the *PCK2* gene (phosphoenolpyruvate carboxykinase 2), which participates in the gluconeogenesis metabolic pathway, was found to be significantly correlated with the content of polyunsaturated fatty acids (PUFAs) that impact the oxidative sensitivity of meat (Du et al., 2022). Its overexpression led to increased gluconeogenesis and re-esterification of free fatty acids (Duś-Żuchowska, 2024). *PCK2* gene contains a repetitive sequence with the AGGTCA motif and can bind to peroxisome proliferator-activated receptor gamma (*PPARγ*), which plays a crucial role in the regulation of adipogenesis (Monroy-Ramirez et al., 2021). Based on the results, Luo et al. (2022) suggested that *PCK2* may also be a candidate for fat deposition. Furthermore, Hudson et al. (2020) found a positive correlation between the expression of *PCK2* and the content of IMF, confirming its involvement in IMF regulation. Future research efforts should focus on identifying and validating rabbit-specific candidate genes for IMF deposition, potentially by leveraging the knowledge gained from other species and tailoring the search to rabbit biology.

2.2. Quantitative trait loci (QTL) regulating intramuscular fat (IMF) in rabbits

Analysis of quantitative trait loci (QTL) is a statistical technique that establishes a connection between phenotypic data (measurements of traits) and genotypic data (often molecular markers) to provide an explanation for the genetic basis of variation in traits. The method has been used to identify regions in the genome that are associated with IMF content (Liu et al., 2021; Silva-Vignato et al., 2022) Most of these specific QTL regions contain genes related to adipogenesis and metabolism of lipids, providing important insights on the genetic control of IMF deposition.

Although the genome of rabbits has been sequenced (https://www.esembl.org/Oryctolagus_cuniculus/ (Ensembl 73, OryCun 2.0), unlike several other livestock species, the genomic resources are very few. Several genomic regions (chromosomal positions) have been identified to harbor specific genes associated with IMF deposition, as shown in Table 3. The genomic regions, 121.0–121.9 in chromosome 1 (OCU1), 25.0–26.9 in OCU3, 12.0–12.5 in OCU9 and 5.0–5.6 in OCU10, were found as regions associated with intramuscular fat deposition using the single marker regressions (Laghouaouta et al., 2020). These regions contain genes related to lipid metabolism, lipid binding, transportation, localization, adipose cell activity, and lipid metabolic activities

Table 3
Quantitative trait loci studies in rabbit IMF.

Chromosome position	Genomic region	Gene(s) present	Function of gene	author
1	121.0–121.9	MTMR2	Involved in lipid metabolic activity and regulates IMF	(Laghouaouta et al., 2020)
		FGFI	Candidate gene for IMF in chicken	
3	25.0–26.9	MR3C1	Lipid metabolism in pigs	
9	12.0–12.5	PPARG	Adipocyte differentiation	
10	5–5.6	IFGB8	Related to lipid metabolic process	
1		BMMR	Functions related to lipid binding, transportation and localization	(Sosa-Madrid et al., 2020)
8		APOLDI		
3		CUG00000027270	Metal binding	

(*MTMR2, FGF1, MR3C1, PPARG,* and *IFGB8*). Additionally, corresponding genomic regions on rabbit chromosomes OCU1, OCU8, and OCU13 were found as genomic regions associated with intramuscular fat deposition using the single marker regressions with data adjusted for genomic relatedness, and a Bayesian multiple marker regression (Sosa-Madrid et al., 2020). Most of these genomic regions have been found to contain important candidates' genes related to lipid metabolism and IMF. For instance, using the Bayes B technique and genome-wide association study (GWAS), Laghouaouta et al. (2020) studied the genomic regions associated with intramuscular fatty acid composition in rabbits. They observed the genomic regions OCU1 and OCU18, to be linked with intramuscular fatty acids (Table 3). Therefore, there is a huge research gap in this area to study the deposition mechanisms of IMF in rabbits.

3. Epigenetic regulation of IMF in rabbits

"Epigenetics" is the word that is used to describe change in gene expression (Al Aboud et al., 2023). It describes the process by which variations in gene expression can be transmitted from one cell cycle to another without alterations to the DNA sequence itself. These changes are brought about by chemical modifications to the DNA molecule itself, known as DNA methylation, or to the proteins that package DNA, known as histone modifications (Lee et al., 2020). These chemical modifications, also known as epigenetic marks, function as molecular switches that determine how tightly DNA is wound around histones, which, in turn, affects the accessibility of genes to the cellular machinery

responsible for gene expression, or transcription (Carter & Zhao, 2021). The key mechanisms of epigenetics are the DNA methylation, the histone modification and the non-coding RNAs (Kiselev et al., 2021).

Like other mammals, epigenetic modifications of rabbit genes can regulate IMF deposition. These changes are of critical importance in controlling IMF deposition in rabbits as observed by Dehghanian Reyhan et al. (2023) and Ran et al. (2023). Understanding the complex nature of these molecular mechanisms is essential in comprehending the cellular mechanisms that are responsible for controlling the deposition of IMF (Ran et al., 2023; Yakovlev, 2018). To gain this understanding, it is necessary to explore a discussion of the ways in which these epigenetic modifications interact with gene networks. This exploration involves studying how genetic and environmental factors influence these modifications, as well as identifying the specific genes and genomic regions that undergo epigenetic changes as described by Ibeagha-Awemu & Ying, (2021) (see Fig. 4). To map and characterize these epigenetic alterations in the rabbit genome, it is essential to make use of advanced techniques such as high-throughput sequencing and chromatin immunoprecipitation (ChIP), particularly those related to IMF genes. Thorough investigations using these techniques are crucial for unraveling the epigenetic regulation of IMF and its potential implications in rabbit production (Powell et al., 2023). Whereas, methyl groups are added to specific DNA regions, often silencing gene expression, demethylation can activate genes. However, chemical modifications on histone proteins, the spools around which DNA is wrapped, affect how tightly DNA is packaged. This tightness influences gene accessibility. Studies like
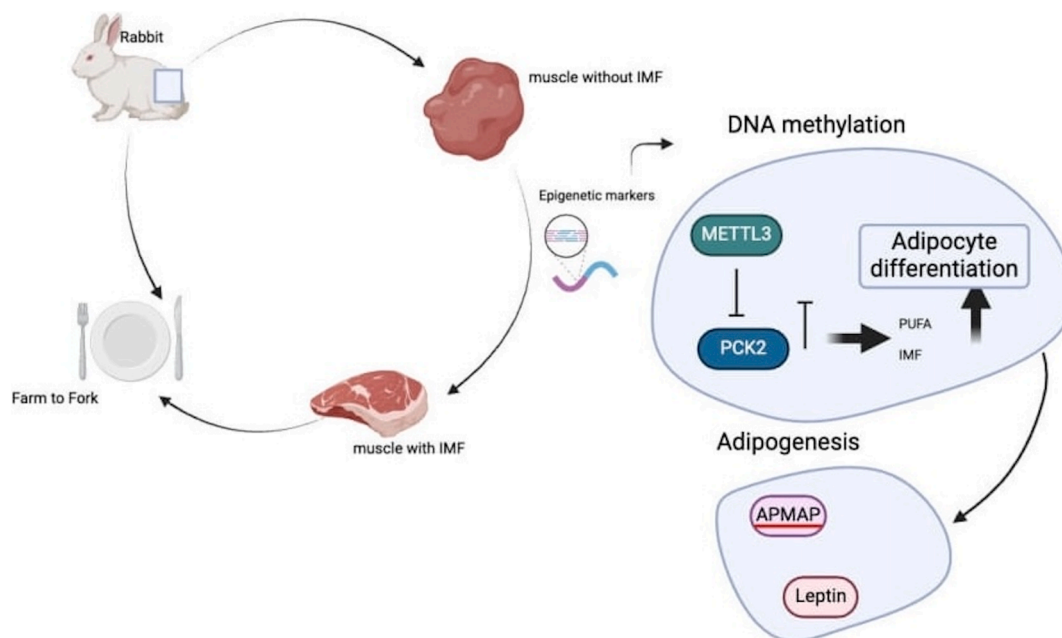

Fig. 3. Advances in Rabbit Intramuscular Fat through epigenetics enhancers and modifiers: This depicts a conceptual framework that outlines the complex process of methylation of genes that regulate the accumulation of intramuscular fat (IMF) in rabbits. It highlights the significance of specific genes and epigenetic modifications (methylation) in the adipogenesis process.
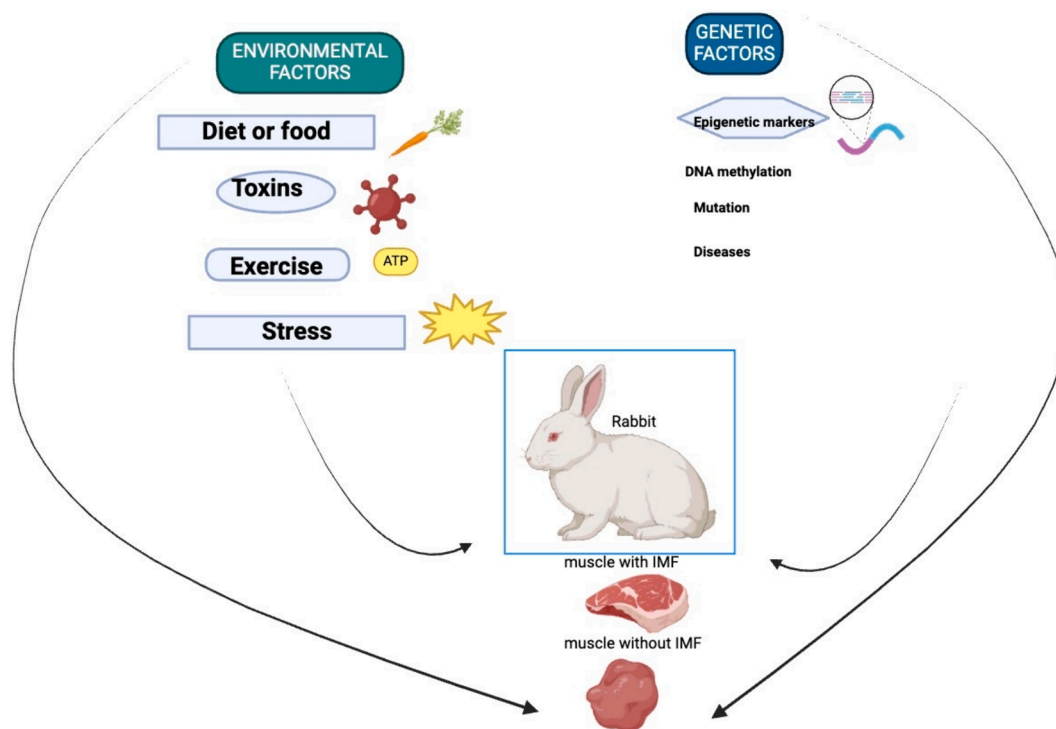
Fig. 4. Complex interplay between environmental and genetic factors influencing intramuscular fat (IMF) deposition in rabbit muscle: This figure highlights the potential interactions between environmental factors (diet, toxins, exercise, stress) and genetic factors (epigenetic markers, DNA methylation, mutations) in regulating the content of IMF in rabbit muscle. Environmental factors can impact IMF through various mechanisms, including changes in energy metabolism (ATP), the induction of stress responses, or exposure to toxins. Genetic factors, such as epigenetic modifications and DNA mutations, can directly affect the expression of genes related to lipid metabolism and muscle development. The interplay between these factors ultimately determines whether IMF is present or absent in the muscle tissue.

those by Li et al. (2021) have identified genes regulated by DNA methylation in rabbit skeletal muscle, potentially influencing IMF content. Furthermore, Wang et al. (2023) explored histone modifications in rabbit muscle and adipose tissue, providing insights into potential regulatory pathways. Epigenetics offers a promising approach for manipulating intramuscular fat deposition in livestock.

Although research on epigenetic targets specifically for rabbit IMF remains limited, researchers are actively pinpointing specific epigenetic targets in rabbits. A typical example is the N6-methyladenosine (m6A), which is the most prevalent internal mRNA modification in eukaryotes. The M6A modification has been found to play an important role in the epigenetic regulation of transcription and cell function. Luo et al. (2023) opined that the main factors responsible for m6A modification are demethylases (FTO), methylase, and methylation recognition enzyme (YTHDF2), and explored the mechanism by which m6A modification regulates IMF in rabbits (see Fig. 1). Furthermore, the gene METTL3 has been found to negatively affect fat cell differentiation, suggesting its potential influence on the amount of intramuscular fat in rabbits (Luo et al., 2022). Also, MicroRNAs (miRNAs), small regulatory RNAs that can silence gene expression, like miR-383-5p, have been linked to fat metabolism (Zhong, Tang, & Kai, 2020). Exploring the roles of these regulatory elements in rabbit IMF deposition is an ongoing area of research. However, studies in other species have identified potential avenues for exploration. For instance, genes like METTL3, has been shown to negatively affect fat cell differentiation in pigs (Cao et al., 2021). Similarly, microRNAs, are known to be regulators of fat deposition during development in chickens (Xu et al., 2020), and they play a crucial role in controlling gene expression and potentially affecting development (Wallace et al., 2020). This warrants investigation of microRNA in the context of rabbit IMF. Surprisingly, through miRNA sequencing and bioinformatics analysis, microRNAs have been discovered to be essential in regulating fat deposition during the growth and development of rabbits, after profiling the perennial adipose at various

post-birth stages (Wang & Ibeagha-Awemu, 2020).

Research has shown that maternal genetic effects can also affect traits such as intramuscular fat and its fatty acid composition in rabbits by 8–22 % (Zubiri-Gaitán et al., 2022). The low adipose tissue deposition in rabbits, which are economically important agricultural animals (Wang et al., 2020), highlights the potential for further engineering of epigenetic markers to increase intramuscular fat deposition, tenderness, juiciness, and marbling density. *APMAP* (Anti-Adipocyte plasma membrane-associated protein), a single transmembrane aryl esterase, plays a crucial role in adipogenesis. Rex rabbit meat with higher *APMAP* content exhibits better meat quality traits than other counterparts (Luo et al., 2022). Further understanding of how epigenetic modifications like DNA methylation and microRNAs influence IMF deposition in established models like pigs and chickens can provide valuable insights for future research on epigenetic manipulation of rabbit IMF. This knowledge can then be used to develop strategies for improving meat quality traits like marbling and juiciness in rabbits. Understanding these epigenetic targets paves the way for potential manipulation strategies, such as dietary interventions and nutraceuticals. Their potential application in rabbits to enhance IMF is an exciting area of exploration. Furthermore, genome editing tools, like CRISPR-Cas9, while ethically complex, could theoretically target specific DNA methylation sites or alter histone modifications to promote optimal IMF levels. However, extensive research and safety evaluations would be necessary before such applications could be considered. Findings from other mammals may not translate directly to rabbits, necessitating species-specific research.

3.1. DNA methylation in rabbits

DNA methylation involves the addition of a methyl group to the C5 position of cytosine, to produce 5-methylcytosine (Kumar, Chinnusamy, & Mohapatra, 2018). This process plays a crucial role in regulating gene

expression, by attracting proteins that inhibit gene activity or by inhibiting transcription factors from binding to DNA (refer to Fig. 2). As a result of its connection to chromosomal structural changes, embryonic development, and the expression of imprinted genes, DNA methylation is an essential epigenetic marker which can cause the development of certain diseases such as X chromosome inactivation and DNA unwinding (Cabrera Zapata et al., 2022). DNA methylation plays a very important role in maintaining normal cellular function in plants and animals such as, regulation of gene expression (Dhar et al., 2021; Sun et al., 2022), genetic imprinting (SanMiguel & Bartolomei, 2018), development of embryo (Dahlet et al., 2020), and formation of tumor (Wang et al., 2018). Altered patterns of DNA methylation can change gene expression, resulting in numerous phenotypes that impact productivity and susceptibility to disease (Hawe et al., 2022). To achieve optimal mammalian development, a balanced expression of genes inherited from both parents is necessary. Genomic imprinting results in different gene expression based on whether they are inherited from the mother or father. Unlike maternally expressed genes, paternally imprinted genes are entirely silent on the maternally transmitted chromosome (Wyss, Song, & Bina, 2022). DNA methylation is known to repress genes and promote chromatin condensation, when controlling how imprinted genes are expressed (Powell et al., 2023). This can result in a reduction in the accessibility of DNA to transcriptional control.

DNA methylation is an important factor in determining the accumulation of IMF in rabbits, directly or indirectly; it influences the expression of genes involved in the development of IMF as an epigenetic regulator, or controls the transition from stem cells to adipocytes, which in turn affects adipogenesis and the rate of fat storage in skeletal muscle (Zhang et al., 2023). Genes involved in hormone control, lipid metabolism, and sensitivity to environmental and nutritional factors can also be impacted through DNA methylation process. This epigenetic system has impacts on breeding and enhancing meat quality as it is possible to create breeding programs that produce rabbits with better meat quality if certain patterns of DNA methylation associated with targeted IMF levels are inherited (de Souza Pinhel et al., 2023; Khan, Li, & Raza, 2023; Zhang et al., 2023). DNA methylation is essential for IMF deposition in meat rabbits, as illustrated in Fig. 3. For example, the DNMT family of DNA methyltransferases has been implicated in intramuscular adipogenesis. DNMT1 primarily functions to maintain methylation (Ren, Gao, & Song, 2018), It has been demonstrated that DNMT3A has the ability to suppress the development of pig intramuscular preadipocytes by modifying the levels of methylation of p21 and PPARγ (Malgwi et al., 2022; Xie et al., 2022). Furthermore, in most cases, DNMT3A/3B are involved in the process of de novo DNA methylation (Andrews et al., 2023). In a separate study, Zhang et al., (2020) found that the levels of DNA methyltransferases, DNMT1, DNMT3A/3B, and TET1/2/3 were considerably down-regulated during the process of intramuscular adipocyte differentiation in chickens, which gives rise to the possibility that whole-genome DNA demethylation takes place during this process. Similarly, during the development of chickens, DNA methylation was found to regulate chicken PPARG and CEBPA, whereas, MBD4 hinders the formation of preadipocytes in pigs via altering the DNA methylation levels of adipogenic genes (Zhang et al., 2020). Meanwhile, the pADRP gene's expression in pigs is controlled in part by promoter methylation (Zhao et al., 2020). Generally speaking, it is considered that the methylation of DNA in the promoter region is responsible for inhibiting gene expression (Bommarito & Fry, 2019). Additionally, Zhang et al. (2020) observed that after the adipogenic differentiation, the DNA methylation level of the COL6A1 promoter was decreased, while mRNA levels were increased. Furthermore, they observed that the methylation inhibitor, 5-AZA-dC, promoted the differentiation of intramuscular adipocytes in chickens by increasing the expression of major adipogenic factors, such as PPARG and CEBPA. Using the function loss and gain experiment, they also found out that DNA methylation regulates the differentiation of chicken intramuscular adipocytes by affecting the expression of ECM-related genes, including COL6A1.

While research on DNA methylation and its role in IMF deposition in rabbits remains limited, most studies on DNA methylation on rabbit fat deposition have focused on subcutaneous and perineal fats. One prevalent form of methylation modification that has been found to play an important role in adipose-related gene regulation in rabbits is N6-methyladenosine (m6A) (Fig. 1). This modification regulates various physiological processes, such as the deposition of fat, immunity level, reproduction and others. N6-methyladenosine, or m6A, is the most common internal alteration in messenger RNAs from eukaryotic organisms and is located on the sixth nitrogen atom of RNA adenylate (You et al., 2023). A set of methyltransferase proteins, which includes *METTL3, METTL14*, and *Wilms tumor 1-associated protein (WTAP)*, is responsible for m6A installation. In contrast, FTO (fat mass and obesity-associated protein) is responsible for m6A demethylase activity and m6A elimination (Yang et al., 2018). The FTO protein, was found as a regulator of adipogenesis through the modulation of mitotic clonal expansion (Wu and Wang, 2021). Initially, through the process of mRNA splicing, it was proposed that m6A controls adipogenesis. Recently N6-methyladenosine has been reported in rabbit adipogenesis by several authors. For instance, using MeRIP-Seq technology, Luo et al. (2023) revealed that rabbit mRNA m6A sites are primarily enriched around stop codons, CDS, and 3′UTRs. They reported several important lipogenic genes that are regulated by N6-methyladenosine. These include *ABCA1, ADRB1, ADAMTS18, FABP3, COL6A5, FAM13A, MYOZ2, EGR2, SOX9, IRX5, PRKAG3*, and *GLI2*. These genes showed variations in both m6A methylation and mRNA expression. Multiple signaling pathways are responsible for the regulation of fat deposition by M6A. These pathways include the MAPK signaling pathway (Jang, Heras, & Lee, 2022), Hippo signaling pathway (Wang et al., 2022), Notch signaling pathway (Yu et al., 2022), Wnt signaling pathway (Zhang et al., 2021), mTOR signaling pathway (Azzam, Alsafar, & Sajini, 2022), AMPK signaling pathway (Yu et al., 2023), cAMP signaling pathway (Yang et al., 2023), the Adipocytokine signaling pathway, the regulation of lipolysis in adipocytes, the metabolism of fatty acids, in addition to the routes linked to non-alcoholic fatty liver disease. According to the findings, m6A is responsible for regulating fat deposition through a variety of different signaling pathways. *METTL14* is a protein that plays a significant part in the accumulation of fat in rabbits (Luo et al., 2022). As a result of its knockdown, alterations occurred in the development of adipocytes, as demonstrated by malfunctioning gene regulation and impaired lipid synthesis (Zhang et al., 2020). Through modulating methylases and regulating genes linked with intramuscular fat infiltration, m6A can modulate the amount of fat that is deposited inside the muscle. It has been discovered that the majority of methylases undergo modification during fat deposition. Luo et al. (2022) observed methylases *METTL14, ZC3H13, YTHDC1, HNRNPA2B1*, and *YTHDC2* in the regulation of adipose tissue expression.

Since DNA methyltransferases (DNMTs) and their role in intramuscular adipocyte differentiation have been studied in other species like pigs and chickens, it suggests that they could be a significant factor for rabbit IMF regulation. However, there are limited studies on the DNA methylation of genes regulating intramuscular fat (IMF) in animals. Hence, understanding how DNA methylation patterns influence rabbit IMF deposition requires further investigation. Future research should focus on identifying specific DNA methylation patterns associated with IMF content in rabbits. By leveraging knowledge from other species and tailoring studies to rabbit biology, we can gain valuable insights into the epigenetic regulation of rabbit IMF.

3.2. Non-coding RNA in IMF regulation

Non-coding RNAs, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), provide another degree of complexity to the epigenetic control of intramuscular fat. miRNAs play a role in post-transcriptional regulation by attaching to messenger RNA (mRNA) and regulating its breakdown or translation into protein. Specific miRNAs

have been shown to target genes involved in adipogenesis and influence IMF content in many livestock species. For example, Huang et al. (2022) identified miRNAs that targeted PPARγ, potentially acting as negative regulators of IMF deposition in chickens. Conversely, Ma et al. (2023) found that specific lncRNAs could promote adipogenesis and IMF accumulation in cattle. According to Tan and Jiang (2024), researchers are actively investigating how epigenetic modifications regulate genes involved in the development of fat cells (adipogenesis) and the synthesis of fatty acids (lipogenesis) within muscle cells, in the study of intramuscular fat (IMF) deposition. Research has shown that the activity of important genes, such as PPARγ, a master regulator of adipocyte development, can be affected by DNA methylation patterns and histone modifications (Małodobra-Mazur et al., 2021). However, till date, no research has elucidated the influence of non-coding RNAs on IMF deposition in rabbits. Several studies on this field have concentrated on the conventional meat animals such as cattle, chicken, pigs, sheep and goat. Thus, creating a huge research gap for future studies. Through the identification and understanding of these particular epigenetic targets, researchers will get a more profound comprehension of the intricate mechanisms that regulate IMF deposition in rabbits. Understanding the intricate interplay between these non-coding RNAs and their target genes is crucial for developing miRNA mimics or inhibitors as potential therapeutic tools to modulate IMF content.

4. Epigenetic regulators of IMF and their potential as therapeutic targets

Epigenetic pathways play a significant part in the process of orchestrating the deposition of IMF. Through the process of deciphering the complex relationship that exists between DNA methylation, histone modifications, and non-coding RNAs, researchers are leading the way toward the development of innovative treatment approaches. While challenges like specificity, delivery, and safety need to be addressed, the potential of manipulating these epigenetic regulators offers a promising avenue for optimizing IMF content and ensuring consumer satisfaction with meat quality. Continued research efforts hold the key to unlocking the full potential of this exciting field and revolutionizing meat production practices.

DNA methylation patterns play a crucial role in regulating gene expression related to IMF. Genes involved in fatty acid synthesis and adipogenesis (fat cell development) exhibit lower DNA methylation levels in high-IMF pigs compared to low-IMF breeds (Malgwi et al., 2022), suggesting that hypomethylation promotes their expression. Furthermore, the peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of adipogenesis, had significantly lower DNA methylation in the promoter region of high-IMF mouse compared to their low-IMF counterparts (Luo et al., 2023). These suggest that manipulating DNA methylation patterns could be a potential strategy to enhance IMF content.

On the other hand, histone modifications, particularly acetylation and methylation on histone tails, also influence chromatin accessibility and gene expression in the context of IMF. Acetylation generally loosens chromatin structure, allowing for easier access by transcription machinery and promoting gene expression. Study by Malgwi et al. (2022) revealed that genes involved in lipogenesis (fatty acid synthesis) displayed increased histone acetylation in high-IMF pigs compared to low-IMF ones. This suggests that histone deacetylase (HDAC) inhibitors, which block the removal of acetyl groups from histones, could be promising therapeutic targets for promoting IMF deposition. Nijhawan et al. (2020) demonstrated that treatment with HDAC inhibitors indeed increased fat deposition, supporting the potential of this approach.

5. Methods for epigenetic manipulation in rabbit livestock

Epigenetic manipulation in rabbits involves various methods, such as transgenic rabbit technology, genome editing technologies (e.g.,

CRISPR/Cas9), and RNA interference to knock down or knock out specific genes of interest. These methods target cells and utilize pathways and machineries such as non-coding RNA, DNA methylation, and histone modifications are included in this category. There has been a significant improvement in the precision of genome manipulation in rabbits because of the advent of these genome editing tools, particularly CRISPR/Cas9. These technologies have also demonstrated the ability to generate rabbit models of human genetic disorders. Nuclear transplantation of embryos using selective markers, for improved adipocyte differentiation has been successfully performed with high success rates for chromosomal removal, fusion, activation, and embryo transfer. Epigenetic processes, such as DNA methylation and histone modification, have also had an impact on livestock health and production traits.

6. Genetic and epigenetic approaches affecting glycerophospholipid metabolites

Glycerophospholipids (GPLs) play vital roles as structural and signaling molecules in cellular membranes. Their metabolism is complex and involves a network of enzymes and pathways. Multiple factors influence glycerophospholipid metabolism, including genes encoding phospholipases, lipid transfer proteins that aid in the movement of GPLs between cellular compartments (Reinisch & Prinz, 2021), and lipid synthesis enzymes involved in de novo synthesis of GPLs (Valentine et al., 2020). Variations in phospholipase genes (e.g., PLA2G, PLD) have been associated with changes in GPL levels and disease susceptibility (Kuefner et al., 2021; Qin et al., 2023; Taketomi, Miki, & Murakami, 2022). Mutations in these genes can affect GPL distribution and metabolism. Transcription factors such as PPAR and SREBP regulate the expression of genes involved in GPL metabolism. Genetic variations in these transcription factors can influence GPL levels and cellular responses (Chew et al., 2022; Karagiota, Chachami, & Paraskeva, 2022; Kopecka et al., 2020; Xie et al., 2023). Membrane protein genes also impact GPL composition and function. Mutations in membrane proteins such as ion channels and transporters can indirectly affect GPL metabolism (Guido et al., 2022). A genome-wide association study identified genetic variation in a locus associated with GPL metabolism and its related phenotype (Meckelmann et al., 2020). Epigenetic factors, including DNA methylation, histone modifications, and non-coding RNAs, can alter gene expression and influence GPL metabolism. Histone acetylation and methylation are key modifications that affect gene expression related to GPL metabolism. Changes in DNA methylation patterns have been observed in genes involved in GPL metabolism in various diseases (Chew et al., 2022; Xie et al., 2023). Dietary factors and environmental exposures can modify DNA methylation and impact GPL levels (Chbihi et al., 2024; Jumentier et al., 2023; Morgan et al., 2022) (Fig. 4). Epigenetic drugs targeting histone modifications have shown promise in modulating GPL levels and disease progression (George, Gladwin, & Graham, 2020; Gutiérrez et al., 2022). Additionally, several miRNAs and lncRNAs have been implicated in regulating GPL metabolism and disease pathogenesis (Cheng et al., 2022; Shi et al., 2023). Several glycophospholipid metabolites have been linked to diseases such as cardiovascular disease, neurodegenerative diseases, cancer, and metabolic disorders. For example, studies by Zhu et al. (2022), Galper et al. (2022) and Lv et al. (2024) found that altered GPL composition and metabolism contribute to atherosclerosis, myocardial infarction, stroke, Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Independent studies by Cífková et al. (2022) and Dickinson et al. (2020) observed various cancer types linked to tumor progression and metastasis due to changes in GPL levels and composition. Furthermore, impaired GPL metabolism has been associated with obesity, type 2 diabetes, and non-alcoholic fatty liver disease (Guerra, Mocciaro, & Gastaldelli, 2022). Glycerophospholipids are crucial components of cell membranes and play essential roles in cellular signaling and metabolism (Penkov & Fedorova, 2024).

Genetic approaches to studying effects of GPL metabolites primarily

focus on identifying specific genes and genetic variations that influence glycerophospholipid metabolism. Certain genetic mutations, for example, can affect the activity of enzymes involved in the synthesis and breakdown of glycerophospholipids, leading to changes in their levels and functions in rabbit tissues (Shan et al., 2021). Genome-wide association studies (GWAS) have been used to pinpoint loci associated with variations in glycerophospholipid levels (Lains et al., 2021; Aboul-maouahib et al., 2022; Harshfield et al., 2021). On the other hand, epigenetic approaches explore how modifications like DNA methylation and histone acetylation affect gene expression related to glycerophospholipid metabolism. These modifications, induced by environmental factors, can result in heritable changes in gene expression without altering the DNA sequence itself (Rothi & Greer, 2023).

Understanding the role of glycophospholipid metabolites in rabbits can be approached through both genetic and epigenetic perspectives. These approaches investigate how genetic variations and epigenetic modifications impact glycerophospholipid metabolism and function. Studies on rabbits have shown that epigenetic modifications can regulate the expression of genes involved in lipid metabolism (Jayalekshmi et al., 2023; Luo et al., 2023), thereby impacting the composition and function of glycerophospholipids in various tissues (Penkov & Fedorova, 2024). By integrating genetic and epigenetic data, a more comprehensive understanding of the regulatory mechanisms governing glycerophospholipid metabolism can be achieved. For example, a study discovered that a genetic variant could alter lipid profiles, while epigenetic modifications can modulate gene expression in response to dietary changes or stress, further influencing glycerophospholipid levels (Espinós et al., 2020). Overall, the integration of genetic and epigenetic research offers valuable insights into the intricate regulation of glycerophospholipid metabolism in rabbits. This comprehensive approach not only deepens our understanding of lipid biology, but also has the potential to impact the management of metabolic disorders associated with lipid metabolism in rabbits and other species.

7. Implications and future directions

This review has highlighted the complex relationship between genetic and epigenetic factors that influence intramuscular fat (IMF) deposition in rabbits. However, there are still several areas in rabbit breeding that require further research using modern molecular and bioinformatic tools. This may be because rabbit meat is not considered a primary source of meat in most countries. Moving forward, there are several key areas that should be explored. One important area is the functional validation of the candidate genes and epigenetic mechanisms that have been identified in IMF deposition. This could involve using CRISPR-Cas9 gene editing, manipulating DNA methylation or histone modifications in vitro, and studying their effects on muscle cell differentiation and lipid metabolism. Additionally, conducting large-scale genome-wide association studies (GWAS) involving diverse rabbit breeds could help identify new genetic markers associated with IMF variation. These markers could then be used to improve meat quality through selective breeding programs.

Furthermore, gaining a deeper understanding of the epigenomic landscape in different rabbit breeds is crucial. Next-generation sequencing technologies can be used to analyze DNA methylation patterns, histone modifications, and non-coding RNA expression in various muscle developmental stages and breeds with different IMF levels. It would also be valuable to investigate the interplay between genetic predisposition and environmental factors, such as diet and exercise, as they relate to the epigenetic landscape and IMF deposition in different rabbit genotypes. From conception to death, genetic and epigenetic systems are responsible for regulating the majority of biological events, including the reprogramming of individual genomes, cell differentiation and maintenance of a committed lineage (Singh et al., 2023). Most epigenetic models, about 65 % have led to exponential increase in improved health, production, reproduction and selection markers.

However, the invasiveness of such methodology appears to be specie specific, as an improvised system in a specie can be deleterious in another of the same phylogenetic relatedness. Although epigenetic modification has been used to improve adipogenesis, regulated by PCK2 gene, this was inhibited by the presence of METTL3. The loss of METTL3 resulted in an increased accumulation of PCK2 gene in Rex rabbits and, insights including the leptin hormone identified through SNP (Single Nucleotide Polymorphism) to affect carcass quality and traits has been used as a selection marker for meat quality, there are still scanty information on the species genetic and epigenetic meat quality improvement. Epigenetic processes like DNA methylation, histone modification, and chromatin remodeling impact livestock health and production traits, improve animal health and productivity management, however, the data that is now available is insufficient. Furthermore, genes which increases and improves adipogenesis have a relative tendency of contributing to IMF in rabbits and other livestock. Subjectively, Transgenic methods suggest how upstream genes can more greatly influence their counterparts and such was proved in the loss of METTL3 which significantly increased accumulation of PCK2 gene. Further studies should be directed on other regulatory function which can serve as a determinant for promoting muscle accumulations and correlation with fatty depositions. It is highly recommended that the modern breeding tools like Crisper, can be applied in this specie to improve on the meat quality, through IMF deposition.

Additionally, the gut microbiome may play a role in nutrient metabolism and IMF deposition. Future studies could explore the correlation between gut microbiome composition and IMF levels in rabbits. Manipulating the gut microbiome through probiotics or prebiotics could also be investigated as a means of modulating IMF content. By integrating data from genetic, epigenetic, and microbiome analyses, researchers may be able to develop predictive models for IMF deposition in rabbits. Such models would be invaluable for breeders looking to select animals with desired meat quality traits.

8. Conclusion

In conclusion, understanding the complex relationship between genetic and epigenetic factors governing IMF deposition in rabbits is key to advancing rabbit breeding and meat production. By pursuing the future directions outlined above, researchers can unlock the full potential of manipulating these factors to optimize meat quality while ensuring animal welfare. This knowledge may also contribute to a broader understanding of fat metabolism regulation in mammals, with potential implications for human health and agricultural practices involving other livestock species.

CRediT authorship contribution statement

Ifeanyi Ahamba Solomon: Writing – original draft, Conceptualization. **Chinyere Mary-Cynthia Ikele:** Writing – original draft. **Lionel Kimpe:** Writing – review & editing. **Naqash Goswami:** Resources. **Hui Wang:** Resources. **Zhen Li:** Funding acquisition. **Zhanjun Ren:** Supervision, Funding acquisition. **Xianggui Dong:** Supervision.

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.

Data availability

No data was used for the research described in the article.

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Appendix A

All the figures and tables are in the body of the paper and labelled as appropriate.

During the preparation of this work the author(s) used (Grammarly) to proofread. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

References

Al Aboud, N.M., Tupper, C., & I, J. (2023). Genetics, Epigenetic Mechanism. *StatPearls [Internet]*.

Aboulmaouahib, B., Kastenmüller, G., Suhre, K., Zöllner, S., Weissensteiner, H., Prehn, C., … Flaquer, A. (2022). First mitochondrial genome-wide association study with metabolomics. *Human Molecular Genetics, 31*(19), 3367–3376.

Andrews, S., Krueger, C., Mellado-Lopez, M., Hemberger, M., Dean, W., Perez-Garcia, V., & Hanna, C. W. (2023). Mechanisms and function of de novo DNA methylation in placental development reveals an essential role for DNMT3B. *Nature Communications, 14*(1), 371. https://doi.org/10.1038/s41467-023-36019-9

Azzam, S. K., Alsafar, H., & Sajini, A. A. (2022). FTO m6A demethylase in obesity and cancer: Implications and underlying molecular mechanisms. *International Journal of Molecular Sciences, 23*(7). https://doi.org/10.3390/ijms23073800

Bommarito, P. A., & Fry, R. C. (2019). The Role of DNA Methylation in Gene Regulation. In *Toxicoepigenetics* (pp. 127-151).

Bozhilova-Sakova, M., Viryanski, D., Ignatova, M., Dimitrova, I., & Stoykova-Grigorova, R. (2022). Genetic factors influencing rabbit breeding. An overview. *Zhivotnovadni Nauki, 59*(6), 46–56.

Burton, N. O., & Greer, E. L. (2022). Multigenerational epigenetic inheritance: Transmitting information across generations. *Seminars in Cell & Developmental Biology, 127*, 121–132.

Buss, C. E., Afonso, J., De Oliveira, P. S., Petrini, J., Tizioto, P. C., Cesar, A. S., & de Almeida Regitano, L. C. (2023). Bivariate GWAS reveals pleiotropic regions among feed efficiency and beef quality-related traits in Nelore cattle. *Mammalian Genome, 34*(1), 90–103.

Cabrera Zapata, L. E., Garcia-Segura, L. M., Cambiasso, M. J., & Arevalo, M. A. (2022). Genetics and epigenetics of the X and Y chromosomes in the sexual differentiation of the brain. *International Journal of Molecular Sciences, 23*(20). https://doi.org/10.3390/ijms232012288

Cao, Y., Xing, Y., Guan, H., Ma, C., Jia, Q., Tian, W., & Li, H. (2023). Genomic insights into molecular regulation mechanisms of intramuscular fat deposition in chicken. *Genes, 14*(12), 2197.

Cao, Z., Zhang, L., Hong, R., Li, Y., Wang, Y., Qi, X., et al. (2021). METTL3-mediated m6A methylation negatively modulates autophagy to support porcine blastocyst development. *Biology of Reproduction, 104*(5), 1008–1021.

Carter, B., & Zhao, K. (2021). The epigenetic basis of cellular heterogeneity. *Nature Reviews Genetics, 22*(4), 235–250.

Chaker, L., & Peeters, R. P. (2022). Thyroid-Stimulating Hormone. In The Pituitary. *Academic Press.*, 173-207.

Chauhdary, Z., Rehman, K., & Akash, M. S. H. (2021). The composite alliance of FTO locus with obesity-related genetic variants. *Clinical and Experimental Pharmacology and Physiology, 48*(7), 954–965.

Chbihi, K., Menouni, A., Hardy, E., Creta, M., Grova, N., Van Nieuwenhuyse, A., & Duca, R. C. (2024). Exposure of children to brominated flame retardants and heavy metals in Morocco: Urine and blood levels in association with global cytosine and adenine methylation. *Environment International, 183*, Article 108409.

Chen, J., Chen, F., Lin, X., Wang, Y., He, J., & Zhao, Y. (2020). Effect of excessive or restrictive energy on growth performance, meat quality, and intramuscular fat deposition in finishing Ningxiang pigs. *Animals, 11*(1), 27.

Cheng, F., Liang, J., Yang, L., Lan, G., Wang, L., & Wang, L. (2022). Systematic identification and comparison of the expressed profiles of lncRNAs, miRNAs, circRNAs, and mRNAs with associated co-expression networks in pigs with low and high intramuscular fat. *Animals, 11*(11), 3212.

Chew, N. W., Chong, B., Ng, C. H., Kong, G., Chin, Y. H., Xiao, W., & Foo, R. (2022). The genetic interactions between non-alcoholic fatty liver disease and cardiovascular diseases. *Frontiers in Genetics, 13*, Article 971484.

Cífková, E., Brumarová, R., Ovčačíková, M., Dobešová, D., Mičová, K., Kvasnička, A., & Holčapek, M. (2022). Lipidomic and metabolomic analysis reveals changes in biochemical pathways for non-small cell lung cancer tissues. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of. Lipids, 1867*(2), Article 159082.

Cui, H., Wang, Y., Zhu, Y., Liu, X., Liu, L., Wang, J., & Wen, J. (2023). Genomic insights into the contribution of de novo lipogenesis to intramuscular fat deposition in chicken. *Journal of Advanced Research*.

Dahlet, T., Argüeso Lleida, A., Al Adhami, H., Dumas, M., Bender, A., Ngondo, R. P., & Weber, M. (2020). Genome-wide analysis in the mouse embryo reveals the importance of DNA methylation for transcription integrity. *Nature Communications, 11*(1), 3153.

David, S. (2021). A current guide to candidate gene association studies. *Trends in Genetics, 37*(12), 1056–1059. https://doi.org/10.1016/j.tig.2021.07.009

de Souza Pinhel, Marcela Augusta, Lígia Moriguchi Watanabe, Rafael Fernandes-Ferreira, Natalia Yumi Noronha, Guilherme da Silva Rodrigues, . . . Souza, C. B. N. (2023). Prospects of Transcriptomics. *Elsevier*, 479–492.

Dehghanian Reyhan, V., Ghafouri, F., Sadeghi, M., Miraei-Ashtiani, S. R., Kastelic, J. P., Barkema, H. W., & Shirali, M. (2023). Integrated comparative transcriptome and circRNA-lncRNA-miRNA-mRNA ceRNA regulatory network analyses identify molecular mechanisms associated with intramuscular Fat content in beef cattle. *Animals (Basel), 13*(16). https://doi.org/10.3390/ani13162598

dela Cruz, J. F., Pacunla, K. W. M., & Hwang, S. G. (2022). Low lysine stimulates adipogenesis through ZFP423 upregulation in bovine stromal vascular cells. *Journal of Animal Science and Technology, 64*(6), 1173.

Dhar, G. A., Saha, S., Mitra, P., & Nag Chaudhuri, R. (2021). DNA methylation and regulation of gene expression: Guardian of our health. *Nucleus (Calcutta), 64*(3), 259–270. https://doi.org/10.1007/s13237-021-00367-y

Dickinson, A., Saraswat, M., Joenväärä, S., Agarwal, A., Jyllikoski, D., Wilkman, T., et al. (2020). Mass spectrometry–based lipidomics of oral squamous cell carcinoma tissue reveals aberrant cholesterol and glycerophospholipid metabolism—A Pilot study. *Translational oncology, 13*(10), Article 100807.

Dorożyńska, K., & Maj, D. (2021). Rabbits–their domestication and molecular genetics of hair coat development and quality. *Animal Genetics, 52*(1), 10–20.

Du, L., Chang, T., An, B., Liang, M., Deng, T., Li, K., & Gao, H. (2022). Transcriptomics and lipid metabolomics analysis of subcutaneous, visceral, and abdominal adipose tissues of beef cattle. *Genes (Basel), 14*(1), 37.

Duś-Żuchowska, M., Nowak, H., Kałużny, L., Rokicki, D., Ciara, E., Piekutowska-Abramczuk, D., & Walkowiak, J. (2024). Pathogenic Potential of a PCK1 Gene Variant in Cytosolic PEPCK Deficiency: A Compelling Case Study. *The American Journal of Case Reports, 25*, e943118–1.

El Nagar, A. G., Heddi, I., Sosa-Madrid, B. S., Blasco, A., Hernández, P., & Ibáñez-Escriche, N. (2023). Genome-wide association study of maternal genetic effects on intramuscular fat and fatty acid composition in rabbits. *Animals, 13*(19), 3071.

Espinós, C., Galindo, M. I., García-Gimeno, M. A., Ibáñez-Cabellos, J. S., Martínez-Rubio, D., Millán, J. M., … Pallardó, F. V. (2020). Oxidative stress, a crossroad between rare diseases and neurodegeneration. *Antioxidants, 9*(4), 313.

Fu, Z., Kern, T. S., Hellström, A., & Smith, L. E. (2021). Fatty acid oxidation and photoreceptor metabolic needs. *Journal of Lipid Research, 62*.

Gai, K., Ge, Y., Liu, D., Zhang, H., Cong, B., Guo, S., …, Sheng, X. (2023). Identification of key genes related to intramuscular fat deposition in Beijing-You chicken by mRNA and miRNA transcriptome analysis. *Poultry Science, 102*(11), Article 103035.

Galper, J., Dean, N. J., Pickford, R., Lewis, S. J., Halliday, G. M., Kim, W. S., & Dzamko, N. (2022). Lipid pathway dysfunction is prevalent in patients with Parkinson's disease. *Brain, 145*(10), 3472–3487.

Gao, G., Gao, N., Li, S., Kuang, W., Zhu, L., Jiang, W., & Zhao, Y. (2021). Genome-wide association study of meat quality traits in a three-way crossbred commercial pig population. *Frontiers in Genetics, 12*, Article 614087.

George, M. P., Gladwin, M. T., & Graham, B. B. (2020). Exploring new therapeutic pathways in pulmonary hypertension. Metabolism, proliferation, and personalized medicine. *American Journal of Respiratory Cell and Molecular Biology, 63*(3), 279–292.

Guerra, S., Mocciaro, G., & Gastaldelli, A. (2022). Adipose tissue insulin resistance and lipidome alterations as the characterizing factors of non-alcoholic steatohepatitis. *European Journal of Clinical Investigation, 52*(3), e13695.

Guido, M. E., Monjes, N. M., Wagner, P. M., & Salvador, G. A. (2022). Circadian regulation and clock-controlled mechanisms of glycerophospholipid metabolism from neuronal cells and tissues to fibroblasts. *Molecular Neurobiology, 1–28.

Gutiérrez, J. R., Salgado, A. R. M., Arias, M. D.Á., San-Juan-Vergara, H., Rada, W. R., & Gómez, C. M. M. (2022). Epigenetic modulators as treatment alternative to diverse types of cancer. *Current Medicinal Chemistry, 29*(9), 1503–1542.

Harshfield, E. L., Fauman, E. B., Stacey, D., Paul, D. S., Ziemek, D., Ong, R. M., … Koulman, A. (2021). Genome-wide analysis of blood lipid metabolites in over 5000 South Asians reveals biological insights at cardiometabolic disease loci. *BMC medicine, 19*, 1–17.

Hawe, J. S., Wilson, R., Schmid, K. T., Zhou, L., Lakshmanan, L. N., Lehne, B. C., & Yew, Y. W. (2022). Genetic variation influencing DNA methylation provides insights into molecular mechanisms regulating genomic function. *Nature Genetics, 54*(1), 18–29.

Helal, M., Hany, N., Maged, M., Abdelaziz, M., Osama, N., Younan, Y. W., & Ragab, M. (2022). Candidate genes for marker-assisted selection for growth, carcass and meat quality traits in rabbits. *Biotechnology, 33*(7), 1691–1710.

Henchion, M., Moloney, A. P., Hyland, J., Zimmermann, J., & McCarthy, S. (2021). Trends for meat, milk and egg consumption for the next decades and the role played by livestock systems in the global production of proteins. *Animal, 15*(100287).

Horman, T., Fernandes, M. F., Tache, M. C., Hucik, B., Mutch, D. M., & Leri, F. (2020). Dietary n-3/n-3 ratio influences brain fatty acid composition in adult rats. *Nutrients, 12*(6), 1847.

Huang, C., Chen, W., & Wang, X. (2023). Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases. *Genes and Diseases, 10*(6), 2351–2365.

Huang, C. J., Choo, K. B., & Chen, C. F. (2022). The MicroRNA-signaling-peroxisome proliferator-activated receptor gamma connection in the modulation of adipogenesis: Bioinformatics projection on chicken. *Poultry Science, 101*(8), Article 101950. https://doi.org/10.1016/j.psj.2022.101950

Hudson, N. J., Reverter, A., Griffiths, W. J., Yutuc, E., Wang, Y., Jeanes, A., … Greenwood, P. L. (2020). Gene expression identifies metabolic and functional differences between intramuscular and subcutaneous adipocytes in cattle. *BMC genomics, 21*, 1–23.

Ibeagha-Awemu, E. M., & Ying, Y. (2021). Consequence of epigenetic processes on animal health and productivity: Is additional level of regulation of relevance? *Anim. Front. Microbiol., 11*(6), 7–18.

Jaffar, A. A., Hassan, A. F., & Kassim, W. Y. (2019). Effect of POU1F1 gene haplotypes on eights and milk production of awassi sheep. *Basrah Journal of Agricultural Sciences, 32*(2), 85–94. https://doi.org/10.37077/25200860.2019.199

Jang, K. H., Heras, C. R., & Lee, G. (2022). m (6)A in the signal transduction network. *Molecules and Cells, 45*(7), 435–443. https://doi.org/10.14348/molcells.2022.0017

Jayalekshmi, V. S., Jaikumar, V. S., Mehra, P., Thulaseedharan, T., Vinod, V. M., & Ramachandran, S. (2023). Differential expression of lipid metabolic genes in hypercholesterolemic rabbit placenta predisposes the offspring to develop atherosclerosis in early adulthood. *Life Sciences, 327*, 121823.

Jiang, G., Ameer, K., Kim, H., Lee, E. J., Ramachandraiah, K., & Hong, G. P. (2020). Strategies for sustainable substitution of livestock meat. *Foods, 9*(9), 1227.

Jiang, Y., Liu, J., Liu, H., Zhang, W., Li, X., Liu, L., …, Wang, C. (2022). miR-381-3p inhibits intramuscular fat deposition through targeting FABP3 by ceRNA regulatory network. *Biology*, 11101497.

Jumentier, B., Barrot, C. C., Estavoyer, M., Tost, J., Heude, B., François, O., & Lepeule, J. (2023). High-dimensional mediation analysis: A new method applied to maternal smoking, placental DNA methylation, and birth outcomes. *Environmental Health Perspectives, 131*(4), Article 047011.

Kang, K., Ma, J., Wang, H., Wang, Z., Peng, Q., Hu, R., & Sun, B. (2020). High-energy diet improves growth performance, meat quality and gene expression related to intramuscular fat deposition in finishing yaks raised by barn feeding. *Veterinary Medicine and Science, 6*(4), 755–765.

Kang, H., Zhao, D., Xiang, H., Li, J., Zhao, G., & Li, H. (2021). Large-scale transcriptome sequencing in broiler chickens to identify candidate genes for breast muscle weight and intramuscular fat content. *Genetics Selection Evolution, 53*(1), 1–23.

Karagiota, A., Chachami, G., & Paraskeva, E. (2022). Lipid metabolism in cancer: The role of acylglycerolphosphate acyltransferases (AGPATs). *Cancers, 14*(1), 228.

Khan, R., Li, A., & Raza, S. H. A. (2023). Genetic regulation of meat quality traits in livestock species. *Frontiers in Genetics, 13*(1092562).

Kim, M., Park, T., Jeong, J. Y., Baek, Y., & Lee, H. J. (2020). Association between rumen microbiota and marbling score in korean native beef cattle. *Animals (Basel), 10*(4). https://doi.org/10.3390/ani10040712

Kiselev, I. S., Kulakova, O. G., Boyko, A. N., & Favorova, O. O. (2021). DNA methylation as an epigenetic mechanism in the development of multiple sclerosis. *Acta Naturae, 13*(2), 45–57.

Kopecka, J., Trouillas, P., Gašparović, A.Č., Gazzano, E., Assaraf, Y. G., & Riganti, C. (2020). Phospholipids and cholesterol: Inducers of cancer multidrug resistance and therapeutic targets. *Drug Resistance Updates, 49*, Article 100670.

Kuefner, M. S., Stephenson, E., Savikj, M., Smallwood, H. S., Dong, Q., Payré, C., & Park, E. A. (2021). Group IIA secreted phospholipase A2 (PLA2G2A) augments adipose tissue thermogenesis. *The FASEB Journal, 35*(10), e21881.

Kumar, S., Chinnusamy, V., & Mohapatra, T. (2018). Epigenetics of modified DNA bases: 5-methylcytosine and beyond. *Frontiers in Genetics, 9*, 640. https://doi.org/10.3389/fgene.2018.00640

Laghouaouta, H., Sosa-Madrid, B. S., Zubiri-Gaitan, A., Hernandez, P., & Blasco, A. (2020). Novel genomic regions associated with intramuscular fatty acid composition in rabbits. *Animals (Basel), 10*(11). https://doi.org/10.3390/ani10112090

Lains, I., Zhu, S., Han, X., Chung, W., Yuan, Q., Kelly, R. S., … Husain, D. (2021). Genomic-metabolomic associations support the role of LIPC and glycerophospholipids in age-related macular degeneration. *Ophthalmology science, 1*(1), 100017.

Lee, H. T., Oh, S., Ro, D. H., Yoo, H., & Kwon, Y. W. (2020). The key role of DNA methylation and histone acetylation in epigenetics of atherosclerosis. *Journal of Lipid Atheroscler, 9*(3), 419–434. https://doi.org/10.12997/jla.2020.9.3.419

Li, X., Fu, X., Yang, G., & Du, M. (2020). Enhancing intramuscular fat development via targeting fibro-adipogenic progenitor cells in meat animals. *Animal, 14*(2), 312–321.

Li, Y., Gan, M., Tang, T., Shao, J., Lai, T., Ma, Y., & Lai, S. (2021). Intramuscular adipocyte and fatty acid differences between high-fat and control rabbit groups subject to a restricted diet. *Veterinary Medicine and Science, 7*(5), 2051–2060. https://doi.org/10.1002/vms3.576

Li, F., Ma, X.-F., Li, W.-T., Han, R.-L., Li, Z.-J., Jiang, R.-R., & Kang, X.-T. (2019). Krüppel-like factor KLF9 inhibits chicken intramuscular preadipocyte differentiation. *British Poultry Science, 60*(6), 790–797.

Li, D., Pan, Z., Zhang, K., Yu, M., Yu, D., Lu, Y., & Du, W. (2020). Identification of the differentially expressed genes of muscle growth and intramuscular fat metabolism in the development stage of yellow broilers. *Genes, 11*(3), 244.

Li, W., Wang, F., Sun, F., Qu, Y., Liu, C., Han, Y., & Ding, C. (2023). Effects of vitamin A on intramuscular fat development in beef cattle: A meta-analysis. *Frontiers in Veterinary Science, 10*, 1105754.

Liu, J., Chriki, S., Ellies-Oury, M. P., Legrand, I., Pogorzelski, G., Wierzbicki, J., …, Hocquette, J. F. (2020). European conformation and fat scores of bovine carcasses are not good indicators of marbling. *Meat Science, 170*, Article 108233. https://doi.org/10.1016/j.meatsci.2020.108233

Liu, Y., Long, H., Feng, S., Ma, T., Wang, M., Niu, L., & Xu, X. (2021). Trait correlated expression combined with eQTL and ASE analyses identified novel candidate genes affecting intramuscular fat. *BMC Genomics, 22*, 1–14.

Luo, G., Hong, T., Yu, L., & Ren, Z. (2023). FTO regulated intramuscular fat by targeting APMAP gene via an m (6)A-YTHDF2-dependent manner in rex rabbits. *Cells, 12*(3). https://doi.org/10.3390/cells12030369

Luo, G., Wang, L., Hu, S., Du, K., Wang, J., & Lai, S. (2022). Association of leptin mRNA expression with meat quality trait in Tianfu black rabbits. *Animal Biotechnology, 33*(3), 480–486. https://doi.org/10.1080/10495398.2020.1804920

Luo, M., Wang, H., Zhang, J., Yixi, K., Shu, S., Fu, C., & Peng, W. (2023). IMF deposition ceRNA network analysis and functional study of HIF1a in yak. *Frontiers in Veterinary Science, 10*(1272238).

Luo, G., Zhu, T., & Ren, Z. (2022). METTL3 regulated the meat quality of rex rabbits by controlling PCK2 expression via a YTHDF2–N6-methyladenosine axis. *Foods, 11*(1549). https://doi.org/10.3390/foods11111549

Lv, J., Pan, C., Cai, Y., Han, X., Wang, C., Ma, J., & Chen, Y. (2024). Plasma metabolomics reveals the shared and distinct metabolic disturbances associated with cardiovascular events in coronary artery disease. *Nature Communications, 15*(1), 5729.

Ma, X., Yang, X., Zhang, D., Zhang, W., Wang, X., Xie, K., & Zan, L. (2023). RNA-seq analysis reveals the critical role of the novel lncRNA BIANCR in intramuscular adipogenesis through the ERK1/2 signaling pathway. *Journal of Animal Science and Biotechnology, 14*(1), 21. https://doi.org/10.1186/s40104-022-00820-1

Malgwi, I. H., Halas, V., Grünvald, P., Schiavon, S., & Jócsák, I. (2022). Genes related to fat metabolism in pigs and intramuscular fat content of pork: A focus on nutrigenetics and nutrigenomics. *Animals, 12*(2), 150. https://doi.org/10.3390/ani12020150

Małodobra-Mazur, M., Cierzniak, A., Kaliszewski, K., & Dobosz, T. (2021). PPARG hypermethylation as the first epigenetic modification in newly onset insulin resistance in human adipocytes. *Genes (Basel), 12*(5), 889.

Martinez-Alvaro, M., Blasco, A., & Hernandez, P. (2018). Effect of selection for intramuscular fat on the fatty acid composition of rabbit meat. *Animal, 12*(10), 2002–2008. https://doi.org/10.1017/S1751731117003494

Matarneh, S. K., Scheffler, T. L., & Gerrard, D. E. (2023). (pp.). (2023). The conversion of muscle to meat. In *Lawrie's meat science*, 159-194.

Meckelmann, S. W., Hawksworth, J. I., White, D., Andrews, R., Rodrigues, P., O'Connor, A., … O'Donnell, V. B. (2020). Metabolic dysregulation of the lysophospholipid/autotaxin axis in the chromosome 9p21 gene SNP rs10757274. *Circulation: Genomic and Precision Medicine, 13*(3), Article e002806.

Monroy-Ramirez, H. C., Galicia-Moreno, M., Sandoval-Rodriguez, A., Meza-Rios, A., Santos, A., & Armendariz-Borunda, J. (2021). PPARs as metabolic sensors and therapeutic targets in liver diseases. *International Journal of Molecular Sciences, 22*(15), 8298.

Morgan, H. L., Furse, S., Dias, I. H., Shabir, K., Castellanos, M., Khan, I., & Watkins, A. J. (2022). Paternal low protein diet perturbs inter-generational metabolic homeostasis in a tissue-specific manner in mice. *Communications Biology, 5*(1), 929.

Nguyen, D. V., Nguyen, O. C., & Malau-Aduli, A. E. O. (2021). Main regulatory factors of marbling level in beef cattle. *Veterinary and Animal Science, 14*. https://doi.org/10.1016/j.vas.2021.100219

Nijhawan, P., Behl, T., Khullar, G., Pal, G., Kandhwal, M., & Goyal, A. (2020). HDAC in obesity: A critical insight. *Obesity Medicine, 18*. https://doi.org/10.1016/j.obmed.2020.100212

Paredes-Sánchez, F. A., Sifuentes-Rincón, A. M., Casas, E., Arellano-Vera, W., Parra-Bracamonte, G. M., Riley, D. G., & Randel, R. D. (2020). Novel genes involved in the genetic architecture of temperament in Brahman cattle. *PLoS One, 15*(8), e0237825.

Penkov, S., & Fedorova, M. (2024). Membrane epilipidome—Lipid modifications, their dynamics, and functional significance. *Cold Spring Harbor Perspectives in Biology*, a041417.

Picó, C., Palou, M., Pomar, C. A., Rodríguez, A. M., & Palou, A. (2022). Leptin as a key regulator of the adipose organ. *Reviews in Endocrine and Metabolic Disorders, 23*(1), 13–30.

Powell, J., Talenti, A., Fisch, A., Hemmink, J. D., Paxton, E., Toye, P., …, Morrison, L. J. (2023). Profiling the immune epigenome across global cattle breeds. *Genome Biology, 24*(1), 127.

Purslow, P. P. (2020). The structure and role of intramuscular connective tissue in muscle function. *Frontiers in Physiology, 11*(495).

Qin, S., Zeng, H., Wu, Q., Li, Q., Zeeshan, M., Ye, L., & Zeng, X. W. (2023). An integrative analysis of lipidomics and transcriptomics in various mouse brain regions in response to real-ambient PM2. 5 exposures. *Science of The Total Environment, 895*, Article 165112.

Ran, H., He, Q., Han, Y., Wang, J., Wang, H., Yue, B., & Wang, H. (2023). Functional study and epigenetic targets analyses of SIRT1 in intramuscular preadipocytes via ChIP-seq and mRNA-seq. *Epigenetics, 18*(1), 2135194. https://doi.org/10.1080/15592294.2022.2135194

Rauch, A., & Mandrup, S. (2021). Transcriptional networks controlling stromal cell differentiation. *Nature Reviews Molecular Cell Biology, 22*(7), 465–482.

Raza, S. H. A., Pant, D. S., Wani, A. K., Mohamed, H. H., Khalifa, N. E., Almohaimeed, H. M., & Zan, L. (2022). Krüppel-like factors family regulation of adipogenic markers genes in bovine cattle adipogenesis. *Molecular and Cellular Probes, 65*, Article 101850.

Reinisch, K. M., & Prinz, W. A. (2021). Mechanisms of nonvesicular lipid transport. *Journal of Cell Biology, 220*(3).

Ren, W., Gao, L., & Song, J. (2018). Structural basis of DNMT1 and DNMT3A-mediated DNA methylation. *Genes (Basel), 9*(12). https://doi.org/10.3390/genes9120620

Ren, H., Xiao, W., Qin, X. C. G., Chen, H., Hua, Z., Cheng, C., & Bi, Y. (2020). Myostatin regulates fatty acid desaturation and fat deposition through MEF2C/miR222/SCD5 cascade in pigs. *Communications Biology, 3*, 612.

Revilla, M., Puig-Oliveras, A., Crespo-Piazuelo, D., Criado-Mesas, L., Castello, A., Fernandez, A. I., & Folch, J. M. (2018). Expression analysis of candidate genes for fatty acid composition in adipose tissue and identification of regulatory regions. *Scientific Reports, 8*(1), 2045. https://doi.org/10.1038/s41598-018-20473-3

Rothi, M. H., & Greer, E. L. (2023). From correlation to causation: The new frontier of transgenerational epigenetic inheritance. *Bioessays, 45*(1), 2200118.

Safaa, H. M., Ragab, M., Ahmed, M., El-Gammal, B., & Helal, M. (2023). Influence of polymorphisms in candidate genes on carcass and meat quality traits in rabbits. *PLoS One, 18*(11), e0294051. https://doi.org/10.1371/journal.pone.0294051

SanMiguel, J. M., & Bartolomei, M. S. (2018). DNA methylation dynamics of genomic imprinting in mouse development. *Biology of Reproduction, 99*(1), 252–262. https://doi.org/10.1093/biolre/ioy036

Schumacher, M., DelCurto-Wyffels, H., Thomson, J., & Boles, J. (2022). Fat deposition and fat effects on meat quality-A review. *Animals (Basel), 12*(12), 1550.

Selim, S., Seleiman, M. F., Hassan, M. M., Saleh, A. A., & Mousa, M. A. (2021). Impact of dietary supplementation with Moringa oleifera leaves on performance, meat characteristics, oxidative stability, and fatty acid profile in growing rabbits. *Animlals, 11*(2), 248.

Shan, S., Xu, F., Hirschfeld, M., & Brenig, B. (2021). Sperm lipid markers of male fertility in mammals. *International Journal of Molecular Sciences, 22*(16), 8767.

Shi, X., Li, P., Wu, X., & Shu, J. (2023). Whole-transcriptome sequencing identifies key differentially expressed circRNAs/lncRNAs/miRNAs/mRNAs and linked ceRNA networks in adult degenerative scoliosis. *Frontiers in Molecular Neuroscience, 16*, 1038816.

Siddiqui, S. A., Gerini, F., Ikram, A., Saeed, F., Feng, X., & Chen, Y. (2023). Rabbit meat—production, consumption and consumers' attitudes and behavior. *Sustainability, 15*(3), 2008.

Silva-Vignato, B., Cesar, A. S. M., Afonso, J., Moreira, G. C. M., Poleti, M. D., Petrini, J., & Coutinho, L. (2022). Integrative analysis between genome-wide association study and expression quantitative trait loci reveals bovine muscle gene expression regulatory polymorphisms associated with intramuscular fat and backfat thickness. *Frontiers in Genetics, 13*, Article 935238.

Singh, A., Rappolee, D. A., & Ruden, D. M. (2023). Epigenetic reprogramming in mice and humans: from fertilization to primordial germ cell development. *Cells, 12*(14), 1874.

Sosa-Madrid, B. S., Varona, L., Blasco, A., Hernandez, P., Casto-Rebollo, C., & Ibanez-Escriche, N. (2020). The effect of divergent selection for intramuscular fat on the domestic rabbit genome. *Animal, 14*(11), 2225–2235. https://doi.org/10.1017/S1751731120001263

Sun, M., Yang, Z., Liu, L., & Duan, L. (2022). DNA methylation in plant responses and adaption to abiotic stresses. *International Journal of Molecular Sciences., 23*(13), 6910.

Taketomi, Y., Miki, Y., & Murakami, M. (2022). Old but new: Group IIA phospholipase A2 as a modulator of gut microbiota. *Metabolites, 12*(2), 352.

Tan, L., Chen, Z., Ruan, Y., & Xu, H. (2022). Differential regulatory roles of microRNAs during intramuscular adipogenesis in Chinese Guizhou Congjiang Xiang pigs. *Epigenetics, 17*(12), 1800–1819.

Tan, Z., & Jaing, H. (2024). Molecular and cellular mechanisms of intramuscular fat development and growth in cattle. *International Journal of Molecular Sciences., 255*, 2520. https://doi.org/10.3390/ijms25052520

Ursachi, C. S., Perta-Crisan, S., & Munteanu, F. D. (2020). Strategies to improve meat products' quality. *Foods, 9*(12). https://doi.org/10.3390/foods9121883

Valdés-Hernández, J., Folch, J. M., Crespo-Piazuelo, D., Passols, M., Sebastià, C., Criado-Mesas, L., & Ramayo-Caldas, Y. (2024). Identification of candidate regulatory genes for intramuscular fatty acid composition in pigs by transcriptome analysis. *Genetics Selection Evolution, 56*(1), 12.

Valentine, W. J., Hashidate-Yoshida, T., Yamamoto, S., & Shindou, H. (2020). Biosynthetic enzymes of membrane glycerophospholipid diversity as therapeutic targets for drug development. *Druggable Lipid Signaling Pathways*, 5–27.

Wallace, D. R., Taalab, Y. M., Heinze, S., Tariba Lovaković, B., Pizent, A., Renieri, E., & Buha Djordjevic, A. (2020). Toxic-metal-induced alteration in miRNA expression profile as a proposed mechanism for disease development. *Cells, 9*(4), 901.

Wang, L., Gao, P., Li, C., Liu, Q., Yao, Z., Li, Y., …, Fu, X. (2023). A single-cell atlas of bovine skeletal muscle reveals mechanisms regulating intramuscular adipogenesis and fibrogenesis. *Journal of Cachexia, Sarcopenia and Muscle, 14*(5), 2152–2167.

Wang, G., Guo, G., Tian, X., Hu, S., Du, K., Zhang, Q., & Lai, S. (2020). Screening and identification of MicroRNAs expressed in perirenal adipose tissue during rabbit growth. *Lipids in Health and Disease, 19*(1), 35. https://doi.org/10.1186/s12944-020-01219-5

Wang, M., & Ibeagha-Awemu, E. M. (2020). Impacts of epigenetic processes on the health and productivity of livestock. *Frontiers in Genetics, 11*, Article 613636. https://doi.org/10.3389/fgene.2020.613636

Wang, C., Liu, X., Gao, Y., Yang, L., Li, C., Liu, W., & Gao, S. (2018). Reprogramming of H3K9me3-dependent heterochromatin during mammalian embryo development. *Nature Cell Biology, 20*(5), 620–631. https://doi.org/10.1038/s41556-018-0093-4

Wang, S., Lv, W., Li, T., Zhang, S., Wang, H., Li, X., …, Wei, W. (2022). Dynamic regulation and functions of mRNA m6A modification. *Cancer Cell International, 22*(1), 48. https://doi.org/10.1186/s12935-022-02452-x

Wang, L., Zhang, Y., Zhang, B., Zhong, H., Lu, Y., & Zhang, H. (2021). Candidate gene screening for lipid deposition using combined transcriptomic and proteomic data from Nanyang black pigs. *BMC Genomics, 22*, 441.

Wu, R., Guo, G., Bi, Z., Liu, Y., Zhao, Y., Chen, N., …, Wang, X. (2019). m (6)A methylation modulates adipogenesis through JAK2-STAT3-C/EBPbeta signaling. *Biochimica et Biophysica Acta, Gene Regulatory Mechanisms, 1862*(8), 796–806. https://doi.org/10.1016/j.bbagrm.2019.06.008

Wu, R., & Wang, X. (2021). Epigenetic regulation of adipose tissue expansion and adipogenesis by N6-methyladenosine. *Obesity Reviews, 22*(2), Article e13124.

Wyss, P., Song, C., & Bina, M. (2022). Along the bos taurus genome, uncover candidate imprinting control regions. *BMC Genomics, 23*(1), 478.

Xie, H., Liu, X., Zhou, Q., Huang, T., Zhang, L., Gao, J., & Wang, C. Y. (2022). DNA methylation modulates aging process in adipocytes. *Aging and Disease, 13*(2), 433–446. https://doi.org/10.14336/AD.2021.0904

Xie, P., Xie, J. B., Xiao, M. Y., Guo, M., Qi, Y. S., Li, F. F., & Piao, X. L. (2023). Liver lipidomics analysis reveals the anti-obesity and lipid-lowering effects of gypnosides from heat-processed Gynostemma pentaphyllum in high-fat diet fed mice. *Phytomedicine, 115*, Article 154834.

Xu, S., Chang, Y., Wu, G., Zhang, W., & Man, C. (2020). Potential role of miR-155-5p in fat deposition and skeletal muscle development of chicken. *Bioscience Reports, 40*(6).

Yakovlev, A. F. (2018). Epigenetic effects in livestock breeding. *Russian Journal of Genetics, 54*(8), 897–909.

Yan, W., Kan, X., Wang, Y., & Zhang, Y. (2023). Expression of key genes involved in lipid deposition in intramuscular adipocytes of sheep under high glucose conditions. *Journal of Animal Physiology and Animal Nutrition, 107*(2), 444–452.

Yang, Y., Hsu, P. J., Chen, Y. S., & Yang, Y. G. (2018). Dynamic transcriptomic m (6)A decoration: Writers, erasers, readers and functions in RNA metabolism. *Cell Research, 28*(6), 616–624. https://doi.org/10.1038/s41422-018-0040-8

Yang, H., Li, Y., Huang, L., Fang, M., & Xu, S. (2023). The epigenetic regulation of RNA N6-methyladenosine methylation in glycolipid metabolism. *Biomolecules, 13*(2). https://doi.org/10.3390/biom13020273

Yao, Y., Cai, X., Fei, W., Ye, Y., Zhao, M., & Zheng, C. (2022). The role of short-chain fatty acids in immunity, inflammation and metabolism. *Critical Reviews in Food Science and Nutrition, 62*(1), 1–12.

You, L., Han, Z., Chen, H., Chen, L., Lin, Y., Wang, B., & Han, Z. (2023). The role of N6-methyladenosine (m6A) in kidney diseases. *Frontiers in Medicine., 10*, 1247690.

You, W., Henneberg, R., Saniotis, A., Ge, Y., & Henneberg, M. (2022). Total meat intake is associated with life expectancy: a cross-sectional data analysis of 175 contemporary populations. *International Journal of General Medicine, 1833–1851*.

Yu, B., Liu, J., Cai, Z., Wang, H., Feng, X., Zhang, T., …, Zhang, J. (2023). RNA N (6)-methyladenosine profiling reveals differentially methylated genes associated with intramuscular fat metabolism during breast muscle development in chicken. *Poultry Science, 102*(8), Article 102793. https://doi.org/10.1016/j.psj.2023.102793

Yu, B., Liu, J., Zhang, J., Mu, T., Feng, X., Ma, R., & Gu, Y. (2022). Regulatory role of RNA N (6)-methyladenosine modifications during skeletal muscle development. *Frontiers in Cell and Development Biology, 10*, Article 929183. https://doi.org/10.3389/fcell.2022.929183

Zhang, J., Jazii, F. R., Haghighi, M. M., Alvares, D., Liu, L., Khosraviani, N., & Adeli, K. (2020). miR-130b is a potent stimulator of hepatic very-low-density lipoprotein assembly and secretion via marked induction of microsomal triglyceride transfer protein. *American Journal of Physiology-Endocrinology and Metabolism, 318*(2), E262–E275.

Zhang, M., Li, D., Zhai, Y., Wang, Z., Ma, X., Zhang, D., …, Sun, G. (2020). The landscape of DNA methylation associated with the transcriptomic network of intramuscular adipocytes generates insight into intramuscular fat deposition in chicken. *Frontiers in Cell and Development Biology, 8*, 206. https://doi.org/10.3389/fcell.2020.00206

Zhang, X., Liu, C., Kong, Y., Li, F., & Yue, X. (2022). Effects of intramuscular fat on meat quality and its regulation mechanism in tan sheep. *Frontiers in Nutrition, 9*, Article 908355. https://doi.org/10.3389/fnut.2022.908355

Zhang, W., Wang, J., Li, B., Sun, B., Yu, S., Wang, X., & Zan, L. (2023). Long non-coding RNA BNIP3 inhibited the proliferation of bovine intramuscular preadipocytes via cell cycle. *International Journal of Molecular Sciences, 24*(4). https://doi.org/10.3390/ijms24044234

Zhao, X., Yang, Y., Sun, B. F., Shi, Y., Yang, X., Xiao, W., …, Yang, Y. G. (2014). FTO-dependent demethylation of N6-methyladenosine regulates mRNA splicing and is required for adipogenesis. *Cell Research, 24*(12), 1403–1419. https://doi.org/10.1038/cr.2014.151

Zhong, H., Tang, H. F., & Kai, Y. (2020). N6-methyladenine RNA modification (m6A): An emerging regulator of metabolic diseases. *Current Drug Targets, 21*(11), 1056–1067.

Zhu, Q., Wu, Y., Mai, J., Guo, G., Meng, J., Fang, X., & Zhong, S. (2022). Comprehensive metabolic profiling of inflammation indicated key roles of glycerophospholipid and arginine metabolism in coronary artery disease. *Frontiers in Immunology, 13*, Article 829425.

Zubiri-Gaitán, A., Mora, M., Casto-Rebollo, C., Santacreu, M. A., Blasco, A., Hernández, P., & Ibañez-Escriche, N. (2022). Maternal effect on the metagenomic composition determining the intramuscular fat content in rabbits. *Proceedings of 12th World Congress on Genetics Applied to Livestock Production (WCGALP) Technical and species orientated innovations in animal breeding, and contribution of genetics to solving societal challenges*, 2073-2076.