

# Unravelling the impact of epigenetic mechanisms on offspring growth, production, reproduction and disease susceptibility

## Review Article

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## Summary

Epigenetic mechanisms, such as DNA methylation, histone modifications and non-coding RNA molecules, play a critical role in gene expression and regulation in livestock species, influencing development, reproduction and disease resistance. DNA methylation patterns silence gene expression by blocking transcription factor binding, while histone modifications alter chromatin structure and affect DNA accessibility. Livestock-specific histone modifications contribute to gene expression and genome stability. Non-coding RNAs, including miRNAs, piRNAs, siRNAs, snoRNAs, lncRNAs and circRNAs, regulate gene expression post-transcriptionally. Transgenerational epigenetic inheritance occurs in livestock, with environmental factors impacting epigenetic modifications and phenotypic traits across generations. Epigenetic regulation revealed significant effect on gene expression profiling that can be exploited for various targeted traits like muscle hypertrophy, puberty onset, growth, metabolism, disease resistance and milk production in livestock and poultry breeds. Epigenetic regulation of imprinted genes affects cattle growth and metabolism while epigenetic modifications play a role in disease resistance and mastitis in dairy cattle, as well as milk protein gene regulation during lactation. Nutri-epigenomics research also reveals the influence of maternal nutrition on offspring's epigenetic regulation of metabolic homeostasis in cattle, sheep, goat and poultry. Integrating cyto-genomics approaches enhances understanding of epigenetic mechanisms in livestock breeding, providing insights into chromosomal structure, rearrangements and their impact on gene regulation and phenotypic traits. This review presents potential research areas to enhance production potential and deepen our understanding of epigenetic changes in livestock, offering opportunities for genetic improvement, reproductive management, disease control and milk production in diverse livestock species.

## Introduction

In the past, it was widely believed that all of an organism's functions were controlled by genetic information contained in 25,000–30,000 genes throughout the genome. However, these genes account for just 5% of the total, with the remaining 95% governed by epigenetic information present in the form of the 'epigenome', which dictates how, when and where the information existing in the genome should be used in the form of a set of instructions known as epigenetic marks (Satheesha *et al.*, 2020).

A multilayer interplay between the genome, epigenome, environmental variables and other non-genetic components results in phenotypic outcome (Ibeagha-Awemu and Khatib, 2023). A shift from genotype + environment = phenotype to genotype + epigenotype + environment = specific phenotype, claiming that genotype and phenotype were linked by a complex set of genetic and non-genetic developmental processes known as the epigenotype (Waddington, 2012). Waddington coined the term 'epigenetic landscape'. Epigenetics is typically defined as the study of heritable changes in gene function that occur without a change in the DNA sequence (Rubio *et al.*, 2023; Zhang *et al.*, 2019a). Several molecular processes, such as paramutation, bookmarking, imprinting, gene silencing, transposon silencing, X chromosomal inactivation, position effect, reprogramming, transvection and maternal effects are at play (Triantaphyllopoulos *et al.*, 2016). Understanding and employing epigenetic mechanisms may help with improving livestock productivity and disease resistance, as well as understanding quantitative traits (Ibeagha-Awemu and Zhao, 2015; Ibeagha-Awemu and Khatib, 2017; Banta and Richards, 2018; Panzeri and Pospisilik, 2018).

Recent studies have further advanced our understanding of epigenetic mechanisms and highlighted the role of non-coding RNAs, such as microRNAs and long non-coding RNAs, in epigenetic regulation (Zhang *et al.*, 2019b). These non-coding RNAs have been shown to interact with the epigenetic machinery and modulate gene expression patterns. Additionally,



studies have explored the impact of environmental factors, such as nutrition and stress, on epigenetic modifications and their trans-generational effects and paternal stress has the potential to alter an offspring's phenotype by means of causing molecular, hormonal, somatic and behavioural alterations. A changed spectrum of regulatory non-coding RNAs in spermatozoa is one putative mechanism for the transmission of paternal effects to offspring. (Malysheva *et al.*, 2023). Paternal transgenerational nutritional epigenetic regulation was a substitute for antibiotics (Li *et al.*, 2022a).

Furthermore, advancements in high-throughput sequencing technologies have enabled comprehensive profiling of epigenetic marks across the genome. Techniques such as ChIP (Chromatin immunoprecipitation) sequencing, ATAC (Assay for transposase-accessible chromatin) sequencing and bisulfite sequencing have provided valuable insights into the distribution and functional significance of epigenetic marks in various species (Ran *et al.*, 2023; Fan *et al.*, 2020). These technological advancements have facilitated the identification of specific epigenetic modifications associated with gene regulation and phenotype variation.

This review aims to provide an in-depth exploration of epigenetics and its role in livestock breeding. It will examine the mechanisms of epigenetic regulation, the impact of epigenetic modifications on gene expression and phenotype and their implications for improving livestock traits. Additionally, it will discuss the challenges and opportunities associated with incorporating epigenetic knowledge into breeding strategies, ultimately highlighting the potential of harnessing epigenetics for enhancing livestock productivity and adaptability.

## Epigenome dynamics in livestock: influences and implications

The epigenome is made up of several interconnected regulatory components like DNA methylation, histone modification, chromatin remodelling, non-coding RNA and nuclear matrix interactions that define phenotypic variation in addition to what the DNA sequence encodes (Dobersch *et al.*, 2021; Zhang *et al.*, 2019b) (Figure 1A). These epigenetic marks play a crucial role in influencing gene expression patterns and are transmitted through mitosis, providing instructions on how genetic information should be utilized. The epigenome is known to exhibit remarkable plasticity throughout an organism's lifespan, influenced by intricate interplay between genetic factors and environmental cues (Cavalli and Heard, 2019; Norouzitallab *et al.*, 2019). Furthermore, the study of non-coding RNAs, such as microRNAs, in livestock has revealed their role in post-transcriptional gene regulation and their potential as epigenetic regulators. MicroRNAs have been implicated in regulating important biological processes in livestock, including muscle development, milk production and immune response (Miretti *et al.*, 2020; Dysin *et al.*, 2021).

## Mechanism of epigenetic expression

### DNA methylation in livestock: mechanisms and functional significance

DNA methylation is a crucial epigenetic alteration for preservation of genomic integrity and control gene expression. Gene expression is impacted by DNA methylation but not the nucleotide sequence or makeup. DNA methyltransferases (DNMTs) are enzymes that covalently transfer a methyl group to the C5 position of cytosine to generate 5-methylcytosine (5mC), most typically at the dinucleotide

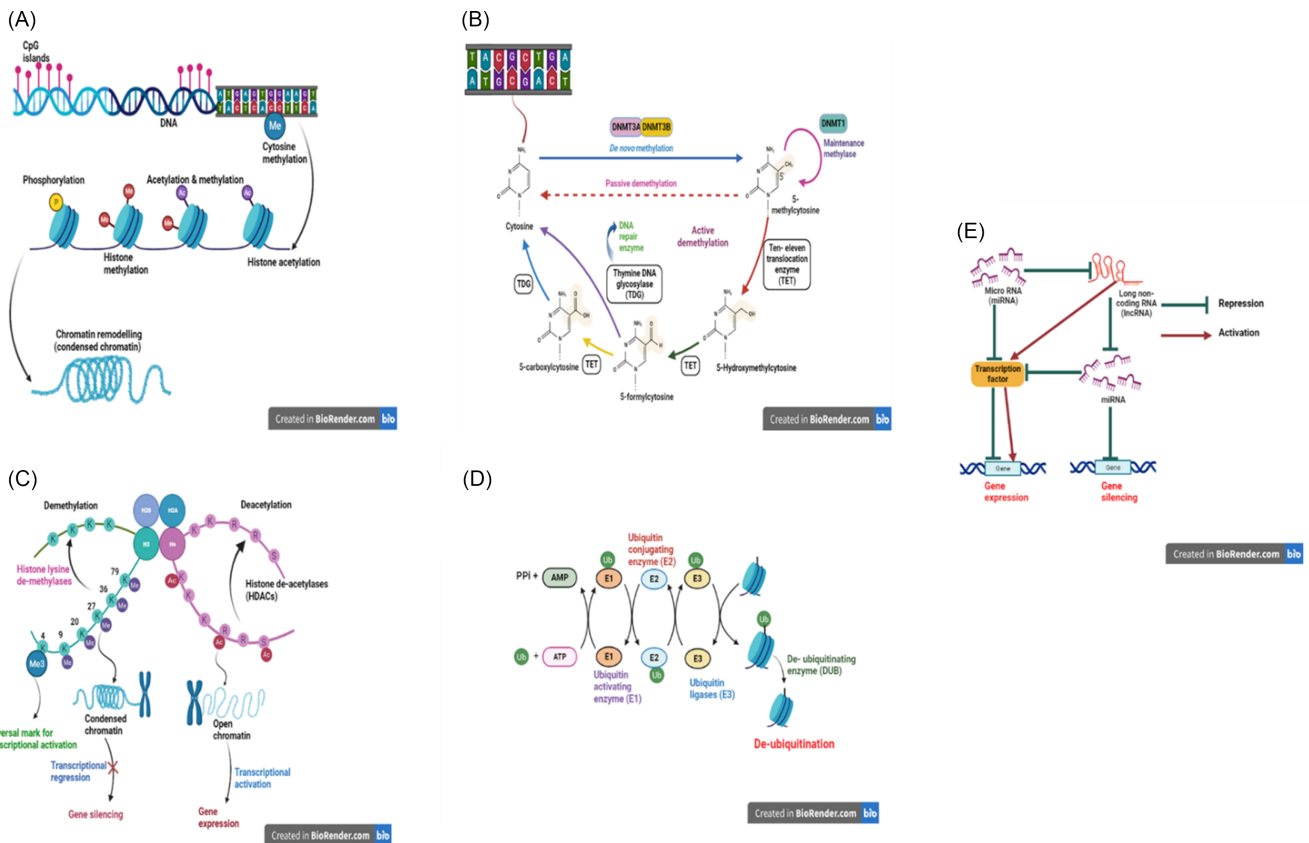
sequence CG (mCG) (Wang *et al.*, 2021). DNA methylation in eukaryotes is mediated by DNMTs. CpG (cytosine-phosphate-guanosine) islands, which are frequently found inside the promoter of protein-coding genes and housekeeping genes, are defined as DNA portions that are longer than 200 base pairs and exhibit a CG:GC ratio greater than 0.6 (Wang *et al.*, 2021). De novo DNMT activity or DNMTs inhibition can both lead to methylation reprogramming. Ten-eleven translocation (TET) enzymes catalyse the oxidation of 5mC, forming several intermediates such as 5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxylcytosine before its complete conversion to cytosine (Rasmussen and Helin, 2016). Methylation of the gene promoter region can cause transcriptional silence, hampering gene expression (Zhang *et al.*, 2023)

The genomic landscape of 5mC results from the continuous activity of both DNA methylation and demethylation processes, creating a dynamic equilibrium that can be changed in response to stimuli, such as changes in the cell's external environment. The importance of maintaining an appropriate equilibrium of DNA methylation is underscored by the correlation between the loss of 5mC and genomic instability and cancer, while the gain of 5mC has been linked to a number of congenital defects and other diseases (Martin and Fry, 2018). Changes in nutritional status and environmental exposure to a variety of agents can alter patterns of genomic DNA methylation, which in turn affects the structure of chromatin and the expression of genes related to disease (Martin and Fry, 2018; Zhang *et al.*, 2023). DNA methylation levels are influenced by RNA interference, aberrant DNA methyltransferase, histone methylation, viral infection, early environmental stimulation, temperature and dietary supply (Zhang *et al.*, 2023).

The discovery of DNA methylation in calf thymus cells by Hotchkiss in 1948 marked a significant milestone in understanding this epigenetic modification (Jurkowska *et al.*, 2011). DNMT1 maintains methylation pattern during DNA replication (Edwards *et al.*, 2017; Luo *et al.*, 2018; Schmitz *et al.*, 2019), while DNMT3a and DNMT3b are de novo methyltransferases required for mammalian genome imprinting (Veland *et al.*, 2019). DNA methylation is particularly prominent in centromeres, transposons, telomeres, gene ontology sites, enhancers, silencers and repetitive regions of the genome (Zhang *et al.*, 2023). Figure 1B demonstrates visual representation of the mechanism of DNA methylation.

DNA methylation-induced epigenetics also plays a significant role on animal reproductive efficiency (Canovas *et al.*, 2017; Jhamat *et al.*, 2020; Usman *et al.*, 2021; Yang *et al.*, 2020; Gross *et al.*, 2020; Fang *et al.*, 2019; Saeed-Zidane *et al.*, 2019; Liu *et al.*, 2019a; Perrier *et al.*, 2018), growth and development (Yang *et al.*, 2021; Ma *et al.*, 2019; Shi *et al.*, 2023; Fang *et al.*, 2017; Johnson and Conneely, 2019), epigenetic clocks (Horvath and Raj, 2018; Horvath *et al.*, 2022;), disease resistance (de Soutello *et al.*, 2022; Zhang *et al.*, 2021a; Jhamat *et al.*, 2020; Usman *et al.*, 2021), sperm DNA methylation as biomarker of male fertility (Phakdeedindan *et al.*, 2022; Li *et al.*, 2020; Costes *et al.*, 2022), milk production (Dong *et al.*, 2021), meat quality (Zhang *et al.*, 2017a), heat stress (Livernois *et al.*, 2021; Canovas *et al.*, 2017) and wool traits in sheep (Wang *et al.*, 2023a), milk production accelerated epigenetic aging in cows by preparing epigenetic clocks (Ratan *et al.*, 2023).

Wang *et al.* (2019a) reported that DNA methylation in the promoter region of the bovine KPNA7 gene in controls its restricted expression in oocytes, and demethylation of CpG sites was strongly correlated with the tissue specificity of the KPNA7 gene. Rekawiecki *et al.* (2018) reported that methylation of PGR-A and PGR-B in promoter region may have an impact on the



**Figure 1.** (A) Diverse array of epigenetic marks in the cell epigenome, (B) DNA methylation: An epigenetic modification regulating gene expression, (C) epigenetic modifications: Regulation of gene expression through histone methylation and histone acetylation, (D) mechanism of histone ubiquitination in gene expression control, (E) regulatory roles of microRNA and lncRNA: Mechanisms of action in gene expression control.

regulation of progesterone in the luteum and endometrium in cows. Ju *et al.* (2020) reported that in *E. coli*-induced mastitis in cows, DNA methylation affects the transcription of protein-coding genes and miRNAs, which helps to explain the role of DNA methylation in the pathogenesis of mastitis. It also provides new target genes like CITED2, SLC40A1 and LGR4 and epigenetic markers for mastitis resistance breeding in dairy cows. *S. aureus*-positive cattle exhibited noticeably more methylation sites on BTA 11 than *S. aureus*-negative controls, suggesting that DNA methylation may play a regulatory role in the immune response to *S. aureus* mastitis (Song *et al.*, 2016; Chen *et al.*, 2019a; Zhang *et al.*, 2018a; He *et al.*, 2016; Wang *et al.*, 2016).

Heat stress also alter the DNA methylation patterns in the liver and mammary gland of dairy cows, affecting milk production and immune response (Dvoran *et al.*, 2022; Qin *et al.*, 2021). Additionally, social stress in pigs has been associated with changes in DNA methylation and gene expression in the hypothalamus, influencing behaviour and stress response (Corbett *et al.*, 2021).

### Histone modifications in livestock traits and biological processes

One important class of chromatin modifications known as histone modifications is in charge of the epigenetic control of gene expression. Under the influence of related enzymes, histones go through a variety of modification processes like as methylation, acetylation, phosphorylation, sumoylation (covalent conjugation of small ubiquitin-like modifier (SUMO) family of proteins to

lysine residues in target substrates via an enzymatic cascade) (Huang *et al.*, 2024) and ubiquitination involved in regulation of DNA damage and transcriptional activities (Zhang *et al.*, 2020; Alhamwe *et al.*, 2018; Shanmugam *et al.*, 2018). Different modifications are linked to the activation or repression of gene expression. The most significant histone modifications, which mainly affect lysine residues in histone H3, are methylation and acetylation (Zhang *et al.*, 2020).

Histone acetylation at particular amino acids, such as histone 3 lysine 9 acetylation, or H3K9Ac, is typically linked to active chromatin. Histone deacetylases (HDACs) remove it, whereas histone acetyltransferases (HATs) mediate it. Additionally, histone methylation takes place at particular amino acids, such as H3 lysine 27 trimethylation, abbreviated H3K27me3, or H3 lysine 4 trimethylation, abbreviated H3K4me3, which can affect the expression of genes in ways that are both repressive and activating. Histone methyltransferases (HMTs), which are mostly represented by histone lysine demethylases (KDMs), mediate both histone methylation and demethylation (Zhang *et al.*, 2020).

Histone modifications play a crucial role in regulating gene expression by altering chromatin structure and influencing the accessibility of DNA to transcription factors and other regulatory proteins (Millán-Zambrano *et al.*, 2022).

In various livestock species, histone modifications have been linked to embryonic development, muscle development and differentiation, adipocyte differentiation, milk production traits like milk fat yield and protein yield in cattle (Luo *et al.*, 2012), meat quality traits like intramuscular fat deposition in pigs (Grade *et al.*,

2019) immune response and stress response in livestock and poultry (Stachecka *et al.*, 2021; Chanthavixay *et al.*, 2020; Xue *et al.*, 2021).

#### **Histone methylation: regulation of gene expression and development**

The regulation of histone methylation patterns in livestock species helps orchestrate gene expression programmes that are essential for various biological processes, including growth, development, reproduction and immune response (Millán-Zambrano *et al.*, 2022).

The specific histone methylation marks are associated with important traits and developmental processes in livestock species like H3K4 trimethylation (muscle development and growth) (Jin *et al.*, 2016), H3K36 methylation (embryonic development and cellular differentiation), which are critical processes for proper organ development and tissue specialization (Li *et al.*, 2022b) and H3K27 trimethylation in subclinical mastitis caused by *Staphylococcus aureus* (He *et al.*, 2016), reproduction and development of oocytes, embryos and preimplantation (H3K4me3 and H3K9me2) (Wu *et al.*, 2020), spermatogenesis in goat (Zheng *et al.*, 2016).

#### **Histone acetylation: modulation of chromatin structure and transcriptional activation**

Histone acetylation is a crucial epigenetic modification that plays a significant role in livestock by regulating gene expression and influencing various biological processes like mastitis and metritis by H3 acetylation (Chen *et al.*, 2019b), reproduction and preimplantation (Wu *et al.*, 2020), in vitro maturation of bovine oocytes (Pontelo *et al.*, 2020), role of H3K27ac3 in bovine rumen epithelial function and development (Kang *et al.*, 2023), adipogenesis and fat deposition in pigs for meat quality traits (Stachecka *et al.*, 2021). Figure 1C demonstrates visual representation of the mechanism of histone methylation and histone acetylation.

#### **Histone ubiquitination: implications for DNA damage response and genomic stability**

Histone ubiquitination is an important epigenetic modification that has been extensively studied in livestock species. It primarily occurs at H2A and H2B histone proteins and involves the covalent attachment of ubiquitin monomers to lysine residues after translation. The process of histone ubiquitination is carried out through a series of enzymatic steps involving ubiquitin activating enzymes (E1s), ubiquitin conjugating enzymes (E2s) and ubiquitin ligases (E3s). Conversely, deubiquitinating enzymes (DUBs) are responsible for removing ubiquitin from histones (Figure 1D) (Yi *et al.*, 2012).

Histone ubiquitination revealed significant association with spermatogenesis and bull fertility (Sutovsky, 2018), histone H2B mono-ubiquitination with spermatogenesis and male fertility in pigs (Yi *et al.*, 2012), reproductive processes, like cell cycle, oocyte maturation, oocyte-sperm binding and early embryonic development (Wang *et al.*, 2022), HSCARG (cell proliferation), a novel regulator of H2A ubiquitination by downregulating PRC1 ubiquitin E3 ligase activity (Hu *et al.*, 2014), apoptosis, cellular stress response and damage mechanisms (Gao *et al.*, 2023; Song *et al.*, 2022), early embryonic development (El-Saafin *et al.*, 2022).

#### **Histone phosphorylation: impact on cell cycle progression**

Histone phosphorylation also modulates gene expression, particularly during cellular processes such as cell cycle progression, cellular differentiation and response to DNA damage, regulation

of reproductive processes (gametogenesis and embryonic development) in various livestock species. Histone phosphorylation (H3S10) has been shown to be dynamically regulated during oocyte maturation and early embryonic development in dairy cows and phosphorylation of H2AS1 regulates expression of immune-related genes in pigs and disease resistance in livestock (Herchenröther *et al.*, 2023).

#### **Livestock-specific histone modifications**

Lysine crotonylation is involved in the identification of active sex chromosome-associated genes in post-meiotic male germ cells (Liu *et al.*, 2017a), lysine crotonylation and 2-hydroxyisobutyrylation plays important role in ovarian development in piglets (Yang *et al.*, 2023) and parasite development like *Toxoplasma gondii* (Yin *et al.*, 2019). Histone neddylation is another important modification observed in livestock species and plays important role in DNA damage repair processes and maintains genome integrity (Xu *et al.*, 2010). Citrullination, the conversion of arginine residues to citrulline, can also occur on histone H3 in livestock and serve as a unique prognostic marker in patients with advanced cancer (Wang *et al.*, 2020a) and histone lactylation plays important role in mammary gland inflammation in dairy cows (Wang *et al.*, 2023b).

#### **non-coding (nc) RNA in livestock**

ncRNAs play significant regulatory functions in chromatin modification and gene expression that affect the health and productivity of livestock (Do and Ibeagha-Awemu, 2017; Benmoussa *et al.*, 2020). A variety of small RNAs, including microRNA (miRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), endogenous small interfering RNA (siRNA), and PIWI-interacting RNA (piRNA), as well as long ncRNA (lncRNA) types with a length longer than 200 nucleotides make up the cellular ncRNA repertoire. A subcategory of lncRNAs is the class of pseudogenes, which mimic protein-coding genes but lack their protein-coding function as a result of mutations (Weikard *et al.*, 2017, Dong *et al.*, 2018). lncRNAs control histone or DNA modification, primarily methylation and acetylation, to control epigenetic modification primarily in the nucleus, which controls gene transcription at the transcriptional level (Jain *et al.*, 2016).

A potential relevance of identified lncRNAs in livestock regulating pigmentation processes (Weikard *et al.*, 2013), meat quality traits (Billerey *et al.*, 2014), bovine horn ontogenesis, horn agnesia (Allais-Bonnet *et al.*, 2013), horn bud formation (Wiedemar *et al.*, 2014), bovine oocytes and early stages of embryo development (Caballero *et al.*, 2015), emotional behaviour in pig (Tatemoto *et al.*, 2023), foetal development of skeletal muscle in pig (Zhao *et al.*, 2015), preimplantation process in pig (Wang *et al.*, 2016), porcine testis development or spermatogenesis (Ran *et al.*, 2016), adipogenesis in pigs (Wei *et al.*, 2015), skin development and pigmentation in goat (Ren *et al.*, 2016), wool fibre diameter in sheep (Yue *et al.*, 2015), muscle development in chicken (Li *et al.*, 2012), Marek's disease virus (MDV) in chicken (Infected birds of the MD-resistant line were the only ones to have strongly expressed linc-satb1 during the latent phase of MDV infection) (He *et al.*, 2015a), lncRNA transcript pouBW1 association with growth traits in chicken (Mei *et al.*, 2016). Arriaga-Canon *et al.* (2014) reported that the nuclear  $\alpha$ -globin transcript lncRNA (lncRNA- $\alpha$ GT) is responsible for the stage-specific activation of the adult *alpha D-globin* gene in chicken. Roeszler *et al.* (2012) reported that lncRNA MHN, a Z chromosome-linked region showed differential expression



in male and female which contributes to the development of the gonadal and embryonic tissues in chickens.

In sheep, a muscle-specific silencer that regulates the expression of cluster DLK1-DIO3 on OAR18, resulting in the CLPG (Callipyge) phenotype (Bidwell *et al.* 2014).

miRNAs are short RNA molecules, approximately 20–24 base pairs in length, that do not encode proteins. The binding of miRNAs to complementary sequences in the 3'-untranslated regions of target mRNAs results in the post-transcriptional regulation of both gene expression and protein translation via the inhibition of translation initiation and elongation (Saliminejad *et al.*, 2019; Neethirajan, 2022). miRNAs are known to regulate the expression of genes involved in various biological processes, including signal transduction (Barbu *et al.*, 2020), cell cycle (Otto *et al.*, 2017), differentiation (Yao, 2016), proliferation (Lenkala *et al.*, 2014) and apoptosis (Shirjang *et al.*, 2019). miRNA used as biomarkers for detection and monitoring of disease progression in animals due to their high stability in the body fluids of livestock (Correia *et al.*, 2017; Zhang *et al.*, 2015).

There is increasing evidence that specific miRNAs are altered in various disease states in livestock (Miretti *et al.*, 2020) like mycoplasma bovis, bovine viral diarrhoea virus and Staphylococcus aureus (Casas *et al.*, 2016; Taxis and Casas, 2017; Sun *et al.*, 2015), which is caused by altered immunity (Lawless *et al.*, 2014), paratuberculosis (Gupta *et al.*, 2018), foot and mouth disease (Basagoudanavar *et al.*, 2018), heat stress (candidate miRNAs: bta-miR-21-5p, bta-miR-99a-5p, bta-miR-146b, bta-miR-145, bta-miR-2285 t, bta-miR-133a and bta-miR-29c) (Lee *et al.*, 2020; Li *et al.*, 2018a), tumorigenesis and cancers (Gebert and MacRae, 2019), microRNA-145 potent tumour suppressor (Ye *et al.*, 2019), ovarian function, uterine receptivity, embryonic development and placental function (Oladejo *et al.*, 2020), miR-21-3p promotes viability and proliferation of epithelial tissue in mammary gland of cattle (Kozomara *et al.*, 2019), miR-21-3p in endometritis (Zhang *et al.*, 2019a), miR-185 in retained foetal membranes (Stenfeldt *et al.*, 2017), bovine mastitis (Lawless *et al.*, 2014) and Aujeszký's disease (Timoneda *et al.*, 2014).

siRNAs are involved in gene silencing, snoRNAs participate in modifications of ribosomal RNA, and lncRNAs are implicated in telomere regulation, genomic imprinting and X-chromosome inactivation. piRNAs play a role in suppressing transposons and regulating DNA methylation. Additionally, circRNAs are involved in gene transcription control and can act as sponges for RNA binding proteins (Xue *et al.*, 2017; Criscitiello *et al.*, 2020; Yuan *et al.*, 2015).

In farm animals, ncRNAs have been found to play diverse roles in different physiological processes, including disease pathogenesis, adipogenesis and milk production (Criscitiello *et al.*, 2020; Yuan *et al.*, 2015; Xue *et al.*, 2017). Only a few public databases, like lncRNAdb, ALDB v1, RNAcentral, NONCODE 2016, deepBase v2.0, etc., can be searched for deposited lncRNAs associated with livestock (Weikard *et al.*, 2017). Mechanism of action of microRNAs and lncRNAs is illustrated in Figure 1E, depicting their involvement in gene regulation and cellular processes in livestock species.

### Transgenerational epigenetic inheritance

Epigenetic markers, such as DNA methylation, can be changed in sperm and oocytes as a result of environmental exposures. It is possible for these epigenetic modifications to be passed on through fertilization, which could have an impact on both the

programming of the fetus and the phenotypic characteristics of the progeny. Transgenerational epigenetic inheritance refers to the transfer of epigenetic marks over several generations. Intergenerational epigenetic inheritance refers to the transmission of epigenetic marks over two generations (Khatib, 2021). According to van Otterdijk and Michels (2016), for inherited epigenetic changes to be deemed transgenerational epigenetic inheritance in females, the marks must be retained for three generations after the mother's direct exposure. Epigenetic inheritance has a significant impact on phenotypic variance during the development of both an individual and their progeny (Triantaphyllopoulos *et al.*, 2016; Nilsson *et al.*, 2018). As a result, epigenetic inheritance, including intergenerational and transgenerational inheritance, supports the idea that individual phenotype modifications may originate from environmental influences on founder generations during vital germline cell developmental stages (Nilsson *et al.*, 2018; Skinner *et al.*, 2018). Therefore, epigenetic inheritance in farm animals involves the transmission of epigenetic biomarkers such as DNA methylation, histone modifications and ncRNAs between generations (Triantaphyllopoulos *et al.*, 2016; Thompson *et al.*, 2020). Many biological processes, including gene expression throughout early embryonic development, imprinting and the silencing of transposons, depend heavily on epigenetic inheritance (Triantaphyllopoulos *et al.*, 2016).

Radford *et al.* (2014) investigated transgenerational epigenetic inheritance in sheep caused by folate supplementation in diet of pregnant ewes during early gestation and found altered DNA methylation patterns in the offspring associated with body weight and wool quality traits in further generations. Tarrade *et al.* (2015) revealed significant association of high-fat diet in pregnant sows and alterations in DNA methylation patterns in the offspring that are associated with metabolic disturbances and adipogenesis in the offspring and subsequent generations.

### Epigenetics in livestock breeding: insights and implications

The participation of dynamic epigenetic alterations in a variety of biological processes, particularly in response to environmental stimuli, is crucial for normal growth and development (Thompson *et al.*, 2020). Understanding of epigenetic regulatory roles in livestock development and health is furthered by the finding of epigenomic patterns in various tissues. Epigenetic processes had significant effect on placental and embryo development of cattle (Wang *et al.*, 2017). According to Perrier *et al.* (2018), the DNA methylome of sperm is typically less methylated than the DNA methylome of somatic tissues and the promoters and exons of hypomethylated genes in bull sperm were enriched for biological processes critical to sperm functions, such as sexual reproduction, fertilization, cell adhesion and migration, meiosis, RNA transport and signalling regulation. Furthermore, it was discovered that male fertility and associated traits are impacted by dysregulation of DNA methylation in sperm (Perrier *et al.*, 2018; Fang *et al.*, 2019) and histone changes, such as histone acetylation and methylation (Kutchy *et al.*, 2018). Epigenetic alterations have an effect on bovine development, health and production, according to epigenomic profiling of somatic tissues such the liver, brain and mammary gland tissues (Kweh *et al.*, 2019; Wang *et al.*, 2020b). DNA methylation controls the activity of the SIRT6 promoter during the development of bovine adipocytes (Hong *et al.*, 2019). Analysis of the epigenetic processes in several pig tissues, such as

the brain, small intestine and longissimus dorsi muscle, revealed that these tissues have important regulatory functions during pigs' growth and development (Su *et al.*, 2016; Larsen *et al.*, 2018). Epigenetic modifications play important role in brain development (Larsen *et al.*, 2018), steroidogenesis and folliculogenesis (Cao *et al.*, 2020), nutrient metabolism in liver (He *et al.*, 2017) and bacterial colonization of preterm neonate's intestine in pigs (Pan *et al.*, 2018). The evolution and development of chickens are significantly influenced by epigenetic mechanisms like DNA methylation and histone modifications for example embryonic muscle development (Liu *et al.*, 2019b), fatty liver syndrome of fat metabolism (Liu *et al.*, 2016), reproductive performance of inbred chickens (Han *et al.*, 2020). Epigenetic changes have been recognized as significant regulatory mechanisms for milk production in dairy cows and other livestock species (Ibeagha-Awemu and Zhao, 2015; Dechow and Liu, 2018; Wang *et al.*, 2019b). A gene closely linked to milk production called *EEF1D* also has its spatial expression controlled by DNA methylation (Liu *et al.*, 2017b). A significant association between different DNA methylation levels and milk-related genes, such as *PPAR*, *RXR*, and *NPY*, as well as genes related to milk fat, such as *ACACA* and *SCD*, in goats has been found (Zhang *et al.*, 2017b) and puberty related genes like *GnRH* and *KISS1* (Robaire *et al.*, 2022; Jeet *et al.*, 2022) and suggests that DNA methylation plays important regulatory roles in goat lactation. Epigenetic mechanisms modulates the expression of genes involved in the regulation of development of muscles (*DLK1*, *NR4A1*, *TGFB3*, *ACSL1*, *RYR1*, *ACOX2*, *PPARG2*, *NTN1*, *SIX1* and *MAPRE1*) (Wei *et al.*, 2018; Cao *et al.*, 2017; Fan *et al.*, 2020), meat quality traits (*TMEM8C*, *IGF2*, *FASN*, *CACNA1S*, *FADS6* and *MUSTN1*) in beef cattle (Fang *et al.*, 2017; Chen *et al.*, 2019c; Ma *et al.*, 2019), beef tenderness (myosin related genes like *ABCA1*, *ABCA7* and *ABCG1*) in angus cattle (Zhao *et al.*, 2020), bovine adipocyte differentiation (*SIRT4*) (Hong *et al.*, 2019) and organ development (*PHF14*) (Leal-Gutiérrez *et al.*, 2020). Epigenetic mechanisms have a major impact on the egg laying performance of poultry (He *et al.*, 2018; Guo *et al.*, 2020; Omer *et al.*, 2020; Omer *et al.*, 2018). DNA methylation and histone acetylation were discovered to be substantially associated with cashmere production and quality traits (*HOXC8* and *HOTAIR* gene) in goat (Wang *et al.*, 2017; Palazzese *et al.*, 2018; Dai *et al.*, 2019; Li *et al.*, 2018b; Jiao *et al.*, 2019). Epigenetic alterations have a substantial impact on the dynamic control of immune responses to stresses like infection (Safi-Stibler and Gabory, 2020; Emam *et al.*, 2019), *Mycobacterium bovis* in cattle (Doherty *et al.*, 2016), Bovine viral diarrhoea (Fu *et al.*, 2017), mastitis (Zhang *et al.*, 2018a; Wu *et al.*, 2020; Usman *et al.*, 2016; Wang *et al.*, 2020b; Sajjanar *et al.*, 2019; Wang *et al.*, 2020c; Ju *et al.*, 2020; Kweh *et al.*, 2019), Scrapie (Hernaiz *et al.*, 2019), porcine reproductive and respiratory syndrome virus (PRRSV) infection (Lu *et al.*, 2017), infectious bursal disease in chickens (Ciccione *et al.*, 2017), New castle disease resistance (Chanthavixay *et al.*, 2020). Various epigenetically regulated gene loci and traits in Livestock and poultry are listed in Table 1.

Environmental factors, particularly EDCs (endocrine disruptors) derived from plastic (bisphenol-A, BPA, phthalate di-2-ethylhexyl phthalate, DEHP and bisphenol-A bis-diphenyl phosphate, BDP), cause oxidative stress and lead to abnormal DNA methylation in both male and female gametes, which results in transgenerational epigenetic modifications (Selvaraju *et al.*, 2021; Skinner, 2016; Liu *et al.*, 2017c). By inducing oxidative stress, BPA alters DNA methylation, which has an impact on male rat pup development and reproductive function (El Henafy *et al.*, 2020).

DEHP exposure during pregnancy and in ancestry has been shown to disrupt DNA methylation in the ovaries of CD-1 mice in each generation by altering the activity of enzymes like DNMT and TET, which changes the expression of genes in pathways like the sex steroid hormone synthesis pathway, the phosphoinositide 3-kinase pathway, cell cycle regulators, apoptosis, steroid hormone receptors and insulin-like growth factors (Rattan *et al.*, 2019) necessary for ovarian cell growth, proliferation and function. Additionally, DBP exposure during embryonic development results in hypomethylation of genes essential for heart development, which results in congenital cardiac abnormalities (Hernández-Cruz *et al.*, 2022). Epigenetic modifications and their potential effects on controlling important phenotypes of agricultural importance are illustrated in Figure 2.

### Nutri-epigenomics and epigenetic regulation in livestock

Nutrients can influence gene expression via epigenetic processes. Nutritional limitations during the early developmental period may have a significant effect on DNA methylation, animal growth and health (Zhang, 2018b). Efforts have been focused on adapting nutritional supplements to livestock animals and their related implications in order to improve livestock health and welfare, decrease production costs and adapt to global warming (Bobeck, 2020). In 2050, it's predicted that the global population will be 9.6 billion people. Heat stress (HS) has become a significant issue for the dairy sector due to rising global temperatures and increased demand for livestock output. The impact of HS on production factors such dry matter intake, milk yield and feed efficiency have been demonstrated to be detrimental. HS has been demonstrated to negatively impact dairy cow reproduction in addition to other production-related factors. The strategic planning of nutrition and environmental factors is required for the mitigation of HS impacts on dairy cow productivity and fertility.

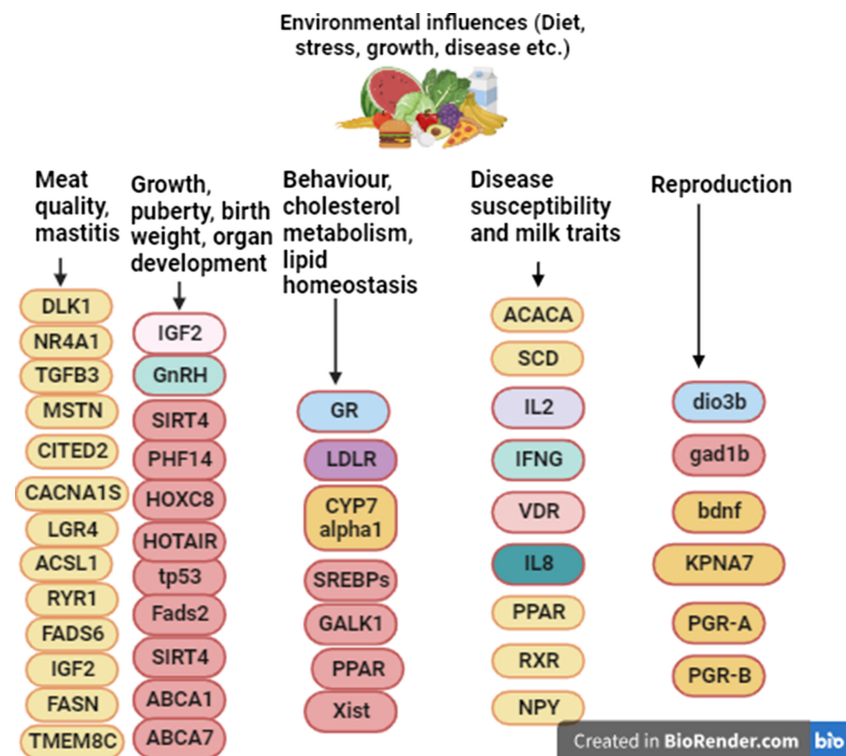
The Dutch famine is among the most famous examples of how nutrition may affect epigenetics and health. The intake of calories consumed was significantly lower than what is advised for human health during a difficult winter during World War II. Adult obesity, type 2 diabetes, cardiovascular disease, a susceptibility for dyslipidemias and even mental disorders were more common in fetuses born under these conditions. Surprisingly, those exposed to these circumstances displayed malnutrition-associated differentially methylated regions (P-DMRs), which are locations in the genome that have varying levels of methylation. These P-DMRs are typically found in regulatory components, especially in areas related to birth weight and LDL cholesterol levels (Goyal *et al.*, 2019; Fernandez-Twinn *et al.*, 2019). miRNAs have a key role in the harmful effects of heavy metals, especially when it comes to altered epigenetic mechanisms of gene expression in neurological illnesses. Lead (Pb) and cadmium (Cd) are two examples of heavy metals that have been linked to the onset of amyotrophic lateral sclerosis (ALS), Parkinson's disease and Alzheimer's disease (Genchi *et al.*, 2020; Wallace *et al.*, 2020). From a nutritional standpoint, it has been established that consumption of glucose stimulates the protein Thioredoxin-Interacting Protein (TXNIP), which then causes the development of miR-204. As a result, type 2 diabetes mellitus is facilitated by miR-204, which targets MAFA, a crucial transcription factor for insulin synthesis (Xu *et al.*, 2013). Nutrition has a significant influence on epigenetic regulators and, as a result, plays a potentially important role in the control of cellular responses like oxidative stress. HS directly influences embryonic development through epigenetic control, or indirectly

**Table 1.** Epigenetically regulated gene loci and traits in livestock and poultry

Trait	Context	References
Altered DNA methylation of selected genes in endometrium and embryos with restricted diet in pig	ACP5, RGS12, EDNRB, TLR3, ADIPOR2, DNMT1 genes	Zglejc-Waszak <i>et al.</i> , 2019
Vit C supplementation in pig causes H3K4me3 and H3K36me3	TET2, DNMT3B, TET3, METTL14, KDM5b and EED	Yu <i>et al.</i> , 2018
Maternal genistein supplementation in laying broiler breeder hens	Cause induced H3K36me3 and H4K12ac at PPAR $\alpha$ promoter in liver	Lv <i>et al.</i> , 2019
Grass fed and grain fed Angus cattle	Epigenetic marker genes ADAMTS3 and ENPP3 in rumen	Li Y. <i>et al.</i> , 2019
Butyrate treatment in Holstein cows (Chromatin remodelling)	H3K27me3 and H3K4me3	Fang <i>et al.</i> , 2019
<i>E.coli</i> challenge in sows in mammary epithelial cells	561 and 898 DMCs at 3 and 24h after challenge, respectively	Sajjanar <i>et al.</i> , 2019
Heat stress induced NDV infection in chicken	Cause histone modifications	Chanthavixay <i>et al.</i> , 2020
Scrapie in sheep	8907 DMRs	Hernaiz <i>et al.</i> , 2019
<i>DNMT</i> gene expression in Marek's disease resistant and susceptible chickens prior to and following infection by MDV.	Role of epigenetics in immunity	Tian <i>et al.</i> , 2013
Hypermethylation of <i>ALVE</i> linked to resistance to Marek's disease	Role of epigenetics in immunity	Triantaphyllopoulos <i>et al.</i> , 2016
Maternal diet supplemented with zinc protects against maternal heat stress	Epigenetics of offspring influenced by maternal diet.	Zhu <i>et al.</i> , 2017a
Manganese supplementation in maternal diet protects embryos against maternal heat stress	Epigenetics of offspring influenced by maternal diet.	Zhu <i>et al.</i> , 2017b
Genistein injected Quail eggs were linked to F3 generation delayed sexual maturity	transgenerational effects of estrogenic compound	Leroux <i>et al.</i> , 2017
Maternal diet in ducks affects F2 generation metabolism	transgenerational effects of methionine in diet	Brun <i>et al.</i> , 2015
Effect of maternal diet restriction during gestation on methylation levels in sheep	Offspring epigenetics affected by maternal diet restriction during pregnancy	Chadio <i>et al.</i> , 2017
Daily maternal supply of Methyl donors throughout pregnancy causes hypermethylation in the liver of offspring of pigs	Offspring epigenetics affected by maternal diet	Jin <i>et al.</i> , 2018
Daily maternal supply of Methyl donors resulted in hypermethylation in small intestine of offspring of pigs	Offspring epigenetics affected by maternal diet	Liu <i>et al.</i> , 2017b
Calf's prenatal environment affects calf and milk production	Environment brings epigenetic changes in the offspring	Engmann, 2018
DNA methylation changes at the promoter region of the casein <i>aS1</i> gene ( <i>CSN1S1</i> ) in bovine mammary tissue	The protein encoded by <i>CSN1S1</i> is important for milk production in cattle	Doherty <i>et al.</i> , 2014
<i>IGF2</i> gene is associated with milk production and carcass traits in cattle	Epigenetic regulation of <i>IGF2</i> gene influenced by dietary strategies.	Doherty <i>et al.</i> , 2014
Meishan piglets from adults fed a low-protein diet have higher levels of H3 acetylation and trimethylation at the <i>MSTN</i> promoter region.	<i>MSTN</i> (double muscling phenotype in cattle)	Doherty <i>et al.</i> , 2014
Hypermethylation of murine Interleukin 2 ( <i>IL2</i> ) and Interferon gamma ( <i>IFNG</i> ) in response to viral antigens	contribute to the reduced cytokine expression in animals with infectious diseases	Killick <i>et al.</i> , 2011
Subacute ruminal acidosis in goat	Decreased methylation of LOC101896713 and CASP8	Chang <i>et al.</i> , 2018
Porcine epidemic diarrhoea virus in Large White piglets	Increased H3K4me3 in jejunum	Wang <i>et al.</i> , 2019
Bovine viral diarrhoea virus	Decreased methylation of miR-29b	Fu <i>et al.</i> , 2017

through decreased DMI and changes to the animal's metabolic state (Abdelatty *et al.*, 2018). According to Vargas *et al.* (2023) DNA methylation was low in the early stages of embryonic development but increased from the six to eight cell stage to the blastocyst stage. Furthermore, a low-protein diet in rats changed the early embryonic de novo methylation process (Abdelatty *et al.*, 2018). In order to regulate the genome's epigenetic state through

DNA methylation and histone modifications, a subset of nutrients known as epi-nutrients are required. The proper addition of epi-nutrients during heat stress may help to control how the embryo develops. These nutrients have an impact on peri-conceptual DNA methylations, which have an impact on embryonic development, post-implantation growth and the health of the progeny. Most epi-nutrients, including folate, vitamin B-12,



**Figure 2.** Epigenetic modifications and their potential effects on controlling important phenotypes of agricultural importance. Important genes proven to be epigenetically regulated by environmental factors, including nutrition, and the combined effect of these factors may have significant effects on aspects related to animal behaviour, growth and health in cattle.

methionine, choline and betaine, can modify the 1-carbon metabolic pathways that are responsible of producing the main methyl donor, S-adenosylmethionine (SAM), which can directly impact DNA methylation. The epi-nutrients choline and folate are crucial for DNA methylation reprogramming during early embryonic development (Abdelatty *et al.*, 2018). Crouse *et al.* (2022) reported that epigenetic modifiers such methionine, choline, folic acid and vitamin B12 take role in methylation responses during early embryonic development. He *et al.* (2015b) reported that supplemental dietary folic acid was effective in reversing changes in the tp53 gene expression and DNA methylation status of intrauterine growth delayed rats. Mennitti *et al.* (2015) reported that fat intake during development causes fatty acid desaturase gene (Fads2) transcription to change persistently in the hepatic polyunsaturated fatty acid status of offspring. According to Osorio *et al.* (2016), methionine-supplemented Holstein cows had reduced levels of overall DNA methylation and hypermethylation in the promoter of a PPAR-specific DNA region. Energy restriction had a significant impact on the DNA methylation level of an IGF2 DMR in foetal beef cattle longissimus dorsi, where IGF2 expression was inversely correlated with fetus weight in Angus-Simmental crossbred cows (Paradis *et al.*, 2017). Additionally, offspring were obese due to their mothers' high-fat diets, and individual variances in obesity may be controlled by epigenetic changes (Keleher *et al.*, 2018; Glendining and Jasoni, 2019). The ability of female children to reproduce can also be impacted by dietary changes during pregnancy, which may be controlled by epigenetic changes, according to reports (Noya *et al.*, 2019; Shah and Chauhan, 2019). In pigs, dietary changes like feed restriction, supplementation with omega-3 fatty acids, vitamin C and methyl donors have been shown to result in altered global DNA methylation patterns, which in turn affect the development of germline cells and embryos, growth and inflammatory issues in piglets and the rate at which piglets grow (Yu *et al.*, 2018; Zglejcz-Waszak *et al.*, 2019; Boddicker *et al.*, 2016). In addition, low serum

concentration of galactose in neonatal piglets in response to betaine-supplemental feeding of sows was associated with inhibited expression of the GALK1 gene through DNA hypermethylation and histone trimethylation in the liver (Cai *et al.*, 2017). In the promoter region of the PPAR gene, histones H3K36me3 and H4K12ac have a role in the regulation of altered lipid metabolism and growth performance after maternal genistein supplementation (Lv *et al.*, 2019) and maternal betaine supplementation affect genes linked to cholesterol and corticosteroid synthesis in offspring pullets through altered DNA methylation (Hu *et al.*, 2017; Idriss *et al.*, 2018; Abobaker *et al.*, 2019). Maternal nutrition during pregnancy has been shown to impact the DNA methylation patterns in offspring, which can have consequences on growth and muscle development (Amorin *et al.*, 2023; Liu *et al.*, 2021; Zhang *et al.*, 2021b; Sandoval *et al.*, 2021), energy metabolism (Muroya *et al.*, 2023; Muroya *et al.*, 2021), reproduction and fertility (Moura *et al.*, 2022) and disease development (Thompson *et al.*, 2020; Goyal *et al.*, 2019), dietary resveratrol supplementation affect muscle fibre types and meat quality in beef cattle (Li *et al.*, 2022c).

Epigenetic modifications, specifically histone modifications, have been implicated in the alteration of CYP7 alpha 1 promoter in the offspring of rats subjected to a maternal low-protein diet, thereby affecting hepatic cholesterol homeostasis (Songstad *et al.*, 2015). The health, growth and productivity of cattle could perhaps be impacted by diet-related changes in a way that has not previously been recognized (Figure 2).

### Assisted reproduction technologies (ART) and epigenetics in livestock: implications for embryo development

Assisted reproductive technologies alter the embryos' transcriptome and epigenome, which may have long-term phenotypic effects (Canovas *et al.*, 2021). Assisted reproductive technology (ART) known as somatic cell nuclear transfer (SCNT) is a rapidly



evolving field. It was discovered that a variety of factors regulating the biological, molecular and epigenetic events govern how effectively animals can produce SCNT-derived embryos, conceptuses and progeny (Skrzyszowska and Samiec, 2021). In pre- and post-implantation cloned goat embryos, the nuclear genome of terminally differentiated somatic cells, such as pituitary cells, can successfully undergo the whole processes of epigenetic remodelling and reprogramming. Deng *et al.* (2019) reported that transcriptional activity of *Xist* gene decreased significantly in lungs and brain of dead cloned does (lack of inactivation of one of the X chromosomes) and increased significantly in ear derived cutaneous fibroblast cells of live cloned does (normal inactivation of one of the X chromosomes). Deng *et al.* (2019) concluded increased levels of hypermethylation and transcriptional suppression of the *Xist* gene occurred in caprine SCNT-derived female fetuses. As a result, neither of the two X chromosomes was inactivated, or active induction of increased transcriptional activity (i.e., biallelic overexpression) of the genes localized in the loci of the paternal and maternal X chromosomes. One of the biggest hurdles deemed to be alleviating the efficiency of somatic cell cloning in mammals, including the domestic goat, is incomplete or inaccurate epigenetic reprogramming of epigenetic memory (Samiec and Skrzyszowska, 2018; Yang *et al.*, 2018). A commonly studied and acknowledged alteration of the somatic cell nuclear genome in cloned embryos is the methylation of cytosine residues in CpG islands (Deng *et al.*, 2020a; Deng *et al.*, 2020b). Han *et al.* (2018) reported enzymatic activity of ten-eleven translocation methylcytosine dioxygenase 3 (TET3) to be a crucial biological mechanism driving active DNA demethylation in preimplantation goat embryos made through somatic cell cloning. The active (i.e., DNA replication independent) demethylation of 5-methylcytosine (5-mC) residues was inhibited in 2-blastomere-stage cloned goat embryos after TET3 gene knockout. Because of this, the pluripotency-related *Nanog* gene's expression was downregulated in the inner cell mass (ICM) compartment of the resulting blastocysts (Han *et al.*, 2018). Blastocysts exhibit sexually-dimorphic DNA methylation patterns, and in vivo embryos exhibited the highest levels of methylation (29.5%), comparable to those produced in vitro with serum, whereas in vitro embryos produced with reproductive fluids or albumin displayed lower global methylation (25–25.4%) (Canovas *et al.*, 2021). The epigenetic memory profile of mammalian SCNT embryos was modified using novel and incredibly effective techniques like applying exogenous nonselective HDAC inhibitors (such as trichostatin A, valproic acid and scriptaid) and/or nonselective DNMT inhibitors (such as 5-aza-20-deoxycytidine) or selective inhibitors lysine K4 demethylases specific for histones H3 within the nucleosomal core of nuclear chromatin (such as trans-2-phenylcyclopropylamine (tranylcypromine; 2-PCPA) (Samiec *et al.*, 2019).

## Cytogenomic techniques for epigenetic studies in livestock

### Next-generation sequencing

NGS is a useful tool for analysing the miRNA transcriptome's complexity. In addition to advances in genome-wide association studies and metagenomics, the use of high-throughput NGS technology in livestock research has also made it possible to better understand the function of miRNAs in cattle health (Oladejo *et al.*, 2020).

### MinION and GridION

The direct electronic analysis of proteins, RNA, DNA and single molecules is made possible by these related technologies, which were created by Oxford Nanopore Technologies (Miretti *et al.*, 2020). These technologies were widely employed for field diagnosis during the 2020 African swine fever outbreak in China (Jia *et al.*, 2012). 'Crush-side genotyping', which has been created especially for the real-time, on-farm genotyping of animals, is one potential application of this technique. Pig *S. suis* bacteria have been functionally characterized using MinION sequencing (antimicrobial resistance). Using the MinION technique, whole-genome generation and characterization profiling, including miRNA sequences, were effectively completed.

### Ion torrent sequencing

Amplicon sequencing is only possible using ion torrent sequencing, which measures the H<sup>+</sup> ions emitted after base incorporation. The sequencing method was used to discover microRNAs that were differentially expressed in heat-stressed Sahiwal (Deiuliis, 2016) and Frieswal breeds of cattle (Sengar *et al.*, 2018). Sengar *et al.* (2018) reported 420 miRNAs out of which 65 miRNAs showed differential expression during the hottest summer days, including bta-miR-2898, which is known to target HSPB8 (heat shock protein 22). In pigs infected with the Aujeszky's disease virus, the expression profiles of the host and viral miRNAs have also been determined by ion sequencing (Sun *et al.*, 2019).

### Electrochemical sensing

Amperometric and potentiometric, voltammetric, impedimetric, conductometric and field effect transistor-based biosensors are all examples of electrochemical sensing (Shirjang *et al.*, 2019; Kozomara *et al.*, 2019). Amperometry-based sensors measure the current at a fixed applied voltage to identify analytes. Voltammetric measurements, in contrast, take the current into account as the potential is raised at a specific rate. Li *et al.* (2023) developed method of sensing nucleic acids with a silicon nanowire field effect transistor biosensor and discovered miRNA in animal cells using this method.

### Loop-mediated isothermal amplification (LAMP)

Compared to PCR, the advantage of LAMP procedures is that they can be carried out without the necessity for exact temperature cycling control (Jia *et al.*, 2012). The method is effective in identifying short RNA sequences like miRNAs (Peng *et al.*, 2020). Multi-miRNAs can be detected using nano-biosensors consisting of graphene oxide and a dye that binds to DN (Wen *et al.*, 2020).

### CRISPR-Cas aided sensor devices

On the basis of CRISPR-Cas (Clustered regularly interspaced short palindromic repeats) high specificity of binding and signal amplification capabilities, have demonstrated remarkable potential and drawn significant interest in site-specific DNA methylation detection (Yu *et al.*, 2023).

### Single-cell DNA methylome sequencing

Describe dynamic methylation events in incredibly varied cell populations. Although the experimental throughput and genomic coverage have grown, this method has low yields and large implementation costs (Wei and Wu, 2022).

### COBRA, or combined bisulfite restriction analysis

Unmethylated cytosine residues are differently converted to uracil using sodium bisulfite chemistry, whereas unaltered methylated cytosines are left. This is a standard method for evaluating DNA methylation. Then, utilizing particular downstream nucleic acid analysis techniques like PCR, qPCR and sequencing, methylated cytosines can be identified (Kumar *et al.*, 2020).

### DNase I Seq

Digital DNase and DNase Seq are two techniques for producing short DNA strands from nuclear-accessible genomic regions through nuclease digestion. Next-generation sequencing is used to identify and analyse these small DNA strands, providing complete sequence details on the genomic segments that are accessible for nuclease digestion (Kumar *et al.*, 2020).

The application of EWAS (epigenome-wide association study) for identifying the epigenetic biomarkers linked to livestock health and productivity traits was severely constrained by the absence of commercially available epigenome analysis assays. Before using epigenetic biomarkers in livestock breeding and production management, epigenome-wide arrays for identifying epigenetic patterns in large samples must be developed. As a result, there is an urgent requirement to create assays tailored specifically for livestock that are based on epigenetic mechanisms (particularly DNA methylation) that are both highly reliable and readily available in the market.

### Fanzor

The 'Fanzor' protein was discovered to be a eukaryotic programmable RNA-guided endonuclease that modifies human cells more precisely in an attempt to find a eukaryotic equivalent of CRISPR (Fadul *et al.*, 2023). Fanzor proteins (and prokaryotic TnpBs) regulate transposable element activity, presumably through methyltransferase activity. TnpB homologs exist in two different forms in eukaryotes: Fanzor1s and Fanzor2s. Fanzor1s and Fanzor2s originate from a single lineage of IS607 TnpBs with an unusual active site configuration, according to the evolutionary links between bacterial TnpBs and eukaryotic Fanzors (Yoon *et al.*, 2023). TnpB has been linked to a novel class of RNA-guided systems known as OMEGA (Obligate Mobile Element-guided Activity) in recent reports. OMEGA systems comprise a non-coding RNA (ncRNA) transcribed from the transposon end region (called  $\omega$ RNA) and an RNA-guided endonuclease protein. CRISPR-Cas systems descended from OMEGA systems, and TnpB gave rise to the single RNA-guided endonuclease Cas12 (Saito *et al.*, 2023).

### Conclusion

Exploring the integration of epigenetic information into breeding programmes offers promise for enhancing desired traits, with strategies including identifying epigenetic markers, conducting epigenome-wide association studies and employing epigenetic editing. However, challenges such as ethical considerations, environmental influences and technical hurdles must be addressed. Ensuring responsible use, understanding heritability, navigating regulatory frameworks and integrating epigenetic data with genomic information are crucial for successful implementation. Collaborative efforts are essential for realizing the potential of epigenetics in breeding while directing these complexities.

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