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REVIEW ARTICLE Agricultural Science Digest, Volume Issue : ()

Epigenetics: Unraveling Hidden Phenotypic Diversity in Livestock

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10.18805/ag.D-5964

ABSTRACT

The missing link between nature and nurture *i.e*. epigenetics is the process of turning genes on and off or can be explained as a phenomenon that includes all the process that affects phenotypic expressions without causing any alteration in the genetic sequence. Epigenetic regulation can be done by post-translational modification of histones but is also linked to the regulation of gene expression by non-coding RNAs, genome instabilities or any other force that could modify a phenotype. Epigenomic patterns in various tissues reveal the regulatory functions of epigenetic mechanisms in livestock growth and health. DNA methylation modifications can explain poor offspring performance due to maternal stressors like metabolic disorder, heat stress and negative energy balance. It is an attractive field for livestock breeding, as it can help identify missing causality and heritability of traits and diseases. Certain methylation patterns are more likely to increase in specific environments, explaining phenotypic diversity between individuals. Accurate recording of the environment and epigenomes can provide more accurate and precise calculations of phenotypic variance. Methods to estimate the contribution of epigenetics to covariance between relatives have been developed which can be beneficial for obtaining favorable methylation patterns that impact disease resistance and economic traits.

Key words: Epigenetics, Genetics, Inheritance, Livestock, Phenotype.

In the field of innovative emerging science, paleobiologist Erwin (2007) concluded that “there is nothing scientists enjoy more than the prospect of a good paradigm shift”. They alter our worldview, the kinds of questions that researchers think are important to addressand even the way we do scientific research. One such shift might be the introduction of Epigenetics. The name “Epigenetics” has been around since the early 1940s, when the theory of genesis was first proposed. British developmental biologist, Conrad H. Waddington coined the term “Epigenetics” and stated in his book “Introduction to Modern Genetics” that the connection between genetics and other branches of biology, such as cytology, embryology, evolutionary theory and cell biology, is much closer than is typically acknowledged. He blended the terms Epigenesis and Genetics, to interpret how genes interact with their environment to produce a phenotype. Waddington (1939) defined epigenetics as “the branch of biology that studies the causal interactions between genes and their products which give rise to phenotypes”. Since then, years of research broadened our grasp of what is meant by the word “epigenetics”. Therefore, any alteration in the expression of genes that result from a source other than a mutation of DNA is usually referred to as epigenetics. This involves DNA methylation, post-translational modification of histones and regulation of gene expression by non-coding RNAs and genome instabilities or any other factor that might change a phenotype (Holliday, 2006; Bird, 2007; Maiti, 2012; Deans and Maggert, 2015).

Epigenetics demonstrates that certain variations that take place throughout the epigenome include genetic material in addition to the sequence found in DNA (Gonzalez-Recio, 2012). The intricate alterations linked to genomic DNA that confer a distinct cellular and developmental identity are called epigenomes. The production of stress-response and neurotropic factors, cytokines, growth factors, alterations in hormone levelsand variations in hormone levels are a few examples of molecules that are “epigenome modifiers” subject to environmental influences. An individual’s epigenome is eventually affected by the many stimuli they are exposed to in their environmentand their unique genetic and epigenetic makeup also influences how they respond to these stimuli (Kanherkar *et al.,* 2014). Moreover, it has been discovered that the environmental-induced epigenetic changes may be transmitted to the next generation *via* the germline. Consequently, the transmission of epigenetic marks between two generations is referred to as intergenerational epigenetic inheritance, whereas transgenerational epigenetic inheritance refers to the transmission of epigenetic markings across different generations (Jirtle and Skinner, 2007).

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How to cite this article: Kumar, I., Nirwan, A., Khan, A., Lalhmingmawii, S. and Vyas, J. (2024). Epigenetics: Unraveling Hidden Phenotypic Diversity in Livestock. Agricultural Science Digest. DOI: 10.18805/ag.D-5964.

Submitted: 08-02-2024 **Accepted:** 17-05-2024 **Online:** 08-07-2024

This highlighted the significance of epigenetics for the livestock population since it can alter populations and the potential to be applied to animal breeding to create desirable phenotypes that would be passed down to the subsequent generation. In light of the importance of epigenetic modification in livestock, the review that follows, which focuses on the function of epigenetics in livestock population and its projected implications, was put together.

Mechanism underlying epigenetics

Every cell in an organism has the same genome, however even if these instructions are stable, variations in the final phenotype of an organism might occur as a result of altered gene expression in response to external stimuli. The main mechanisms that regulate these modifications include histone modification, RNA-associated silencingand DNA methylation (Kanherkar *et al.,* 2014).

DNA methylation

The covalent insertion of a methyl group at position 5’ of Cytosine’s pyrimidine ring, known as 5-methyl C or 5 mC, is known as DNA methylation. Transposable and viral elements, which comprise around 45% of the mammalian genome, are silenced by bulk methylation (Schulz and Hatina, 2006). Most of these elements are rendered inactive through DNA methylation or mutations that arise across time due to 5 mC deamination (Walsh *et al.,* 1998). A methyl group is transferred from S-adenyl methionine (SAM) to the fifth carbon of a cytosine residue, or 5 mC, by a class of enzymes known as DNA methyltransferases (DNMTs), which catalyze DNA methylation (Fig 1). Environmental genotoxins and maternal dietary constraints, such as methionine deficiency during pregnancy (lack of substrate for DNA methylation), have been shown to affect epigenetics of future generations (Burdge and Lillycrop, 2010).

Given their ability to introduce a novel methylation pattern to unmodified DNA, Dnmt3a and Dnmt3b are known as de novo Dnmt. Conversely, Dnmt1 copies the parental DNA strand’s DNA methylation pattern onto the freshly synthesized daughter strand during replication (Goto *et al.,* 1994; Feng *et al.,* 2005).

Moreover, the majority of mammalian genes that code for proteins are transcriptionally regulated in locations where abundant CG sequences are present. At these places, cytosine is positioned adjacent to a guanine nucleotide connected by a phosphate called a CpG site. We refer to these brief regions of CpG-rich DNA as CpG islands. When CpG islands are methylated, chromatin becomes tightly compacted, blocking the start of transcription and gene expression. Conversely, chromatin structure next to CpG island promoters promotes transcription (Kanherkar *et al.,* 2014).

DNA methylation could perturb gene expression activities through direct inhibition of transcription factor (TF) binding or indirect mediation by methyl-binding domain (MBD) proteins that recruit chromatin modifying activities to methylated DNA (Razin and Kantor, 2005; Zhu *et al.,* 2016; Yin *et al.,* 2017; Greenberg and Bourc’his, 2019; Yin *et al.,* 2020). DNA methylation in recognition sequences of some TFs was revealed to alter their binding specificity (Zhu *et al.,* 2016).

MBDs contain a transcriptional repressor complex that may induce histone deacetylation and chromatin remodeling, contributing to gene silencing (Razin and Kantor, 2005; Greenberg and Bourc’his, 2019). MBD such as Methyl-CpG binding protein 2 (MeCP2), revealed that DNA methylation is connected with chromatin structure and gene expression. CpG-rich regions (also known as CpG islands) are frequently distributed in the promoter regions and usually non-methylated, whereby its abnormal methylation may cause the repression of corresponding transcription and gene silencing (Deaton and Bird, 2011; Smith *et al.,* 2020).

Histone modification

Histones are the basic proteins that make up chromatin complexes. They control the packing of DNA, which impacts transcriptional silence and transcriptional activity and

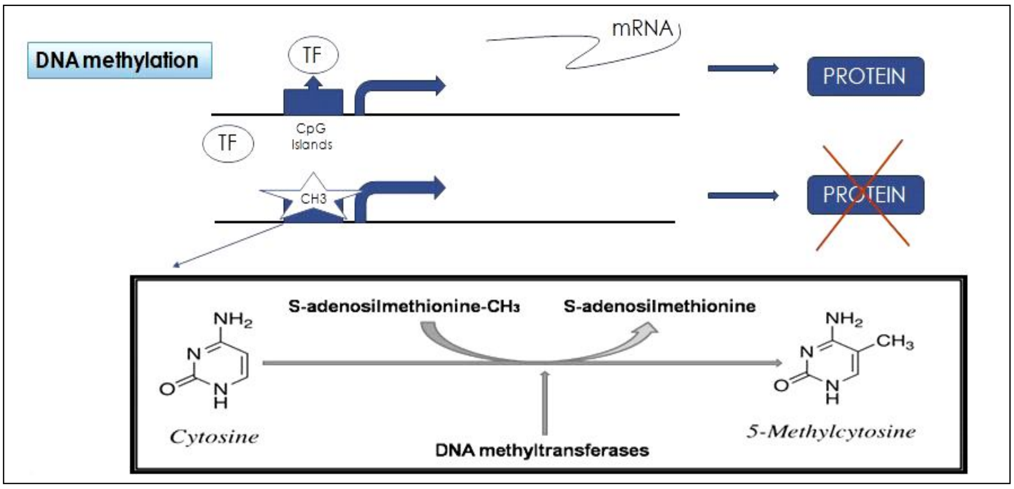

Fig 1: Process of 5-methylationcytosine formation.

significantly influences the degree of chromatin compaction (Luger *et al.,* 1997). The nucleosome, the initial level of chromatin structure, is made up of two copies of each histone H2A, H2B, H3 and H4. These copies create an octameric core, which is firmly surrounded by DNA.

The phrase "histone modifications" refers to post-translational changes made to the flexible segments of N or C terminal residues that extend from the globular histone octamer. Histones can be modified *via* acetylation of lysine residues, methylation of arginine and lysine residues, phosphorylation of serine and threonine residues, ubiquitination of lysine residues on histone tails, sumoylationand ADP ribosylation-related processes. Transcriptional alterations in DNA are all related to this (Fig 2).

Histone acetyltransferases are responsible for histone acetylation, which play important roles in releasing chromatin structure (histone-DNA interaction) and promoting transcriptional activities, while histone deacetylases cause deacetylation to repress gene expression (Dose *et al.,* 2011; Schmauss, 2017). The dynamic changes of histone methylation are regulated by histone methyltransferases and demethylases. Additionally, histone phosphorylation, ubiquitylationand ADP ribosylation are involved in the regulation of DNA damage and transcriptional activities (Liu *et al.,* 2017; Alaskhar Alhamwe *et al.,* 2018; Shanmugam *et al.,* 2018). The insertion or removal of methyl groups on DNA and histones or acetyl groups on histones are the major ways of modifying the epigenetic landscape (Cedar and Bergman, 2009).

RNA silencing

Unlike histone modifications, RNA silencing is a type of post-transcriptional gene modification in which short non-coding RNA segments known as microRNAs (miRNA) and small interfering RNAs (siRNA) block or downregulate the expression of one or more genes (Fig 3). These RNAs can

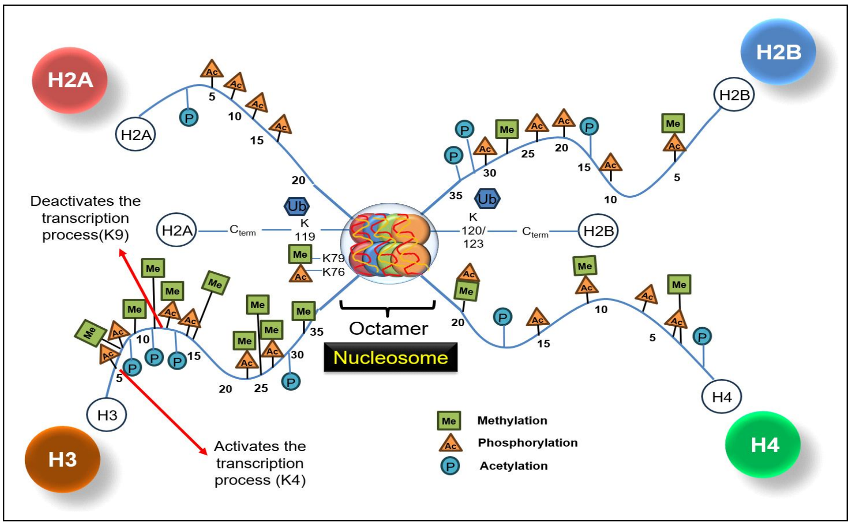

Fig 2: Process of Histone modification.

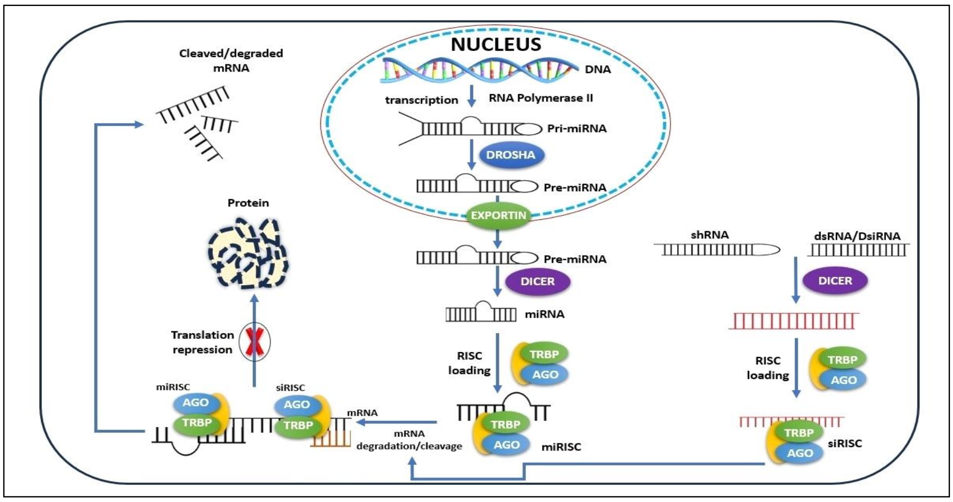

Fig 3: RNA silencing.

have a wide range of effects both within and outside of the cell by acting as switches and modulators (Kanherkar *et al.,* 2014). Due to their specific modulatory properties based on the cell-type specialization of the organism, these RNAs accurately control gene expression throughout both normal development and pathological states (Giraldez *et al.,* 2005; Girardot *et al.,* 2012 Baer *et al.,* 2013).

Fig 3 describe that: siRNA and miRNA precursors undergo synthesis within the nucleus, where they are initially processed by specific enzymes of the RNAi pathway, like Drosha, resulting in the formation of short hairpin structures. These products are subsequently transported out of the nucleus into the cytoplasm by Exportin, a small nucleic acid exporter. Within the cytoplasm, Dicer processes the short hairpin RNAs, generating either siRNAs or miRNAs. These siRNAs/miRNAs are then integrated into the RNA induced silencing complex (RISC). Within RISC, one strand, known as the guide or antisense strand, remains, while the complex binds to a complementary target mRNA. Perfect complementarity between the siRNA/miRNA and the target mRNA results in target degradation, while incomplete complementarity leads to the inhibition of protein translation from the target.

Epigenetics affecting livestock production system

Understanding the regulating roles of epigenetic processes in cattle growth and health has been furthered by the identification of epigenomic patterns in several tissues. Research has indicated that some low performance in offspring resulting from maternal stresses such as metabolic disorders, heat stressand negative energy balance might be partially explained by changes in DNA methylation patterns (Desmet *et al.,* 2016; Mohammed *et al.,* 2024). Thus, the dynamic involvement of epigenetic alterations in a variety of biological functions, particularly in response to environmental stimuli, is imperative for proper growth and development (Del Corvo *et al.,* 2020; Thompson *et al.,* 2020). In bovine, screening of DNA methylation patterns in the the embryo at various stages of development, particularly during epigenetic reprogramming, revealed significant regulatory roles of DNA methylation in the *via*bility and development of the fetus (Ispada *et al.,* 2020; Salilew-Wondim *et al.,* 2018; Cao *et al.,* 2021; Ivanova *et al.,* 2023; Amran *et al.,* 2024). Male fertility and associated traits are also impacted by the dysregulation of DNA methylation (Kropp *et al.,* 2017; Perrier *et al.,* 2018; Fang *et al.,* 2019) and histone modification particularly acetylation and methylation in bovine sperm (Kutchy, 2017 and Kutchy *et al.,* 2018). Additionally, a methylation analysis of the population of bulls with high and low motile sperm revealed methylation variations in genes located in the pericentric regions, which are involved in chromatin remodeling and repetitive element activities. This finding suggested significant epigenetic regulatory roles in sperm functionality and fertility (Capra *et al.,* 2019). Furthermore, epigenetic alterations affect bovine development, productivity and health according to epigenomic profiling of somatic tissues taken from the liver, brain and mammary gland (Zhou *et al.,* 2016; Kweh *et al.,* 2019; Wang *et al.,* 2020a). For instance, DNA methylation controls SIRT6 promoter activity during the development of bovine adipocytes, wherein the SIRT6 gene is a highly conserved gene found in various animal species encoding a protein Sirtuin 6 which regulates various cellular processes such as gene expression, DNA repair and aging (Hong *et al.,* 2018).

In pigs, an epigenetic process was analyzed in various tissues and revealed that a significant impact occurred during the growth and development (Su *et al.,* 2016; Larsen *et al.,* 2018). DNA methylation patterns in embryo tooth germ were examined and 2,469 differentially methylated genes (DMGs) were discovered along with 104 DMGs that may play important regulatory roles in the development of porcine teeth (Su *et al.,* 2016). DNA methyltransferase genes (DNMT genes) which encode enzymes responsible for DNA methylation by the addition of a methyl group (CH3) to cytosine residues in DNA molecules were analyzed during the mid-gestation period. It was found that the expressions of three genes DNMT1, DNMT3A and DNMT3B decreased, suggesting that DNA methylation may be able to control how the piglets' brains develop (Larsen *et al.,* 2018). Moreover, profiling of transcriptional N6-methyladenosine (m6A) in porcine liver at different ages revealed that 33% of transcribed genes with functions in the regulation of growth and development, protein metabolic and catabolic processes were modified by m6A, suggesting that m6A methylation may be essential for the regulation of nutrient metabolism in the liver (He and Li, 2018; Mishra *et al.,* 2023). Furthermore, daily oral intake of broad-spectrum antibiotics decreased bacterial infection and changed the DNA methylation profile in the small intestine. After preterm birth, daily oral boluses of broadspectrum antibiotics reduced bacterial density, diversityand fermentation and changed the DNA methylation profile in the small intestine of piglets. These results show that epigenetic processes may have an impact on bacterial colonization in the intestine of preterm neonates (Pan *et al.,* 2018).

Previous studies have studied the patterns of DNA methylation and histone modification in several breeds of chickens, indicating a possible role for epigenetic processes in the development and evolution of chickens. DNA methylation was highly implicated in chicken growth and development by epigenetic study of several tissues, including the brain, cornea, retina, liverand muscles chicken (Liu *et al.,* 2016; Lee *et al.,* 2017; Liu *et al.,* 2019). When the profiles of DNA methylation were compared between broilers and layers of different embryonic stages, it was discovered that methylation level was lower in broiler genes relating to ontology were enriched, suggesting that DNA methylation may play a role in embryonic muscle development (Liu *et al.,* 2019). Additionally, a comparison of histone H1 subtypes in a*vian* species - chicken, quail, duck, gray partridge and pheasant proposed the involvement of histone modification in the structure of chromatin and the genesis of poultry (Kowalski and Pałyga, 2017). Epigenetic mechanisms directly affect and regulate various livestock and poultry products such as milk (Table 1), meat (Table 2), wool (Table 3) and egg production.

1. **Milk production (Table1)**
2. **Meat production (Table 2)**
3. **Wool fiber production**

Genome-wide scanning revealed potential regulatory roles of DNA methylation and RNA methylation in the growth and development of cashmere fibers in cashmere goats (Li *et al.,* 2018; Wang *et al.,* 2020b). DNA methylation was associated to the genetic stability of cashmere traits between generations of cashmere goats (Dai *et al.,* 2019). DNA methylation and histone acetylation were found to actively contribute to the regulation of goat fetal fibroblast cells, which is critical for cashmere production (Wang *et al.,* 2020b).

4. **Egg production**

Changes in DNA methylation was identified in response to betaine supplementation and were associated with improved egg laying performance in hens (Xing and Jiang, 2012). Egg laying in poultry relies on the reproductive maturation of the ovaries, where epigenetic mechanisms play important regulatory roles (He *et al.,* 2018). Epigenetic modifications in ERα were identified during ovarian development and maturation, whereby higher DNA methylation rates in specific CpG sites, higher histone H3K27ac associated the abundance of ERα expression with important roles in egg laying (Guo *et al.,* 2020). Promoter region methylation which supported the synthesis and release of yolk precursor substances in the liver and consequently promoted egg laying performance (Omer *et al.,* 2020).

Opportunities in livestock producation

Environment and its stressors are important to understanding the evolutionary forces in natural populations (Charmantier and Garant, 2005). Nowadays, it is critical to accurately predict environmental changes that have an impact on animals to enhance their performance. Consequently, the study of epigenetics is appealing to livestock breeders because it has the potential to fill in some of the gaps in the etiology and heredity of a wide range of quantitative characteristics and illnesses. The variation in phenotypes across people may be explained by certain methylation patterns that are more likely to increase in particular contexts. Eliminating this variance from the phenotypic decomposition equation (infinitesimal model) may allow for more accurate parameter estimation (Gonzalez-Recio, 2012).

Table 1: Epigenetic mechanism in affecting milk production.

Species	Mechanisms	Gene	Functions	References
Cow	DNA methylation	EEF1D	Regulates milk production	Liu *et al.,* 2017
Cow	DNA methylation	AKT and PPARg	Enhanced viability and multiplication capacity of mammary epithelial cells	Wang *et al.,* 2014
Cow	miR-148a miR-152	DNMT1, DNMT3A	Milk synthesis	Iqbal *et al.,* 2022
Goat	DNA methylation	ACACA and SCD	Milk fat production and composition	Tian *et al.,* 2017
Goat	DNA methylation	FASN, SCD1, PPARG and SREBF1	Milk fat synthesis	Wang *et al.,* 2017

Table 2: Epigenetic mechanism affecting meat production.

Species	Mechanism	Gene	Function	Reference
Sheep, Cattle	DNA methylation	DLK1, NR4A1, TGFB3, ACSL1,RYR1, ACOX2, PPARG2, NTN1 and MAPRE1	Muscle development	Couldrey *et al.,* 2014; Cao *et al.,* 2018; Fan *et al.,* 2020
Poultry	DNA methylation and GSTT1L	ABCA1, COL6A1 fat deposition	Intramuscular 2017;	Zhang *et al.,* Zhang *et* al., *al.,* 2020
Cattle	DNA methylation	DNMT3A, DNMT3B and DNMT1 (DNA methylation gene)	Meat and carcass quality	Guo *et al.,* 2012; Liu *et al.,* 2015
Cattle	DNA methylation	SIX1 gene	Muscle development	Wei *et al.,* 2018
Cattle	DMRs	TMEM8C, IGF2, FASN, CACNA1S, FADS6 and USTN1	Muscle development and meat quality	Chen *et al.,* 2019; Sun *et al.,* 2022

Table 3: Epigenetic mechanism affecting wool production.

Species	Mechanism	Gene	Function	Reference
Goat	Methylation	HOTAIR	Cashmere fiber growth	Jiao *et al.,* 2019
Goat	Methylation	HOXC8 exon 1	Cashmere fiber growth	Bai *et al.,* 2017
Goat	1,311 DMRs	493 DMGs	Hair cycling and cashmere growth	Li *et al.,* 2018

In cattle, only 32-80% of the genetic variation (SNPs, replacements, *etc*.) can be attributed to additive genetic variance (Haile-Mariam *et al.,* 2013). Therefore, a 'missing heritability' component is believed to be present (Yang *et al.,* 2010). However, it is also possible that environmental and epigenetic factors may have an impact. If the environment in which livestock are raised is accurately recorded along with the epigenomes, it will undoubtedly provide a more accurate and precise calculation of phenotypic variance, which cannot be done by considering genetic variance alone (Slatkin, 2009). In addition, approaches to quantify the effect of epigenetics to covariance between relatives have been devised (Tal *et al.,* 2010). Therefore, identifying the strategies linked to achieving advantageous methylation patterns will be highly advantageous as they will further influence disease resistance and other economic qualities. Also, this information can be further used by farmers to enhance their livestock production (Gonzalez-Recio, 2012). Epigenetic status of buffalo fibroblasts treated with sodium butyrate a chromatin remodeling agent. The increase population doubling times and decreases the proliferation rate in the dose dependent manner (Sharma *et al.,* 2018). A buffalo-embryos produced by Hand made cloning at NDRI, Karnal after CBHA (m-carboxycinnamic acid bishydroxamide) treatment and those produced by IVF. The female calf was named "Deepasha" CBHA increased the blastocyst rate (63.77±3.97% vs 48.63±3.55%) (Saini *et al.,* 2015).

Future challenges

One of the major challenges is tracking epigenetic features that alter from one generation to the the next (Monk *et al.,* 2006). Using next-generation sequencing techniques like WGBS, RRBS, ChIP-Seq, *etc*., it is now possible to profile epigenetic markers across the entire genome of livestock species. However, because applying these technologies is expensive, only a small number of samples can be analyzed at once. Additionally, data gathered from a small sample size is insufficient for use in improvement management or breeding. To assist the use of epigenetic information in livestock production, less expensive tools that support application in a large number of samples are required. In order to apply the epigenetic biomarkers in the field of livestock breeding and production, the development of epigenome-wide arrays for identifying epigenetic patterns in large samples is required. Therefore, there is a pressing need to create tests that are specific to livestock and are based on epigenetic mechanisms, particularly DNA methylationand are also readily available in the market. Although gaps exist in the application of epigenetic information in breeding, studies into livestock epigenetics are progressing, with the potential to increase the accuracy and dependability of estimations of breeding values with potential applications in livestock management, breeding and selection (Wang and Awemu, 2021).

CONCLUSION

The investigation of epigenetic forces is a complex mystery to the researchers. Epigenetics offers countless opportunities to improve the health and productivity of livestock. To fully comprehend the significance of diverse epigenetic mechanisms, such as DNA methylation, on genome-wide prediction and the illuminating effects of various epigenetic forces on the state of nature for complex traits, additional knowledge is still required. Investigations into the relationships between the genome, epigenome and phenotype are needed and knowledge of the epigenome may reveal some new information on the connections between genotype and phenotype. Therefore, it would be vital to identify the managemental strategies linked to favorable methylation patterns that boost livestock production.

Conflict of interest

There is no conflict of interest.

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