VETERINARY TODAY INTERNATIONAL
ISSN 2583-8288

Role of Epigenetics in Livestock Improvement

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DOI:10.5281/Vettoday.17798442

Abstract

This review article will present an overview of the historical development of epigenetics. It explains how epigenetic mechanisms regulated by various epigenomes, hence controls gene expression as per tissue requirement and surrounding environment. From embryonic to old age, various additional modifications occur in DNA as CpG methylation, acetylation and methylation of histone, chromatin remodelling as euchromatin and heterochromatin, further ncRNA also control gene expression as per requirement of tissue and surrounding environment. In foetal stage, epigenetic mechanisms repress XIST-gene to avoid superfemale condition, as well as participate in genomic imprinting. Hence, after birth regulates animal development, growth, production, reproduction and health. Epigenetics prepared the animal to sustain in adverse conditions and maintain the stability of genome. However, epigenomes greatly influenced by stress, nutrition, age, chemical exposure, diseases and surrounding environment. In India, limited exploration in epigenetics field due to its instability and requirement of a broad scale epigenome sequencing at a large population. However, it has significant role in animal's production, so it is essential to analyse all epigenetic effects in order to understand both mechanisms and the extent to which they influence an animal's production and reproduction capacity.

Key words: Epigenetic, Epigenome, DNA methylation, DNA acetylation, Histone, Chromatin

INTRODUCTION

Epigenetics mediates diverse gene expression in various type of body cells and tissues, without any change in original DNA sequence and inherited from one generation to next. It is like additional instructions or chemical modification for genetic material, i.e. occurs when animal ages, any change in environment and diet, pathogenic cause, stress and chemical exposure (Safdar & Ozaslan, 2023). Whereas, genetics all about the stability and resistant to adverse conditions, unlike epigenetics. Epigenetics maintain stability of genome by various mechanisms (Feng & Riddle, 2020). The earlier concepts of epigenetics were given by various scientists. Firstly in between 1940-1960, Conrad Waddington coined the term 'epigenetics'. He described epigenetics as a possible causal mechanism acting on the genes that govern phenotypic outcome and he gave a famous 'epigenetic landscape model' to describe how gene regulation modulates development (Allen, 2015). In 1948, DNA methylation firstly described by Rollin Hotchkiss in calf thymus (Moore et al., 2013). Likewise, (Nanney, 1958) studied, expression and repression of gene controlled by epigenetic components. After that, (Allfrey et al., 1964) conducted research on histone post-translational modifications and observed the acetylation and methylation of histone subunits.

As we know, all cells of animal's body contain same type of DNA but expression of genes varied from organ to organ, it is because different units of gene turned on/off in different types of cells and resultant generation of

multiple phenotypes from the same genotype (Zeric., 2012). Epigenetic mechanisms proceed with the guidance of epigenomes. These are multiple biomacromolecules/proteins (Zsidó & Hetényi, 2020), regulating expression of genome as per tissue demand and governing the production of proteins in particular cells, outcome is a differentiation of cells. Hence, epigenomes govern epigenetic works in different forms and affects gene expression by some chemical modifications like as DNA methylation, histone modifications, chromatin remodelling, alternating function of small coding RNAs etc. (Ibeagha-Awemu & Yu, 2021).

HOW EPIGENETICS WORKS?

As per (Hu & Barrett, 2017) swift change in environment, create a compulsion for the population to undergo selection. When species go through stressful environmental conditions then phenotypic plasticity is the mechanism mitigate adverse effect. Some studies conclude that epigenetic mechanisms independently contribute into this.

DNA methylation

DNA methylation often occurs at specific DNA sequence that rich in cytosine and guanine dinucleotides, called 'CpG island'. Frequently, this 'CpG islands' are located near gene promoter and regulatory regions. An addition of methyl group on 5'C of cytosine, thereby generating 5-methylcytosine (5mC). This reaction catalysed by the DNA methyltransferase (DNMT) enzymes i.e. DNMT1, DNMT3a & DNMT3b (Ibeagha-Awemu & Zhao, 2015). Methylation occurs at various stages of life from gametic to adult stage. *De novo* methylation occurs at non-CpG region of undifferentiated cells in embryonic stage, associated with DNMT3a and DNMT3b DNA methyltransferase enzymes (Ziller et al., 2011). During early embryonic stage, particularly during implantation methylation takes place by DNMT3b. Later, in differentiated cells of embryo, methylation catalysed by DNMT3a. Both the enzymes DNMT3a/b required DNMT3L as a coactivator (Auclair & Weber, 2012). Whereas, 'Maintenance methylation' ensure complete methylation of hemi-methylated (methylated cytosine residue) DNA by adding methyl group to newly synthesised strand, during S-phase of DNA replication. This reaction catalysed by DNMT1 enzyme with the help of UHRF1 as cofactor (Bostick et al., 2007). By attachment of methyl groups to promoter region (CpG region) of a gene physically blocking the binding of a specific transcription factor to the site and transcription process becomes effectively inactivated or either MBD protein (methyl-CpG-binding proteins) bound to methylated DNA, mould it to compact chromatin and DNA created as 'repressor marker' (Riehn., 2024).

Post-translational histone modifications

In eukaryotic cells, DNA is approximately 2 meters long and needs to fit within a small nucleus. To achieve this, it is packed into a well-organized structure called nucleosomes (McGinty & Tan, 2015). A nucleosome contains a histone octamer ($H2A_2$, $H2B_2$, $H3_2$ & $H4_2$) with 146 base pairs of DNA wrapped around it. This arrangement compacts the DNA into a form known as chromatin (Sadakierska-Chudy et al., 2015). This chromatin becomes changes in to euchromatin and heterochromatin as per the chemical modification in histone protein subunits. Mainly, H3 & H4 subunits of histone involved in acetylation and methylation of DNA. Histone acetyltransferase (HAT) enzymes facilitate the acetylation of histone proteins, particularly at the lysine residues K9 and K14 in the N-terminal tails of histone H3 subunits (Rice & Allis, 2001). This process involves the replacement of hydrogen ions (H+) with acetyl groups (-COCH3), which reduces the positive charge of histones. The decrease in positive charge weakens the affinity between the negatively charged DNA and the histones, resulting in a looser DNA structure known as euchromatin (Bannister & Kouzarides., 2011). In this open configuration, transcription factors can more easily bind to promoter regions, promoting the attachment of RNA polymerase and initiating transcription (Müller & Muir, 2015). Conversely, histone deacetylase

(HDAC) deacetylate to DNA, which restores histones to their positively charged state, leads to the formation of heterochromatin and a more tightly packed DNA structure, inhibiting transcription (Saleh et al., 2020). During methylation, methyl groups (CH3) are added to specific lysine residues within the histone proteins. Specifically, these methyl groups are added to K9 and K27 in the H3 subunit (du Preez & Patterton, 2017) and K20 in the H4 subunit at the N-terminal (Cheung & Lau, 2005), by replacing the hydrogen atoms from the NH3+ end of the lysine residues. This process increases the basicity of the histones (Ramazi et al., 2020), which enhances the affinity of the acidic DNA for the histones. As a result, the DNA becomes more compact and structured as heterochromatin. However, not all histone methylations lead to transcriptional repression. Methylation at specific sites such as K4, K36, and K79 in the H3 subunit can make DNA transcriptionally active (Jambhekar et al., 2019). Likewise, one study indicated that H3K4 methylation reduces transcriptional-replication conflicts during intense transcription in cell division, slowing down DNA replication and maintaining transcription. It is essential for accurate DNA synthesis under replication stress (Chong et al., 2020).

Chromatin remodelling

Chromatin remodelling plays crucial role in gene regulation by altering the structure of chromatin by ATP-dependent nucleosome remodelers. These remodeleres unwrapped DNA segments from nucleosome surface by moving nucleosome positions, histone exchange or complete expelling of nucleosomes (Flaus & Owen-Hughes, 2004). In eukaryotic cells, based on different ATPase subunits chromatin remodelers are divided in four subunits like Switch/sucrose non-fermentable (SWI/SNF) involved in nucleosome disassemble and straighten out of DNA, initiation switch (ISWI) disturb interaction between histone and DNA, INOsitol requiring 80 (INO80) for exchange of histone protein and chromodomain helicase DNA-binding (CHD) translocate nucleosome along chromatin (Cabot & Cabot, 2018). Hence, chromatin remodelers utilised energy from the hydrolysis of ATP molecule and shifting the position of histone protein with respect to wrapped DNA by various mechanisms. Likewise, in “loop recapture model” unwinding of DNA segment from histone octamer in nucleosome, making up a loop of DNA thread on histone and this loop translocate over octamer. It would change the transcriptional position of nucleosome (Längst & Manelyte, 2015).

Non-coding RNA

Majority of transcripts are not participated in protein synthesis, they act as non-coding RNA (ncRNA). These ncRNAs play significant role in post-transcriptional mRNA regulation. As per (wei et al., 2017) long ncRNA (>200 nucleotides) associate with X-chromosome inactivation and genomic imprinting. Although short ncRNAs (19-30 nucleotides) like siRNAs, miRNAs and piRNAs participate in transcriptional gene silencing (TGS). Such as double stranded siRNA exogenous in origin, processed by dicer in cytoplasm and further impeded histone methylation, as for example silencing of EZH2 gene. Whereas, miRNA is endogenous, present as characteristic stem loop structure in nucleus. This miRNA cleaved into small fragments in nucleus and cytoplasm by Drosha and Dicer, respectively. Both siRNA and miRNA in cytoplasm are converted into single strands by helicase. After that, they function similarly by binding to the RNA-induced silencing complex (RISC) and subsequently degrading target mRNA.

SOME EPIGENETIC REGULATIONS IN EMBRYONIC STAGES

To avoid superfemale condition, chromatin remodelling and histone (H3K27) deacetylation responsible for X-chromosome inactivation. Initially, in a female zygote, both X-chromosomes are active. However, by the blastocyst stage one chromosome become inactivated. The X-inactive specific transcript gene (XIST-gene) located on X chromosomes, transcript a ncRNA i.e. responsible for recruiting ‘chromatin modifying proteins’ to

one of the X-chromosome. Resultant, heterochromatinization of one X chromosome and transcriptional inactivation (Żylicz et al., 2019).

In genomic imprinting expression of certain genes determined by whether the gene inherited from the sire or dam. It is regulated by 'imprinting control regions' (ICRs) where sex-specific DNA methylation and histone modifications occurs during gametogenesis. Like IGF2 (insulin like growth factor 2) and H19 gene are parent specific and monoallelic in expression, with IGF2 being active in males and H19 being active in females (Brabazon et al., 2022). The enhancer is present at H19 downstream in both maternal and paternal chromatids. In maternal chromatid enhancer promote binding of CTCF protein (CCCTC-binding factor) at promoter region/ICR (at upstream of H19) and activate the gene, but in paternal chromatid ICR region has been methylated during gametogenesis and it inhibits the binding of CTCF protein. Resultant, enhancer act on IGF2 gene promoter i.e. located at upstream of H19 (Chang & Bartolomei, 2020). If there is any loss or disturbance in genomic imprinting then abnormal conceptus development, embryonic growth and placental functions (Costa et al., 2020). One case of large offspring syndrome (LOS) in bovine and ovine causes postnatal mortality, it come into view when disturbance in IGF2 (insulin like growth factor 2) and H19 gene functioning. IGF2 gene encode IGF-II protein that regulates foetal growth by promoting cell proliferation, carcass trait and body weight in beef cattle, developing of muscle mass and fat deposition in swine (Smith et al., 2015). While, H19 gene encode long ncRNA which show negative effect on body growth and limits the body weight by controlling cell proliferation. In bovines, it plays role in the differentiation of skeletal muscles by deactivating some genes i.e. Sirt1/Fox01 (Xu et al., 2017).

UTILITY OF EPIGENETICS IN LIVESTOCK

By understanding molecular epigenetics related to animal's development, nutrition, reproduction, environment stress and diseases resistance, we can improve management practices and able to obtain maximum production (Wang & Ibeagha-Awemu, 2021). Moreover, it provides insight into the heritability of complex trait and diseases, by incorporating epigenetic data with genomic selection. It is advantageous in enhancing animals breeding value and making the evaluation more precise and efficient (Triantaphyllopoulos et al., 2016). In accordance with (Bian et al., 2015) miR-29s resulted in mammary gland development and if marked reduction of DNMT3a and DNMT3b expression in dairy cow mammary epithelial cells, it decreases global methylation level and increases in the expression of lactation-related gene involving CSNISI, EIF5, PPARγ and GLUT1. The blocking of miR-29s lower the secretion of lactose, lactoproteins and triglycerides. Another study by (Kutchy et al., 2017) proved that for higher fertility and more successful fertilisation the intensity of TH2B (testis-specific H2B) should be less, which is associated with nucleosome destabilisation, DNA packaging, chromatin condensation and silencing. It leads to transition of histone by protamine through various epigenetic mechanisms like methylation, acetylation and phosphorylation, hence DNA become more compact while sperm maturation (Wang et al., 2019). Further, N6 methyladenosine (m6A) is the most prevalent internal modification occurs in mRNA of higher eukaryotes. In fine and coarse type, wool producing Liaoning cashmere goats, total 1170 differential m6A sites were identified. Those were involved in keratin and intermediate filament synthesis, under which 527 m6A sites for upregulation and 643 sites associated with downregulation of 19 m6A modified genes (KRT79, KRT 82, LOC108636561, GJB6 etc.) (Wang et al., 2020). In perspective of nutrition, according to (Tian et al., 2017), for long term feeding of high concentrate and lipid diet in lactating goat, causes down regulation of milk fat producing gene by DNA methylation in mammary gland. Consequently, observed declining in milk fat

and shifting of fatty acids profile with less MUFAs (mono unsaturated fatty acids) and more SFAs (saturated fatty acids).

FACTORS AFFECTING EPIGENETIC PROCESSES IN LIVESTOCK

Here some studies that support nutrition, aging, stress, chemical exposer and any diseases or pathogen affects DNA methylation. Like, methionine is precursor of SAM (S-adenosyl methionine) that carries methyl group for DNA methylation. If there is deficiency or excess of this amino acid in animal's diet, affects DNA methylation and it interrupts 'hepatic lipid metabolism' and growth performance (Zhang et al., 2018). As highlighted by (Prell et al., 2023), sperm methylation increases with donor's age, in such a way it is a part of evolutionary mechanism for environmental adaptation. Likewise, heat stress also affected epigenetic processes, when a foetus exposed with intrauterine heat stress in late gestation stage, it made alteration of mammary gland DNA methylation profile. Later, in adulthood animal had smaller mammary gland alveoli (Skibiel et al., 2018). When compared conventional (CON) and antibiotic treated (AB) pre-term piglets, (Pan et al., 2018) found that AB treatment leads to change in DNA methylation pattern across small distal intestine. Hence, differences observed in innate immunity, metabolism and improved resistance to necrotizing enterocolitis. In case of mastitis, DNA methylation occurs around the STAT5-binding enhancer of the αS1-casein promoter. It negatively regulates αS1-casein synthesis in milk during lactation (Vanselow et al., 2006).

CONCLUSION

Currently, genomic selection is widely used in livestock breeding to achieve maximum genetic gain in shortest period. However, its reliability can be affected by epigenetic modifications, which are influenced by environmental factors, aging, nutrition and any chemical exposures to the animal. Since same genotype interact uniquely with different surroundings. In India, the scrutiny and exploration of epigenetic studies in veterinary field are relatively limited. But, it has significant role in animal breeding because it may help to uncover some missing causality and lacking heritability of complex traits and diseases. Knowing this missing causality would provide assistance in rising animals under favorable or unfavorable circumstances, by monitoring epigenetic mechanisms. These mechanisms occur with the help of epigenome, therefore epigenome-wide association assessments are essential to identify what epigenetic modification negatively or positively affect the traits of interest. By understanding epigenetic changes, can improve management practices and elevate animal production, as epigenetics play a pivotal role in animal development, production, reproduction, and health. Thusly, important changes in livestock breeding sector comes up and improves genomic selection accuracy.

Main challenges in applying epigenetic information are tracing of epigenetic information that changes with every successive generation at the cellular level. Different from genome, epigenome is instable during an animal's lifetime, this brings about lack of standard methods and protocols for studies. Moreover, scarcity of epigenetics data, it leads to difficulty in integration of epigenetic, genetic and phenotypic data. A considering aspect is instability of epigenetics that uncertain the heritability of epigenetic data. It is also expensive to study so limiting the exploration of area, limited data collected from restricted number of samples i.e. insufficient to utilize in breeding strategies. Therefore, needing cost effective technologies and inexpensive tools for broad scale epigenome sequencing in large number of samples to precisely estimate small epigenetic effects at a population level. Requirement of developing statistical tools that integrate complete epigenetic data with vast DNA sequence information and surrounding environment.

COMPETING INTERESTS

The author declares that he has no competing interests.

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