**Role of Nutrition in Epigenetics and Its Impact on Milk Production in Farm Animals: A Review**

**Abstract:** Milk production in farm animals is a vital component of global nutrition, significantly influenced by epigenetic mechanisms. Epigenetics, encompassing heritable changes in gene expression without altering the DNA sequence, plays a crucial role in mammary gland function and milk production. This review explores the historical development of epigenetics and its key mechanisms, including DNA methylation, histone modifications, and non-coding RNAs. Nutritional factors profoundly impact these epigenetic processes, with specific nutrients such as methionine, choline, and omega-3 fatty acid influencing DNA methylation and gene expression in the mammary gland. Studies demonstrate that dietary modifications can lead to significant changes in milk yield, composition, and quality. For instance, methionine supplementation in cows enhances milk protein and fat synthesis, while dietary resveratrol improves milk composition in sows. Understanding these mechanisms provides insights into optimizing milk production and animal health. The review underscores the potential of tailored nutritional strategies to enhance dairy production, emphasizing the need for further research on the epigenetic effects of dietary interventions in livestock.

**Keywords**: Epigenetics, Histone, Methylation, Milk Production, Farm Animals.

**1. INTRODUCTION**

Milk and dairy products are indispensable for global nutrition and provide livelihoods for millions involved in dairy value chains worldwide. Currently, livestock products contribute to 28% of the value of agriculture and fish output, with an annual growth rate of 2. 6% predicted to increase this share to 31% by 2032. India and Pakistan are primary drivers of this growth, especially in dairy products. Global milk production, mainly from cows (81%), buffalo (15%), and a combination of goats, sheep, and camels (4%), is expected to grow by 1. 5% annually over the next decade, reaching 1039 Mt by 2032. India and Pakistan will contribute over half of this increase, making up 32% of world production by 2032. The dairy sector is set to expand the fastest among all animal sectors, with a 17% increase in global milk production over the next ten years. Milk production relies on the quantity and activity of mammary gland cells. Understanding how environmental factors influence mammary gland function and milk production through cell signalling and epigenetic pathways is crucial. Conrad H. Waddington (1905–1975) coined the term epigenetics to describe the link between gene and protein expression. Key discoveries in epigenetics include X-chromosome inactivation in mammals (Lyon, 1962), cytoplasmic inheritance in Paramecium (Beisson & Sonneborn, 1965), nucleosome structure (Kornberg & Thomas, 1974), Histone acetylation and methylation studies (Allfrey et al., 1964) and DNA methylation research (Riggs, 1975; Holliday & Pugh, 1975) have advanced our understanding of epigenetic mechanisms. Epigenetics is now defined as the study of heritable changes in gene function that do not involve changes in DNA sequence (Riggs et al., 1996). Despite debates on the necessity of heritability in epigenetics, the term encompasses both transient and permanent gene expression changes not caused by DNA sequence alterations. Epigenetics plays a crucial role in gene regulation, cell differentiation, development, and phenotype expression. Unlike genetic variations, epigenetic changes are reversible, do not alter the DNA sequence, but can significantly impact gene expression. Epigenetic marks link environment, nutrition, and disease are dynamic throughout life, heavily influenced by external factors. These reversible modifications offer insights into how environmental exposures affect milk production through epigenetic mechanisms. This review explores the role of epigenetics in milk production.

**2. MECHANISMS OF EPIGENETICS**

**2.1 Histone Tail Modifications**

Histone post-translational modifications encompass chemical alterations occurring on histone proteins, which constitute the primary components of chromatin, the complex comprising DNA and proteins forming chromosomes [Allfrey et al., 1964]. Histone modifications, including acetylation, methylation (see Figure 1), and phosphorylation, affect gene expression by altering chromatin structure. Tightly packed chromatin turns off genes, while loosely packed chromatin activates them. Histone modifications regulate gene expression, chromatin structure, replication, and DNA repair (Rothbart & Strahl, 2014). DNA methylation involves adding a methyl group to the promoter region of a DNA sequence, turning off the gene. Conversely, acetylation adds an acetyl group, turning on the gene. X-chromosome inactivation in mice (Lyon, 1961) exemplifies this mechanism. DNA methylation, first detected in calf thymus cells (Hotchkiss, 1948), was later linked to gene expression repression (Riggs, 1975; Holliday & Pugh, 1975). Methylation occurs mainly on cytosine residues at CPG dinucleotides, influencing gene expression and cell differentiation (Jurkowska et al., 2011). These functions intricately regulate gene expression and contribute to the development of genetic disorders and early mammalian development [Esmaeili et al., 2020: Izzo, et al., 2016; Martire, et al., 2020].

**2.2 Acetylation**

The acetylation of histones is mediated by two enzyme families, histone acetyltransferases (HATs) and histone deacetylases (HDACs), which modify lysine residues of histones. HATs translocate an acetyl group to the lysine side chain, whereas HDACs inverse this process [Xhemalce, et al., 2011]. Phosphorylation of histones occurs on serine, threonine, and tyrosine residues and is regulated by kinases and phosphatases [Oki, M et al., 2007].

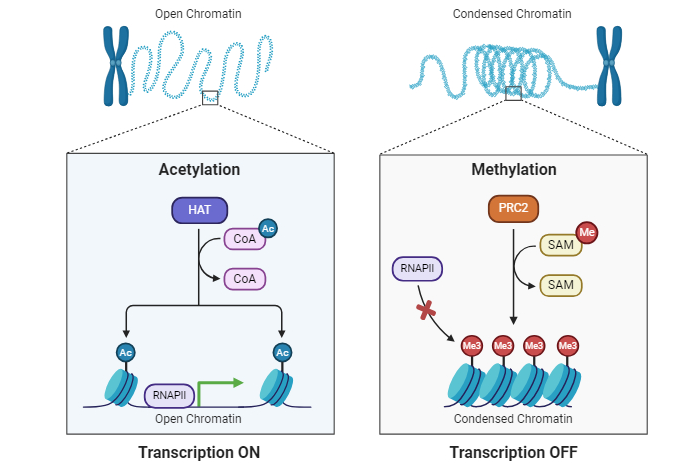


Fig 1- Histone modifications, including acetylation, methylation

Methylation of histones transpires on lysine and arginine side chains, facilitated by specific methylases and demethylases [Bannister, et al 2002, Copeland, et al., 2009]. These histone modifications regulate multiple biological processes, with crucial implications in early mammalian development. For instance, modifications in lysine residues 4 and 27 of histone 3 (H3K4 and H3K27) modulate the formation of the trophectoderm and the inner cell mass in mice [Dahl, et al., 2010]. Moreover, other histone modifications are intertwined with the regulation of genomic imprinting, HOX gene expression, and the maintenance of pluripotency in mammalian early development, among other processes [Jambhekar, et al., 2019].

**2.3 Methylation**

In mammals, DNA methylation serves as a pivotal mechanism in orchestrating diverse biological functions, encompassing chromosomal stability, genomic imprinting, and X-chromosome inactivation [Smith and Meissner, 2013]. This process entails the addition of methyl groups to cytosine within CPG islands and is catalyzed by three conserved enzyme families: DNA methyl transferase (DNMT) 1, DNMT3a, and DNMT3b [Hoang, N.M.; Rui, L. 2020; Okano, M et al 1999 and Zhang, J et al 2020]. These enzymes are instrumental in DNA methylation, an epigenetic modification entailing the addition of methyl groups to the DNA molecule. DNA methylation governs gene expression and participates in various cellular processes such as development, differentiation, and genomic stability. DNMT1 (DNA methyltransferase 1) primarily upholds DNA methylation patterns during DNA replication. It recognizes hemimethylated DNA and methylates the unmethylated strand, ensuring faithful transmission of DNA methylation patterns to progeny cells. DNMT3a (DNA methyltransferase 3a) acts as a de novo DNA methyltransferase, pivotal in establishing new DNA methylation patterns during development and cellular differentiation. DNMT3A methylates previously unmethylated DNA regions and is critical for embryonic development, hematopoiesis, and neuronal differentiation. DNMT3b (DNA methyltransferase 3b), akin to DNMT3a, contributes to establishing DNA methylation patterns during development and cellular differentiation, with a particular emphasis on methylating repetitive sequences, such as transposable elements in the genome. Collectively, these enzymes dynamically regulate DNA methylation patterns in cells, playing indispensable roles in normal development, gene expression, and disease processes [Leonhardt, et al 1993;; Deng, et al 1998,; Robertson, et al 1999; Hamidi, et al 2015; Montaner-Angoit et al. 2023; Luu, et al 2021].

For these enzymes to execute their function, they necessitate a methyl donor, which can be influenced by methyl groups (e. g., choline, betaine, methyl-folate, or methionine) obtained from the diet. These substances serve as precursors to the universal methyl donor, S-adenosylmethionine (SAM) [Nilsson, et al., 2015; Salbaum et al., 2012; Zeisel, 2017]. An illustrative example of methyl group impact on enzyme function is the regulation of the insulin-like growth factor II (IGF2) gene. IGF2 expression hinges on the methylation of a specific region, Igf2DMR2, within the H19 gene. Feeding pregnant rats a choline-deficient diet induces hypermethylation in these regions, inhibiting H19 and boosting IGF2 expression [Kovacheva et al., 2017]. A poignant instance of this regulation occurred during the Dutch Hunger Winter of 1944/1945, where reduced DNA methylation in the IGF2 gene was noted in the offspring of famine-stricken pregnant women [Heijmans et al., 2008]. Numerous studies underscore the significance of nutrition in shaping epigenetic marks in livestock. Methyl-group donors like choline, folate, and betaine exert notable effects on DNA methylation. Moreover, pregnant sows fed betaine-supplemented diets yield piglets with modified methylation patterns [Cai et al., 2014]. Sheep subjected to diets deficient in vitamin B12, folate, and methionine exhibit hypomethylation in offspring, impacting birth weight, immune responses, and blood pressure levels [Salah et al., 2014]. The most economically significant traits in dairy cows relate to quantitative trait loci (QTL), encompassing milk yield and milk components. Some of these QTL are governed by epigenetic mechanisms, including methylation regulation, potentially influencing phenotypic variation in livestock production [Fan et al 2019 and Gibbs et al., 2010]. Hence, it is imperative to undertake studies on epigenetic regulation, particularly through DNA methylation, as it pertains to traits of interest in livestock production. Such investigations should spotlight how animal nutrition influences these methylation changes.

**2.4 Small Non-Coding RNA: miRNA as Epigenetic Regulators**

The discovery of the first microRNA (miRNA), lin-4, in the nematode Caenorhabditis elegans dates back to 1993, but its significance was fully realized with the discovery of let-7, another miRNA [Mitani et al., 1993 and Reinhart et al, 2000]. MiRNAs are small RNA molecules, approximately 20–24 nucleotides in length, devoid of protein-coding capacity [Chen et al 2004; Doench and Sharp, 2004; Heneghan et al., 2010]. They are ubiquitous across various organisms, including humans, and participate in diverse biological processes such as development, cell proliferation, differentiation, and apoptosis [Heneghan et al 2010, Macfarlane and Murphy, 2010]. The primary function of miRNAs lies in regulating gene expression by binding to messenger RNA (mRNA) molecules, either leading to their degradation or inhibiting their translation into proteins.

Other non-coding RNAs also function as epigenetic regulators. Piwi-interacting RNA (piRNA), small interfering RNA (siRNA), small nucleolar RNA (snoRNA), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs) can modulate gene expression through various mechanisms, including heterochromatin formation and translational inhibition [Ozata et al., 2019; Shuwen et al 2020; German and Shapiro, 2020;]. These RNA molecules play a pivotal role in shaping the epigenetic landscape [Bravo et al., 2020; Kumar et al 2020; Panni et al 2020]. However, the precise connection between nutrition and the regulation of these non-coding RNAs remains elusive.

**2.5 Epigenetic Regulation Based on Nutritional Changes and Its Effect on Milk Production in Farm Animals**

Epigenetic regulation plays a pivotal role in milk production among farm animals. Throughout lactation, mammary gland cells undergo substantial epigenetic modifications that activate genes essential for milk production and secretion. A key mechanism in milk production involves DNA methylation, where methylation of promoter regions of genes implicated in milk synthesis and secretion can suppress their expression. This methylation profile intricately regulates milk production [Xie et al., 2012] and correlates with the protein and fat levels in milk. Recent findings by Wang et al. (2021) showcased differentially methylated CPG sites co-located with quantitative trait loci (QTLs) for milk protein and fat. Hypomethylation of the lactation enhancer, binding to the activator of transcription (STAT) 5, in bovine lactating mammary glands regulates casein expression. Specifically, an increase in methylation of the STAT5 binding CPG Island was observed with prolonged post-milking duration, potentially linked to mammary involution and the decline in milk protein levels [Vanselow et al 2006; Singh et al., 2010].

Nutrition exerts a profound influence on epigenetic regulation in the mammary gland, consequently impacting milk production. Studies indicate that maternal diet during pregnancy and lactation can shape epigenetic modifications in the mammary gland, altering gene expression and milk composition. For instance, maternal protein restriction during pregnancy and lactation was shown to modify DNA methylation patterns in the mammary gland of offspring, leading to changes in the expression of genes involved in milk production and secretion in cattle and goats [Singh et al., 2012; Tian et al., 2017; Liu et al., 2017]. DNA methylation patterns and gene expression in the mammary gland are subject to alteration with the supplementation of certain nutrients like choline and folic acid. Certain amino acids, notably methionine (Met), partake in one-carbon metabolism governing purine synthesis and methylation. Additionally, metabolites such as choline, betaine, and folate provide methyl donors for methyl transferases, crucial in regulating S-adenosylmethionine (SAM) [DelCurto et al., 2013, Sutter et al., 2013].

The impact of Met supplementation on cows has been extensively studied both in vivo and in vitro. Met, an essential amino acid, is integral to various biological processes such as growth and milk production.

**Table 1: Epigenetic changes due to alteration in nutrition, and related phenotypic effects in milk production in farm animals.**

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| --- | --- | --- | --- | --- |
| **Sl. No** | **Nutritional Factors** | **Epigenetic change** | **Phenotypic effects in milk production** | **References** |
|  | Protein restriction | α-S1 casein encoding gene region methylated at 3 CPG dinucleotides | Shutdown the synthesis of alpha S1 casein during mammary involution and mastitis | Singh *et, al.* 2012 |
|  | Long-term feeding of high concentrate diet in goats | Methylation in the promoter regions of SCD and ACACA genes | Decrease in production of milk fat | Tian *et, al.* 2017 |
|  | Protein restriction | Hypomethylation of first CpG island in the promotor region of EEF1D gene during dry period | mRNA expression of EEF1D gene was higher during dry period | Liu *et, al.* 2017 |
|  | Supplementation of methionine during third trimester in cows | Changes in mRNA expression | Changes in immune function and abundance of microRNA and mRNA in Holstein calf polymorphonuclear leukocytes | Jacometo *et, al.* 2018 |
|  | Supply of methionine and choline during the periparturient period | Upregulation of gene expression | Alter Polymorphonuclear Leukocyte Immune Response in Holstein Cows | Zhou *et, al.* 2018 |
|  | Supply of methionine during the periparturient period | Phosphorylation of the antioxidant transcription regulator NFE2L2 | Alters mammary gland antioxidant gene networks in cattle | Han *et, al.* 2018 and Liang *et, al.* 2019 |
|  | Supplementation of methionine | Upregulation of gene expression via SNAT2-PI3K signalling pathway | Increased milk protein and fat synthesis and mammary cell proliferation | Qi *et, al.* 2018 |
|  | Supplementation of methionine in cows | Methylation of promotor region of PPARα target genes leads to upregulation of gene expression | Leads to improved lipid metabolism, immune function and milk production in dairy cows | Osorio et.al., 2016 |
|  | Dietary resveratrol supplementation during gestation and lactation of sows | Upregulation of gene expression | Improved the lactose content in the colostrum and fat content in milk at day 21 of lactation and also increased the HDL and LDL in the plasma of piglets. | Sun *et, al.* 2019 |
|  | Omega-3 fatty acid supplementation in Sannen goats | Histone acetylation patterns decrease the activity of LPL and SCD enzymes. | It leads to increase in milk production in goats | Javaheri *et, al.* 2023 |
|  | Feeding a high-Concentrate Corn Straw Diet | Decrease in Histone H3 acetylation | Leads to higher lipopolysaccharide concentrations in mammary tissue in dairy cows | Dong *et, al.* 2014 |
|  | Feeding a high-Concentrate Corn Straw Diet | Methylation of the stearoyl-coenzyme A desaturase gene | Increase in milk fat synthesis but decrease the protein synthesis in dairy cows | Dong *et, al.* 2014 |
|  | Linseed oil supplementation in dairy cows | DNA methylation patterns altered | It regulates the fatty acid synthesis in dairy cows | Li *et, al.* 2017 |
|  | High fat supplementation | It leads to decreased DNA methylation increases the microRNA-152 expression | Development and lactation processes in the mammary glands of dairy cows | Wang *et, al.* 2014 |
|  | Energy restriction | MiRNA expression patterns altered | Milk production and composition in  cattle | Billa *et, al.* 2021 |

**3. CONCLUSION**

Epigenetic regulation emerges as a crucial determinant for the proper functioning of the mammary gland during lactation, with dysregulation potentially leading to lactation insufficiency or other milk-related disorders. Nutrition exerts a profound influence on epigenetic mechanisms in the mammary gland, thereby modulating gene expression and milk production. Understanding the interplay between nutrition and epigenetic regulation holds significant promise for enhancing milk production, optimizing milk composition, and promoting the health and well-holing of offspring. This review underscores adequate intake of essential nutrients, including Met supplementation, emerges as pivotal for optimal cow health and productivity. Met supplementation not only improves milk protein and fat content, milk quality, and production but also supports immune function, reproductive accomplishment, and overall growth and development. Developing precise and tailored nutritional strategies that optimize animal health, performance, and offspring development is essential for sustainable and efficient livestock production practices in farm animals.

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