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REVIEWS
AND THEORETICAL ARTICLES

Epigenetic Effects in Livestock Breeding

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Abstract—Epigenetic effects are considered as a mechanism of the emergence of new inherited traits with their transmission between generations through meiosis. Modern genomic evaluation does not explain the entire phenotypic variance of traits. It is quite obvious that a significant part of the unaccounted dispersion reflects epigenetic effects carried out through DNA methylation, histone and chromatin modifications, and activity of noncoding types of RNA. Epigenetic effects could potentially be used in breeding programs. The obtained data testify to the significant role of epigenetic factors in the expression of imprinting genes, cellular processes, development of muscle tissue, and fat metabolism in animals. The ability of various additives in the diet to induce epigenetic modifications with phenotypic variability has been convincingly proven. However, there are still many contradictions and limitations in the justification of the hereditary component of epigenetics for introduction into animal breeding. Development of modern technologies, such as chromatin immunoprecipitation with microchips of DNA (ChIP-Chip), next-generation sequencing (ChIP-Seq), and epigenomic editing based on CRISPR-Cas9, gives grounds for optimism in solving problems of introducing epigenetic phenomena in livestock breeding.

Keywords: epigenetics, DNA, RNA, histones, methylation, modifications, animals, gene expression, breeding
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INTRODUCTION

The term epigenetics, proposed by C. Waddington [1], reflects one of the mechanisms of phenotypic expression of genes. In the process of revealing new genetic data, this term began to reflect the possibility of the emergence of new inherited traits with their transmission between generations through meiosis without changes in nucleotide sequences of DNA, where the expression of the genotype and the formation of phenotypic traits may depend on internal and external factors. Despite the fact that the genome of the cell is quite stable, the epigenome is very dynamic throughout life and is determined by the complex interaction of genetic and environmental factors [2]. The main epigenetic mechanisms change the expression of genes, which includes DNA methylation processes, histone modification, activity of noncoding RNA (ncRNA), and chromatin remodeling [3], contributing to new phenotypic manifestations in the formation of productivity [4], reproduction [5], aging [6], and diseases [7, 8]. The development and introduction of genomic selection provided an opportunity to significantly enhance genetic progress in livestock breeding [9, 10]. However, epigenetic traits remain unaccounted in indices of pedigree value of animals. Inclusion of the results of the analysis of these traits in the breeding process would be useful in improving the accuracy of the pedigree value of animals. It is generally believed that genes from both parents are equally involved in the development of the embryo. However, these views contradict the obvious genomic imprinting and the manifestation of the differential activity of the maternal and paternal alleles [11]. In mammals, more than 100 genes with monoallelic expression are known [12]. Epigenetic mechanisms regulate a wide range of biological processes, including fetal growth and development, metabolism, and behavior [13]. It is important that epigenetic information is preserved and transmitted to the next generation [14]. The mechanisms of epigenetic heredity probably evolved in the course of evolution [15]. The cognition and use of epigenetic mechanisms can have serious consequences for the formation and analysis of quantitative traits [16] and will ensure that information on epigenetic processes is included in the overall assessment of breeding value, followed by an increase in animal productivity and resistance to diseases.

DNA METHYLATION

Methylation of the fifth carbon of cytosine (5-methylcytosine) is currently the best studied epigenetic modification of DNA. DNA methylation is carried out through enzymatic activity of DNA methyltransferases and is essential for genomic stability and main-

tenance of development. For example, DNA(cytosine-5)-methyltransferase 1 (DNMT1) maintains mainly DNA methylation during replication, while DNMT3a and DNMT3b are responsible for *de novo* methylation of unmodified DNA. DNA methylation occurs, as a rule, on cytosine-phosphate-guanosine dinucleotides (CpG) [17] and is associated with transcriptional repression, while hypomethylation, conversely, is associated with transcriptional activation.

In fertilization, the paternal genome is actively demethylated, whereas in the maternal genome this process occurs passively. Most of the blastocyst genome is demethylated during implantation. After implantation, the genome of the developing zygote undergoes *de novo* methylation. After the formation of primary germ cells, the genome is demethylated. This marks the start of the second wave of reprogramming. After sex determination and gametogenesis, the gene is remethylated at different times, depending on the sex. After implantation, the developing zygote undergoes *de novo* methylation and completes the first wave of reprogramming [18]. In the process of gametogenesis, the genome is remethylated for each sex at different times and in varying degrees. The second wave of reprogramming continues during the growth of the oocyte [19]. In embryos of cattle, demethylation occurs in the stage from eight to 16 cells [20]. As noted, the paternal DNA is more demethylated than the maternal DNA [21, 22]. The difference in methylation levels between male and female pronuclei was observed as early as 8 h after copulation in mice and after 10 h in rats [23]. Thus, the maternal genome is more resistant to the effects of active demethylation, but loses most of the methyl groups of DNA during development [24]. There are significant differences in the features of DNA methylation in sperm and oocytes [25–27]. There are specific differences in the course of these processes. Thus, it should be noted that no evidence of a global demethylation of the DNA of the paternal pronucleus in the horse during the first cell cycle was found [28]. Both parental genomes demonstrated stable and similar levels of methylation and hydroxymethylation during the pronuclear process. However, there are reasons to assume that the properties of the differentially methylated regions of the maternal and paternal genomes differ [29–31]. During prenatal development, primordial germ cells, which are gamete precursors, undergo epigenetic reprogramming with DNA demethylation, followed by sexual specific *de novo* methylation with specificity for a particular sex [32, 33].

The best evidence of transgenerative epigenetic inheritance in mice is the study of epialelles, such as viable yellow and axin agouti, in which the levels of DNA methylation of retrotransposons control the expression of a neighboring gene [34]. DNA methylation of the intracisternal part of the retrotransposon is inserted in front of the agouti gene and controls the expression of this gene. This particle belongs to a small group of long repetition terminals that appear to form germline resistance to reprogramming in sex cells and early embryos of agouti mice leading to a range of coat colors from yellow, yellow and brown spots to brown color depending on the degree of DNA methylation [35]. Methylation of the genome can be controlled by hormonal signals and modifications involving damage to alkylated nucleic acid elements that are closely related to certain diseases [36]. Methylation persists throughout both the preimplantation period and at later stages of development [37, 38].

The change in the status of DNA methylation can have a profound effect on the expression of genes of cloned animals and the induction of epigenetic disorders. Although most offspring from somatic cloning are normal [39], some somatic cloning protocols are associated with pathological side effects, probably as a result of nonstandard epigenetic reprogramming [40]. It is important to note that the kinetics of DNA methylation and demethylation in cloned embryos after nuclear transfer differs from that in normally fertilized embryos [41]. Consequently, assisted reproductive technologies may be responsible for some of the epigenetic disorders in the development process [5, 42]. Epigenetic reprogramming occurs aberrantly in most cloned embryos, and incomplete reprogramming may contribute to low cloning efficiency [43]. Compared to normal fetuses, cloned embryos in the middle of pregnancy have subtle abnormalities of DNA methylation [44]. Data are presented showing the association between DNA methylation features and perinatal mortality in cattle, together with the contribution of epigenetic factors to phenotypic variability [45].

Considering epigenetic processes, one should note that methylation is not the result of specific target mechanisms, and it is better to consider it as part of the general methylation processes in female and male gamete lines. Only a fraction of these gametes survive in the early stages of development; that is, there is selection of preimplantation embryos.

Obtaining the profiled DNA methylation maps of the entire genome makes it possible to identify the nature of changes in DNA methylation that occur during growth and development [46, 47]. Analysis of genomic DNA methylation profiles makes it possible to identify specific CpG sites associated with the phenotype. Observation data on the features of DNA methylation made it possible to develop a classifier for predicting DNA methylation levels provided high resolution of the CpG site [48]. Undoubtedly, these approaches help determine genomic mechanisms that interact with DNA methylation and suggest processes involved in the modification of DNA methylation and regulation of the connections with various epigenetic processes. Epigenetic markers can change over time owing to the cellular type of specificity [49]. Therefore, it is not surprising that epigenetic effects play an important role in the differentiation of cells [50],

pathological processes [51], and, in particular, carcinogenesis [52].

In epigenetic studies of agricultural animals, next-generation sequencing techniques based on DNA methylation were used to study the contribution of methylation to the phenotypic variability of the corresponding economically important features. DNA methylation responds to feeding and environmental conditions leading to a change in the phenotype associated with changes in productivity and the risk of animal disease [53]. Thus, the use of this method made it possible to reveal the number and localization of regions of differential methylation of DNA when omega-3 fatty acids are added to the diet of sows, which affect growth and inflammatory processes [54]. A comparison of DNA methylation profiles between fast and slow growing broilers was carried out [55]. The study revealed candidate genes, including several known growth factor genes (*IGF1R*, *FGF12*, *FGF14*, *FGF18*, *FGFR2*, and *FGFR3*) with differential methylation, which potentially regulate muscle development at the age of seven weeks. A total of 13294 methylated genes were detected, including 4085 differentially methylated genes, of which 132 were differentially methylated genes associated with growth and metabolism.

POST-TRANSLATIONAL HISTONE MODIFICATIONS

The structure of chromatin is under the control of several mechanisms involving the modification of histones and total chromatin, which play an important role in transcription processes [56]. As is known, eukaryotic DNA is tightly packed with the formation of nucleosomes, which are formed into an octamer of four histones (H2A, H2B, H3, and H4). In such a structure, histones are susceptible to many post-translational modifications that form a potential for encoding epigenetic information. Structural changes in chromatin resulting from histone modification tend to result in a set of effector proteins, such as transcription factors, which modulate gene expression [2, 57]. In addition to acetylation, histones undergo various reversible post-translational modifications, including methylation, ubiquitination, ADP ribosylation, and phosphorylation [58]. Ubiquitination can carry both inhibitory [59] and activating [60] effects, depending on the modification of specific sites. The modification of histones and DNA methylation pathways depend on each other, and the amplifying effects occur as a result of the interaction of the corresponding enzymes and the factors associated with them [61, 62]. Chromatin modifications function in two mutually exclusive ways [63] and can directly affect the chromatin structure or can provide dynamic binding of platforms for proteins with specific domains. An example of the first method is acetylation of histones, which neutralizes the positive charge of lysine and thereby disrupts the electrostatic interaction. This contributes to the formation of chromatin with a reduced compact state [64]. In addition, histone acetyltransferases function as a transcriptional coactivator, and deacetylases function as repressors. These transformations provide a stepwise model for the formation of transcriptional-repressive heterochromatin [65]. Maternal chromatin is organized in such a way that DNA methylation and chromatin modifications often take place during fertilization [66]. They include both nucleohistone modifications and chromatin proteins associated with active and repressive configurations [67, 68]. As a result of the development of the paradigm of allosteric control of mammalian DNA methyltransferases, two new regulatory principles were discovered for them. Thus, it has been shown that their catalytic activity is under the allosteric control of N-terminal domains with autoinhibitory functions in a number of domains [69]. In addition, the activity of DNA methyltransferases has been found, which should be regulated in concert with interaction with post-translational modifications. Here, the state of enzymes DNMT1 and DNMT3, their binding to DNA, and the catalytic mechanism, as well as multimerization (the combination of protein subunits in one complex) and the processes controlling their stability in cells, play a big role. Of particular interest is the reprogramming of histone modification when manipulating cloned embryos.

Methylation of lysine-4 of histone H3 is mainly associated with transcriptionally active chromatin, and methylation of lysine-9 of histone H3 is associated with repressive chromatin [70]. The disruption of reprogramming in cloned mice correlates with their poor potential for early development. Similar data were obtained on cloned embryos of cattle [71]. These results indicate a link between methylation of DNA and histones in mammalian embryos with the identification of associations between epigenetic markers and the potential for the development of cloned embryos. Similar disorders occurred in the differential acetylation of histone H4 in blastomeres of cloned cattle [72]. During the embryonic development of mammals, along with DNA methylation, histone modification plays an important role in regulating gene expression and epigenetic reprogramming. In cloned and in vitro fertilized preimplantation embryos of cows in the stage before eight cells, the levels of acetylation and methylation of histones of H3K9as, H3K18ac, H4K5ac, H4K8ac, H3K4me3, and H3K9me2 were abnormally high [73]. These results indicate that somatic cells in the recipient oocytes produce aberrant histone modifications in several places before the donor genome of the cell is activated. Chromatin research involves repositioning or restructuring of nucleosomes inside the chromatin to facilitate or inhibit access to nearby DNA. This is mainly carried out by ATP-dependent remodeling of chromatin complexes and nucleosomes [74, 75]. Nevertheless, the dynamics in the organization of chromatin in the development process is not a unique system for all ver-

tebrates; for example, it has its specific features in mammals (mice) and in birds (chickens) [76].

NONCODING RNA

Although DNA methylation and histone modifications are the most studied epigenetic mechanisms, there are epigenetic processes that play an important role in the regulation of gene function. A striking demonstration is the role of noncoding RNAs, which can indirectly affect the regulation of gene expression and chromatin modification. There are several known types of noncoding RNA involved in epigenetic heredity: long noncoding RNAs (lncRNA), small interfering RNAs (siRNA), RNAs of 26–32 bp (piwi RNA or piRNA), and microRNAs of 18–25 bp (miRNA), which are involved in the regulation of transcription, translation, and stability of mRNA [77]. Maternal reserves of information RNAs can also be attributed to these categories of RNA with epigenetic properties [78]. Noncoding microRNAs of approximately 22 bp are capable of controlling the activity of about 60% of all protein-encoding genes and are involved in the regulation of almost every studied cellular process in mammals [79, 80]. The number of microRNAs found in various species of farm animals varies considerably from a few dozen to several hundred [81]. The role of microRNA in the formation of the productivity of agricultural animals is associated with many processes [82], including lactation and milk production [4, 83], lipogenesis [84], and morbidity [7]. Long noncoding RNAs (lncRNA) are a heterogeneous group of transcripts longer than 200 bp, which play a noticeable regulatory role in many biological processes [85, 86]. This type of RNA is the largest part of the noncoding transcriptome of mammals [87]. LncRNA have common pathways of biogenesis with other classes of noncoding RNA. Most lncRNAs result from the activity of RNA polymerase II. Many lncRNAs function as epigenetic modulators by binding to chromatin, emergence of catalytic activity on specific sites in the genome, and influence on gene expression [88]. Thousands of genes encoding the lncRNA have been identified in mammalian genomes [89]. The regulating properties of lncRNA associated with pathological states and development of the immune system and aging [90, 91], as well as with the regulation of skin pigmentation processes in cows [92], are noted. Other studies [93] provided characteristics of 584 lncRNA in muscles of cows, some of which were localized within the loci of quantitative traits and correlated with traits of meat productivity. There were 4227 lncRNAs identified in the mammary gland, including 26 lncRNAs that differentially respond to a diet high in alpha-linolenic acid, which suggests their role in the synthesis of fatty acids and lipid metabolism [94]. It was shown that microRNA-103, which consists of 20–24 nucleotides, participates in various biological processes, including brain development, lipid metabolism, adipocyte differentiation, hematopoiesis, and immunity, and also participates in the differentiation of porcine preadipocytes [95]. In cattle, microRNAs are regulated by DNA methyltransferase 1 and are involved in the development of the mammary gland and lactation [96]. Evidence of the effect of stimulation by endogenous miRNA-143 on the differentiation of intramuscular fat of cows through regulated expression of adipocyte genes has been obtained [97].

Several studies of lncRNA in chickens have been carried out to improve understanding of the biology and differentiation of preadipocytes [98, 99]. Comprehensive analysis facilitated the detection of lncRNAs and target genes that can contribute to the regulation of various stages of skeletal muscle development. *Cis*- and *trans*-regulation of target genes by differentially expressed lncRNAs were determined and lncRNA and gene interaction networks were constructed [100]. The available data suggest that the lncRNA function contains a hidden layer of regulatory information that not only acts as a mediator between DNA and protein but also plays a role in genome organization and gene expression [101]. Specific roles of lncRNA in the development of various organs and tissue types have been determined. For example, in neonatal cardiomyocytes, the knockdown of specific lncRNA alters gene expression and inhibits the normal development of maturation of cardiomyocytes in mice [102] and can lead to embryonic death [103]. Using the constructed chicken ncRNA library, 125 ncRNAs were isolated, which play an important role in the development and differentiation of tissues during evolution [104]. Expression profiles of lncRNA and mRNA in three different stages of skeletal muscle development in chickens were determined [100]. Differentially expressed lncRNAs were analyzed in *cis*- and *trans*-interaction and used to construct correlation networks of lncRNA genes. An important role of lncRNA in the regulation of transcription [86, 105], in epigenetic modification [106], and in organogenesis and development [107, 108] was noted. The lncRNA group functions as regulators of gene expression and also participates in development and in a number of physiological processes [109]. It should be emphasized once again that lncRNA is the largest part of the noncoding mammalian transcriptome [110]. By pairing bases with mRNA, microRNAs regulate gene expression in animals through inhibition of translation initiation, elongation, and other mechanisms [111]. Many lncRNAs affect the expression of genes by binding to chromatin-modifying proteins, altering the catalytic effect on certain sites in the genome [112].

Analysis of the results of sequencing in chickens identified the localization of nucleotide sequences of lncRNA: 1493 as intergenic and 177 as intragenic, that is, located within the protein-encoding genes [113]. There were also differences in the types of level of mRNA expression in the mammary glands between lactating and nonlactating cows [114, 115]. These

manifestations are associated with the action of genes through a variety of biological pathways [116]. In the mammary glands of goats, differential expression of microRNA was detected between lactation and dry-period peaks and between early and late lactation [117, 118]. It was shown that microRNA-15a inhibits the expression of casein and the number of epithelial cells, as well as the expression of the growth hormone receptor gene, both through mRNA and via protein [119]. MicroRNA-103 of the mammary gland was involved in the control of fat content in milk during lactation of goats [83]. It was revealed that endogenous microRNA-143 plays a role in the differentiation and proliferation of intramuscular fat cells in cows [97]. These data on the participation of epigenetic markers in the regulation of the synthesis of milk lipids and muscles provide the basis for developing ways to manage the quality of milk and meat through the optimization of the concentration of fatty acids. The relationship of the state of microRNAs of ovarian tissues in chickens with low and high levels of productivity was analyzed [120]. Eleven known and six new microRNAs were detected. All 11 known microRNAs were involved mainly in the regulation of reproduction, such as steroid hormone biosynthesis and dopaminergic synapses. Some of the six miRNAs (for example, gga-miR-34b, gga-miR-34c, and gga-miR-216b) regulate proliferation, cell cycle, apoptosis, and metastasis. Thus, in recent years, there has been an explosion in understanding of the previously hidden role of RNA regulation [101]. Currently, there are a large number of databases of expression and analysis of the microRNA sequences [121]. Although many microRNAs have been identified, it is obvious that there may be many more still undetected. The use of genomic techniques with deep sequencing has shown that there are tens of thousands of loci in mammals that express large transcripts that do not encode proteins but have intergenic and intron localization, where many of these transcripts play a functional role [122]. In accordance with their role in differentiation and development, a number of genetic and biochemical data indicate that one of the main functions of lncRNAs and many small RNAs is the regulation of epigenetic processes [123]. Indeed, it seems that noncoding RNAs are an important component of cellular biology, developmental biology, brain function, and, possibly, even evolution [124]. The complexity and interconnection of these systems is a motivation for studying the vast and largely unknown area of regulating biological processes through RNA. It is possible to annotate transcriptional units and identify functional SNPs through the use of epigenetic maps that delineate thousands of lncRNA genes and hundreds of thousands of *cis*-regulating elements [125, 126].

INFLUENCE OF THE ENVIRONMENT

It is known that the effects of chemicals [127], nutritional supplements and nutrient availability [128, 129], maternal behavior [130], pathogenic microorganisms [131], and temperature [132] cause changes in gene expression [130, 133]. An example is the aforementioned change in the phenotype of agouti coloring in mice under the influence of a maternal diet, including folate and betaine [134]. The animal ration can manifest itself as a source of epigenetic modifications [135], including the expression of microRNAs in the subcutaneous and visceral adipose tissue of cattle [84, 136, 137]. The introduction of methylating compounds into the ration of pigs showed significant differences in DNA methylation and gene expression between groups in the generation F2 [138]. Differentially methylated regions in gene promoters were significantly associated with inhibition of expression of obesity-related genes [139]. In cattle, the expression of tissue-specific adipogenic and lipogenic genes of the longest muscle in the back is regulated by the status of DNA methylation [140]. The DNA methylation levels of all five sites of the CpG promoter of the *FABP4* gene were lower ($p < 0.001$) in intermuscular fat than in the muscular part. The mRNA levels of the *PPARG1* and *FABP4* genes were negatively correlated with the level of DNA methylation in the regulatory CpG regions of the corresponding genes. Adding maize concentrate to the diet of dairy cows leads to a change in the state of methylation of specific genes involved in fat formation and protein synthesis. Fatty acids can contribute to changes in expression of specific genes during critical growth periods [141]. Lipids and lipoprotein components interact directly with the structure of chromatin with subsequent influence on gene expression [142, 143]. Adding fodder rich in unsaturated fatty acids to the diet of dairy cows produces significant changes in the expression of two histone acetyltransferases [144]. There are various points of potential interaction between nutrition and epigenetics, including the effect of supplements or the deficiency of macroelements as well as a number of secondary plant metabolites on methylation [145, 146]. Targeted dietary supplements with folic acid, choline, and betaine may increase DNA methylation [147–149]. There is evidence of an increase in DNA methylation levels in the regulatory regions of the *ZIP4* gene [150] in connection with the use of zinc-containing supplements in the diet.

The change in feeding during late pregnancy can affect the reproductive capacity of daughters [151]. In heifers born to mothers who received a diet high in protein in the second trimester of pregnancy, a decrease in the number of antral follicles was observed [152]. The restriction or excess of protein in the pig's diet during pregnancy influenced the expression of key metabolic genes in the offspring [153, 154]. A low-protein maternal diet during pregnancy and lactation affects the hepatic cholesterol metabolism of offspring by modifying the epigenetic regulation of the 3-hydroxy-3-methylglutaryl coenzyme A reductase and cholesterol-alpha-hydroxylase genes, which suggest

possible long-term effects in cholesterol homeostasis later in adulthood [155].

Features of feeding affect the expression of microRNA in subcutaneous and visceral adipose tissue of cattle [136]. A higher amount of microRNAs was found in animals treated with high-fat fodder [156–158]. Epigenetic modifications unlock the loci of the milk protein gene during the development and differentiation of the mammary gland of the mouse. The role of epigenetic factors in unlocking the milk protein loci in the development and differentiation of the mammary gland was demonstrated [159]. In addition, there is increasing evidence that epigenetic factors regulate milk production in cows [4]. There are reports of differences in mRNA expression levels in the mammary glands between lactating and nonlactating cows [114]. It is obvious that epigenetic markers regulate the synthesis of lipids and the production of milk. It remains to be determined how epigenetic factors can be controlled to improve the milk productivity of cows.

There are a number of studies on the relationship of the epigenetic state and pathological processes in animals [160, 161]. DNA methylation around the STAT5-binding enhancer in the αS1-casein promoter is associated with a sharp discontinuation of the synthesis of αS1-casein during acute mastitis. Experimental infection of the mammary gland with pathogenic *E. coli* revealed the involvement of epigenetic factors in the synthesis of αS1-casein and the occurrence of mastitis in cattle [162] through hypomethylation of the upper promoter region of the alpha-casein S1 gene. It was shown that the presence of bacteria changed the status of methylation of the CD4 differentiation cluster promoter in cows with mastitis [161].

With the help of the latest generation of deep sequencing technologies, the involvement of microRNAs in the development of viral and bacterial infections in cattle was shown [163]. A number of studies have shown that microRNAs are expressed in a wide range of cattle tissues, including those associated with immunity [164, 165]. It is becoming increasingly evident that microRNAs play a significant role in the formation of cow immunity. Castration in pigs can significantly affect the model of expression of microRNAs involved in lipogenesis. Differentiated expressed miRNAs can play an important role in fat deposition after castration [166, 167].

Thus, a number of external factors affect the formation of phenotypic features, which may have a direct relationship to the breeding and productive qualities of animals.

EVALUATION OF PROSPECTS OF INTRODUCTION OF EPIGENETIC EFFECTS IN LIVESTOCK BREEDING

Epigenomic mutations, as in the case with DNA mutations, can carry positive, neutral, and harmful effects with different potentials of adaptation to environmental signals. Unfortunately, the main limitation of studying the epigenomic effects in livestock breeding is the insufficient recognition of the importance of the contribution of these effects to the formation of economically significant phenotypes, including the risk of diseases. There is much evidence of the involvement of the epigenome, in particular, microRNAs, in many aspects of the formation of the productive qualities of farm animals, such as milk production [168], fat formation [84, 169, 170], early embryonic development [82], and animal morbidity [8]. Usually, two types of epigenetic inheritance are employed: inheritance in the somatic cell line and preservation of changes during mitosis [171], that is, transgeneration epigenetic inheritance through the germline, which controls patterns of gene expression with transmission from one generation to the next [172]. Some authors suggest models for the quantitative evaluation of epigenetic dispersion inherited in populations [173, 174]. However, it should be borne in mind that epigenetic markers are inherited in the germline, at least in mammals, in no more than three generations [175], since epigenetic traits are usually removed during meiosis and are not transmitted to the offspring unless the fourth generation is subject to such influence. Some epigenetic markers avoid this stage of cleansing. Therefore, the majority of hereditary epigenetic dispersions do not cover any broad populations of animals [176]. In addition, there is the problem of differentiation of the additive epigenetic effect from the effect of epistasis, dominance, and other effects on genetic dispersion [177], although epigenetic markers are established in the early stages of development, and adaptation takes place throughout life in response to internal and external stimuli and leads to phenotypic manifestation of a trait in the late stage of an animal's life [178].

It should be noted that the introduction of improved breeding programs, where imprinting is taken into account, will require making changes in the existing standard breeding programs. This will require the inclusion of variable figures for the breeding value of producers and females, as well as an assessment of the influence of dominance and additive genetic deviations. It is necessary to reveal the details of the transmission of hereditary information through epigenetic processes and to more deeply assess the changes in the epigenome that occur during the formation of germ cells and the early ontogeny, and also to have more evidence about the degree of influence of epigenetic factors on the formation of economic characteristics, for example, on the synthesis of milk in cows [4, 168].

With the development of DNA sequencing technologies, the genomic part of the variability of animal traits is currently assessed at a faster rate. Therefore, ways should be developed to take into account the epigenetic contribution to the true value of the breeding value of the individual. This is a new field of activity in animal breeding studies, in which the heterogeneity of epigenetic markers and the differences in their tissue affiliation and developmental stages complicate the task. Transgenerative epigenetic inheritance is a field for discussion in the scientific community, since it includes radically new biological phenomena, affecting even the inheritance of acquired characteristics. There is much uncertainty in the problem of including transgenerative inheritance of epimutations in breeding programs. New research approaches need to be developed to determine quantitative information on phenotypic variability caused by epimutations [179]. The development of new technologies (immunoprecipitation of chromatin with microchips of DNA (called ChIP-Chip), next-generation sequencing (ChIP-Seq), editing of the epigenome based on CRISPR-Cas9, and others) gives hope for solving the problems of introduction of epigenetic effects in livestock breeding [180].

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