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Perspectives

Epigenetic and gene therapy in human and veterinary medicine

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Abstract

Gene therapy is a focus of interest in both human and veterinary medicine, especially in recent years due to the potential applications of CRISPR/Cas9 technology. Another relatively new approach is that of epigenetic therapy, which involves an intervention based on epigenetic marks, including DNA methylation, histone post-translational modifications, and post-transcription modifications of distinct RNAs. The epigenome results from enzymatic reactions, which regulate gene expression without altering DNA sequences. In contrast to conventional CRISP/Cas9 techniques, the recently established methodology of epigenetic editing mediated by the CRISPR/dCas9 system is designed to target specific genes without causing DNA breaks. Both natural epigenetic processes and epigenetic editing regulate gene expression and thereby contribute to maintaining the balance between physiological functions and pathophysiological states. From this perspective, knowledge of specific epigenetic marks has immense potential in both human and veterinary medicine. For instance, the use of epigenetic drugs (chemical compounds with therapeutic potential affecting the epigenome) seems to be promising for the treatment of cancer, metabolic, and infectious diseases. Also, there is evidence that an epigenetic diet (nutrition-like factors affecting epigenome) should be considered as part of a healthy lifestyle and could contribute to the prevention of pathophysiological processes. In summary, epigenetic-based approaches in human and veterinary medicine have increasing significance in targeting aberrant gene expression associated with various diseases. In this case, CRISPR/dCas9, epigenetic targeting, and some epigenetic nutrition factors could contribute to reversing an abnormal epigenetic landscape to a healthy physiological state.

Key words: epigenetics; histone code; DNA methylation; RNA modifications; CRISPR-dCas9; gene therapy

Introduction of basic epigenetics mechanisms

Epigenetic processes are reversible events in chromatin involving histone proteins and DNA carrying genetic information. Epigenetics is the field of science that examines how a combination of genetic, biochemical, environmental, and lifestyle factors affect gene expression without changing the DNA sequence. Epigenetics is a multidisciplinary science that exists at the intersection between Mendelian genetics, biochemistry, molecular and developmental biology, and nutrition science. The study of epigenetic processes is an important part of understanding gene expression regulation. In the genome, there are several epigenetic processes, including DNA methylation, histone post-translational modifications, the function of non-coding RNAs, and co-transcriptional modifications of distinct types of RNA (mRNA, rRNA, tRNA, miRNAs, or lncRNAs) [1, 2]. The term epigenetics was first established by Conrad Waddington in the early 1940s. Epigenetic features/marks are influenced by developmental processes and are meiotically unstable which resonates with Waddington's ideas [3, 4]. Due to this fact, epigenetic processes can change in response to environmental conditions or even under the influence of epigenetic therapy or epigenetic diet [5, 6]. For example, the maternal diet during pregnancy can influence epigenetic marks present on the DNA of offspring, potentially affecting their health and development [7]. Epigenetic processes take place predominantly in the cell nucleus and therefore are related to DNA and core (H2A, H2B, H3, and H4) or linker (H1) histones. It is generally established that DNA and core histones form nucleosomes which represent the fundamental building blocks of chromatin (Fig. 1A). Chromatin is arranged into specifically organized structures such as 30 nm chromatin fibers, subsequently forming loop domains or topologically associated domains (TADs), which play a role in overall chromatin organization. For example, TADs are responsible for separating transcriptionally active and inactive regions in the genome that are finally arranged into the highest organized structures, which are the interphase and metaphase chromosomes [8–10] (Fig. 1A).

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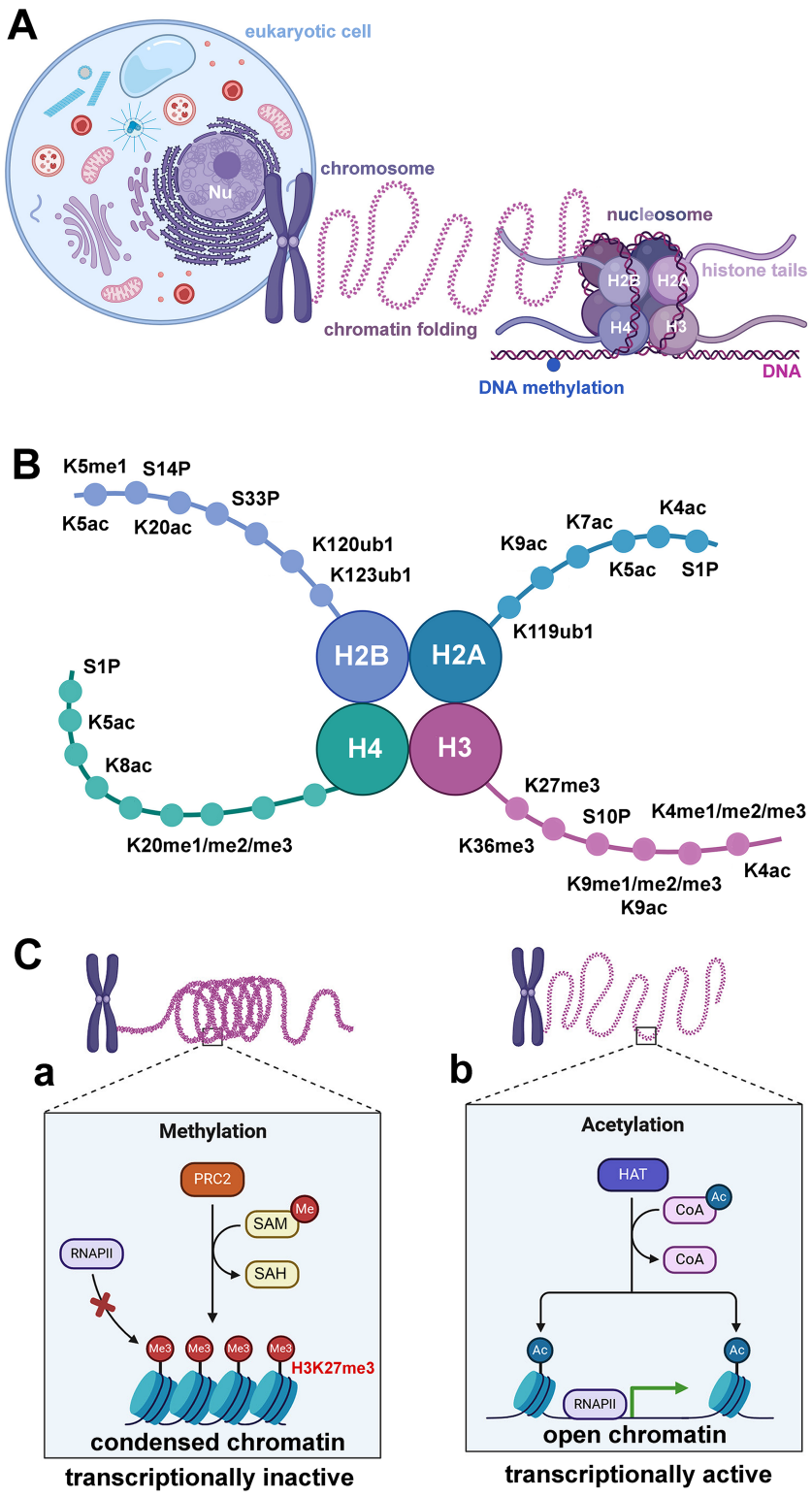

Figure 1: (A) An example of the eukaryotic cell and its chromatin folding. The nucleus is labeled as Nu. N-terminal tails of nucleosomes are illustrated as well as methylated DNA that is wrapped around a histone octamer to form nucleosomes. (B) An example of core histones (H2A, H2B, H3, and H4) and examples of their post-translational modifications, including mono-, di-, tri-methylation (me1/me2/me3), acetylation (ac), ubiquitination (ub), and phosphorylation (P). (C) Graphical illustration of (a) methylated, condensed, and transcriptionally inactive chromatin, and (b) acetylated, transcriptionally active chromatin. Abbreviations mean the following terms: HAT—histone acetyltransferase; PRC2—polycomb repressive complex 2; SAM means S-adenosylmethionine, SAH is an abbreviation of S-adenosylhomocystein. This illustration was created using BioRender software (https://www.biorender.com/).

Epigenetic modification of DNA and histone proteins

DNA methylation is a specific epigenetic mark that is formed by the covalent transfer of a methyl group from S-adenyl methionine (SAM) to the C5 position of the cytosine to form 5-methylcytosine [11] (Fig. 1A). DNA methylation is catalyzed by a family of DNA methyltransferases (Dnmts), including de novo Dnmt1, Dnmt3a, and Dnmt3b. For example, Dnmt3a and Dnmt3b are responsible for the installation of a new methylation profile in unmodified DNA, while the maintenance Dnmt1 acts during DNA replication transferring DNA methylation patterns from the parental DNA strand onto the newly synthesized strand of DNA [12]. Conversely, methyl groups can also be removed from DNA via demethylation processes. Two main mechanisms of DNA demethylation are known: (I) passive DNA demethylation that occurs during DNA replication when newly synthesized DNA is not immediately methylated. This process does not involve specific enzymatic reactions [13]. However, (II) active DNA demethylation is where an enzymatic reaction leads to the removal of methyl groups from DNA. Ten-Eleven Translocation (TET1, TET2, and TET3) dioxygenases are key players in this epigenetic event [14]. TETs oxidize 5-methylcytosine (5mC), converting it into 5-hydroxymethylcytosine (5hmC). In successive steps, TET enzymes further hydroxylate 5hmC to generate 5-formyl cytosine (5fC) and 5-carboxyl cytosine (5caC). Thymine DNA glycosylase (TDG) identifies 5fC and 5caC, intermediate forms in DNA, and excises the glycosidic bond. The results of this reaction are apyrimidinic (AP) sites. Another demethylation process involves the deamination of 5hmC via the function of AID/APOBEC deaminases (activity-induced cytidine deaminase/apolipoprotein B mRNA editing complex) creating 5-hydroxymethyluracil (5hmU) or alternatively, 5mC can be converted to thymine (Thy). After this reaction, TDG or other glycosylases cleave 5hmU and the Base Excision Repair (BER) mechanism can be engaged in the repair of AP sites and T/G mismatches [15]. Such an orchestrated mechanism shows that the interplay between DNA methylation and demethylation is crucial for normal cellular function, and disruptions in these processes have been implicated in various diseases, including cancer and neurological disorders [16].

Also, other epigenetic marks are histone post-translational modifications (PTMs) that appear on N-terminal histone tails [17, 18]. Specific PTMs of histones, including methylation, acetylation, ubiquitination, or phosphorylation, regulate chromatin condensation, gene expression, or DNA damage repair [19]. Epigenetic marks of transcriptionally repressed gene loci are di-/tri-methylated histones H3 at lysine (K) 9 (H3K9me2/me3) or lysine 27 (H3K27me2/me3) [18] (Fig. 1B, Ca). Histone methylation/demethylation processes are regulated by histone methyltransferases and demethylases. For example, the lysine-specific histone demethylase 1 (LSD1) was discovered in 2004, and its enzymatic activity is conserved among eukaryotes. LSD1 contains an amine oxidase domain and is responsible for the removal of mono- and di-methylation at histones H3K4 or H3K9 [20]. In many cases, LSD1 functions as a gene-silencing factor because it removes H3K4me1/me2 marks from transcriptionally active chromatin [20]. On the other hand, when LSD1 interacts with the androgen receptor, it promotes androgen-dependent transcription of target genes. This process is accompanied by ligand-induced demethylation of mono- and dimethylated histones H3 at lysine 9 (H3K9me1/me2) [21]. Also, specific epigenetic functions have been revealed in the case of the JmjC domain-containing histone demethylases [22, 23]. One example is Jmjd2a, also known as KDM4A (lysine demethylase 4A), which is responsible for the removal of methyl groups from methylated histones H3K9me2/me3 or H3K36me2/me3 [23]. This function predisposes Jmjd2a to the dynamic regulation of chromatin structure, allowing the activation or repression of specific genes that subsequently regulate the cell cycle or cell differentiation [24]. Also, Jmjd2a may play a role in DNA repair mechanisms by influencing the chromatin structure around damaged genomic regions [25]. The aberrant function of histone demethylases is associated with malignant cell transformation [26].

A specific histone signature for transcriptionally active loci represents histone acetylation. An example of this is where promoters of up-regulated genes are associated with acetylated histones H3 (H3K9ac) or H4 (H4ac, H4K16ac) (Fig. 1B, Cb) [18, 19]. Acetylation of lysine residues on histone tails weakens their positive charge, which reduces the affinity of core histones for the negatively charged phosphate backbone of DNA [27]. This causes chromatin de-condensation enabling regulatory proteins to access these genomic regions [27]. Important to histone acetylation is the function of specific molecular "writers" (histone acetyltransferases, HATs) and "erasers" (histone deacetylases, HDACs) [28]. In addition to histones, non-histone proteins and certain RNAs can also be acetylated via acetyltransferases that need acetyl coenzyme A for their function (Fig. 2A, B) [28, 29]. Conversely, HDACs are responsible for the removal of acetyl groups from N-acetyl lysine residues on both histones and non-histone proteins. This process contributes to the regulation of histone signatures and subsequently to the regulation of many cellular processes [29, 30]. One example represents the influence of HDAC1 deficiency on the neural differentiation process in mice. In this case, the function of HDAC1 and HDAC3 was observed to be essential for both embryonic brain development and neuro-differentiation. HDAC1-deficient mouse embryonic stem cells (ESCs) were characterized by early H3K9 deacetylation, Sox2 downregulation, and enhanced astrogliogenesis. Interestingly, the hippocampi of schizophrenia-like animals showed H3K9 deacetylation mediated by both HDAC1 and HDAC3 proteins [31]. These experiments are a good example of how epigenetic factors can regulate developmental processes.

Epigenetic drugs affecting DNA and histones

Importantly, the function of histone-modifying enzymes can be modulated by specific inhibitors of activators that change the epigenome and can be potentially used in nutrition therapy as well as in the treatment of serious human and animal diseases. The use of epigenetic drugs (epi-drugs) and epigenetic diet (epi-diet) is often studied in the context of diseases such as cancer or neurological disorders [5, 32]. From this perspective, the safety and efficacy of these compounds for long-term use, especially in the context of nutrition, need further investigation because physicians vary on potential side effects that must be carefully considered [33]. For example, DNA methyltransferase inhibitors, 5-azacytidine (5-aza) or decitabine, have been studied for their potential for cancer treatment and could have implications in epigenetic regulation [34]. Also, in the context of cancer therapy, HDAC inhibitors, including suberoylanilide hydroxamic acid (SAHA, Vorinostat), have the potential to alter gene expression by influencing histone acetylation profiles [35]. BIX-01294, an inhibitor of the G9a histone methyltransferase, is also a focus of interest because this compound regulates H3K9 methylation

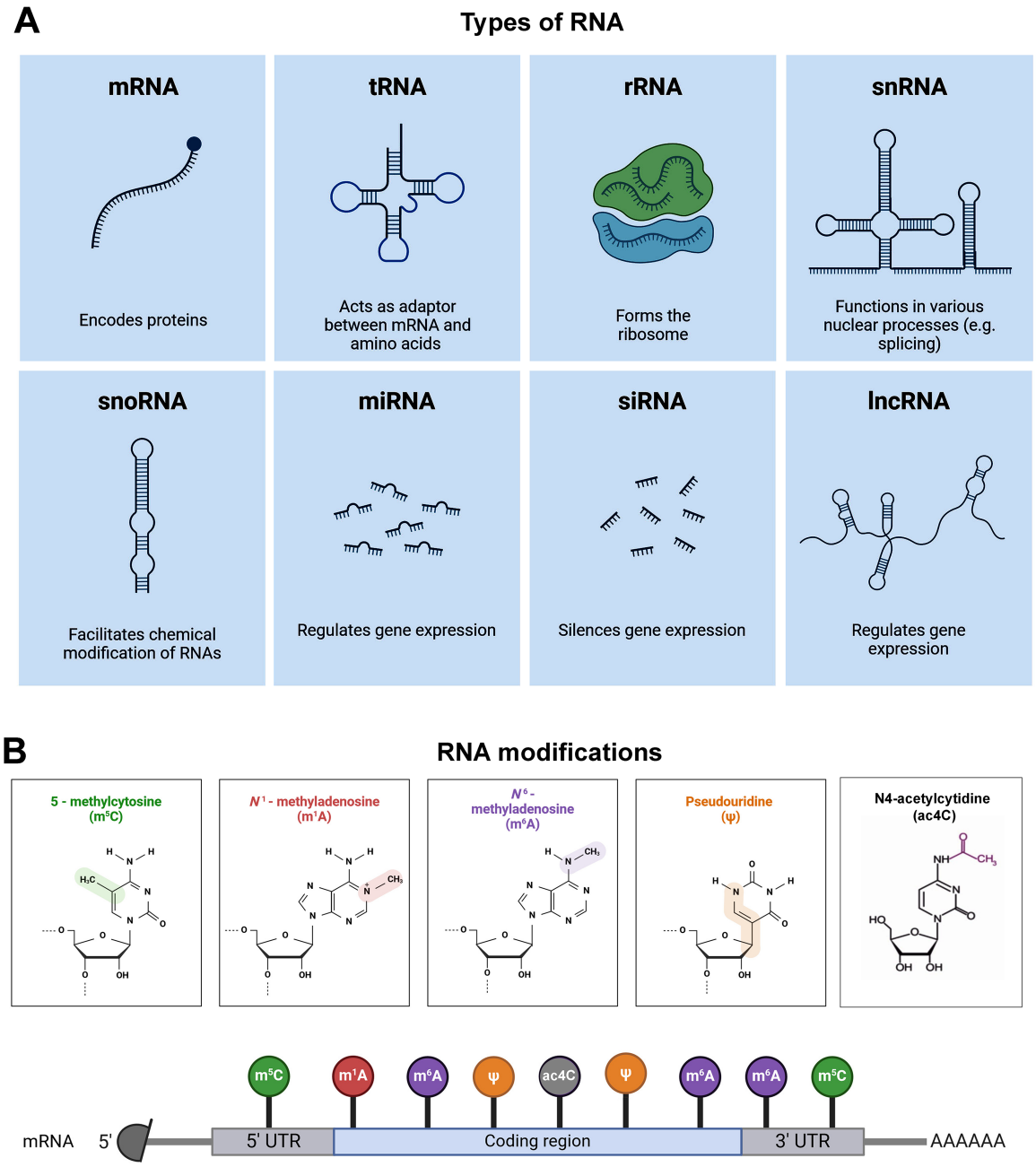

Figure 2: Post-transcription modifications of distinct types of RNA. (A) Types of RNA. (B) RNA modifications, including N^5-methylcytosine, N^1-methlyadenosine, N^6-methyladenosine, pseudouridine (Ψ), and N^4-acetylcytidine (ac4C). Images were created using BioRender software (https://www.biorender.com/).

and therefore has the potential to change gene expression [36]. In the case of gene expression regulation, inhibition of the histone demethylase JMJD (KDM6B) by the chemical compound GSK-J4 has considerable clinical potential as an anti-cancer therapy [37]. Also worth mentioning is the effect of curcumin as a prospective component in an epigenetic diet [38]. Curcumin has anti-inflammatory and anticancer properties. Some studies suggest that curcumin may influence HDAC activity, leading to changes in gene expression. However, it is important to note that the evidence regarding curcumin as a direct HDAC inhibitor is not as robust, in comparison with some synthetic HDAC inhibitors that have been developed for therapeutic purposes [39]. The exact mechanisms of how curcumin may modulate HDAC activity are not fully understood, but curcumin shows promise in various preclinical studies for its potential anti-cancer and anti-inflammatory effects [39]. From this view, future studies may provide more insights into the specific molecular mechanisms involved in epigenome regulation and new experimental data must show whether curcumin or its derivatives could be used as effective HDAC inhibitors in clinical practice.

Post-transcriptional modifications of RNA

The term "RNA modifications" is generally used to refer to the post-transcriptional (co-transcriptional) chemical alterations that occur in RNA molecules (Fig. 2A, B). These modifications play cru-

cial roles in various cellular processes, including RNA stability, processing, transport, and translation [1, 2]. Unlike DNA, which is relatively stable, RNA is a more dynamic molecule subjected to many biochemical processes, some of which modify the structure of nucleosides or can be modulated by the presence of chemical modifications (Fig. 2B). For instance, RNA methylation is a very significant regulatory epitranscriptomic element. Methylation is one of the most common RNA modifications and occurs on adenosine (m6A), cytosine (m5C), and guanosine (m7G). The addition of a methyl group to the nitrogen at the sixth position of adenosine (N6-methyladenosine; m6A) is a reversible modification and is known to regulate mRNA stability and translation [40]. Another form of RNA methylation is the most common 2′-O-methylation that is prevalent in small nuclear RNAs (snRNAs), rRNA, and mRNA. This modification acts in various ways. For instance, it can potentiate RNA hydrophobicity, protect RNAs from nucleases, or stabilize RNA structure [41]. Also, methylation occurs at the N1-position of adenosine (N1-methyladenosine; m1A), which is present in tRNAs or rRNAs and plays a role in tRNA stability, and therefore the translation process [42] (Fig. 2B). In the RNA world, many additional RNA modifications exist. For example, methylation of the fifth carbon in the cytosine ring (5-methylcytosine; m5C) [43] or the presence of inosine (I). In this case, the deamination of adenosine leads to inosine pairing with cytosine in RNA. This modification is involved in the regulation of RNA editing [44]. Another modification found in distinct types of RNA is pseudouridylation, which appears as the consequence of the isomerization of uridine to pseudouridine [45]. Pseudouridine is found in various types of RNA, and its presence can influence RNA structure and function (Fig. 2A, B). Worth mentioning is also N4-acetylcytidine in RNA. This biochemical modification, mediated via the function of an acetyltransferase NAT10, results in a variety of regulations, including translation efficiency [46–48]. Taken together, all the RNA modifications mentioned above are dynamically regulated and can impact RNA functions, structure, and interactions with other molecules. In the field of RNA biology, researchers are actively studying the roles of RNA modifications in various cellular processes and their implications for health and diseases. Thus, the field of RNA epigenetics/epitranscriptomics is continually evolving, and ongoing research continues to uncover new RNA modifications and their functional significance, especially in the human genome.

Applications of gene therapy in human and veterinary medicine

Gene therapy is a rapidly advancing biomedical discipline in both human and veterinary medicine, offering promising prospects for the treatment of various diseases. The basic idea behind gene therapy is to introduce, modify, or replace genetic material in pathological cells to treat or prevent disease. For example, gene therapy has shown success in treating monogenic disorders, which result from mutations in a single gene [49]. Examples include severe combined immunodeficiency (SCID), hemophilia, and certain types of muscular dystrophy [50]. Also, in oncology, gene therapy is being explored to target and eliminate cancer cells. This includes the use of modified viruses to deliver therapeutic genes or the engineering of T cells to express chimeric antigen receptors (CAR-T therapy) [51]. Gene therapy is also being investigated for neurodegenerative disorders such as Parkinson's and Alzheimer's disease. Researchers are exploring ways to deliver therapeutic genes to affect such neurodegenerative diseases [52]. Furthermore, some gene therapies, including genome editing technologies, have been suggested for both inherited and non-inherited retinal diseases in humans [53]. Gene therapy is also promising in veterinary medicine, for example, in therapy for cancer, muscular dystrophy, or various hereditary pathophysiologies [54, 55]. Gene editing might also be used to prevent the transmission of zoonotic diseases from animals to humans, enhancing both animal and human health [56]. Here, it is essential to mention that gene editing has ethical concerns in both humans and domestic animals, especially regarding the potential for unpredictable long-term genetic changes that could cause unexpected side effects.

Genome editing: CRISP-Cas9 and CRISPR-dCas9 technologies enable precise control of DNA sequences as well as epigenetic processes

In addition to epigenetic factors, genes can be regulated or modified via well-established methods of gene editing, such as CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats-associated protein 9) technology or RNA interference (RNAi) [57–60]. CRISPR-Cas9 is a revolutionary gene editing methodology that allows scientists to precisely manipulate DNA sequences in living organisms (Fig. 3 Aa) [57, 58]. CRISPR- Cas9 is an RNA-guided endonuclease that, in combination with single-guided RNA (sgRNA), acts like molecular scissors that can be designed to target and cut specific DNA sequences at precise genomic regions. This ability to cut DNA at specific sites makes CRISPR-Cas9 methodology a powerful tool for gene engineering because a new DNA sequence can be inserted into the genome or selected sequences can be deleted. The current delivery of the CRISPR-Cas9 complex can occur via several methods, such as viral vectors, electroporation, or direct injection. After this, the guide RNA binds to the complementary DNA strand of the target gene, and the Cas9 endonuclease cuts specific DNA sequences, forming double-strand breaks (DSBs) in the desired sites. As a consequence of this, the native DNA repair mechanisms of the cell are activated [61]. There are two main canonical DNA repair pathways; the G1-phase dependent Non-Homologous End Joining (NHEJ) pathway recognizes DSBs, but when the cells enter the S phase or proceed to the G2 phase of the cell cycle, the Homology-Directed Repair (HDR) pathway is activated [62–64]. The HDR pathway is more precise because it relies on a template DNA sequence with homology to the region surrounding the break. When HDR is utilized, the cell can repair the DNA break using the provided template. On the other hand, the NHEJ repair mechanism is more frequently used, especially when the factors of HDR fail [65]. In general, the HDR pathway is less common, especially as many of the cell populations used in research are characterized by a long G1 phase of the cell cycle [66]. Exceptions to this represent ESCs, which are characterized by a specific cell cycle profile. Asynchronously growing ESCs spend most of their time in the S-phase or G2 phases of the cell cycle, but when induced to differentiation, these cells are characterized by a short S-phase of the cell cycle [67]. Based on this fact, it makes sense that HDR should be highly engaged in ESCs when the DNA repair process is activated either naturally or in experimental systems, including CRISPR/Cas9 [68, 69].

Regarding the epigenetic aspects of CRISPR/Cas9 technology, it seems to be functionally advantageous if sgRNA is specifically modified [70]. Epitranscriptomic modifications could be experimentally installed in sgRNA, which could stabilize this molecule

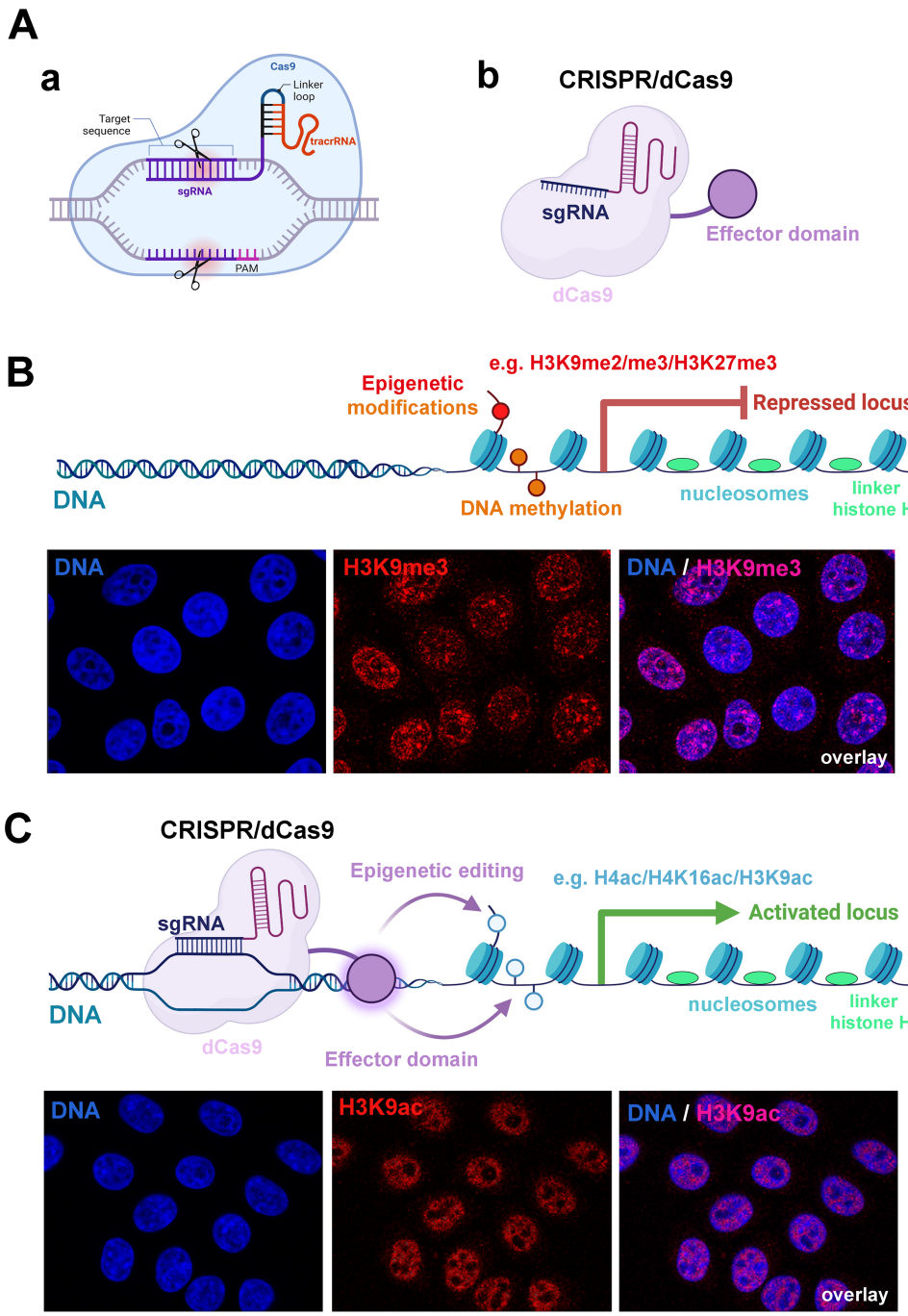

Figure 3: The use of CRISPR/Cas9 and CRISPR/dCas9 technology for gene editing and epigenetic editing. (A) An example of the (a) CRIPR/Cas9 and (b) CRISPR/dCas9 complexes. Abbreviations in panel Aa: single guided RNA (sgRNA); the protospacer adjacent motif (PAM) is a short DNA sequence (usually 2-6 base pairs in length) that follows the DNA region targeted for cleavage by the CRISPR system, is generally found 3-4 nucleotides downstream from the cut site. Trans-activating RNA (tracrRNA) is a type of RNA molecule that, along with crRNA (CRISPR RNA), is involved in the CRISPR-Cas9 system. (B) Histone marks and DNA methylation, specific for transcriptionally silent chromatin. Nucleosomes are connected by linker DNA occupied by a linker histone H1. An example of a silencing epigenetic mark, H3K9me3, accumulated into well-visible foci, is shown in HeLa cells studied by immunofluorescence and confocal microscopy (Leica SP5). These unpublished results were obtained using immunohistochemistry (IHC) with the following antibody was used (NBP1-30141, Novus Biologicals). (C) CRISPR/dCas9 maintains the ability to bind the targeted DNA sequence but dCas9 loses endonuclease cleavage activity. The binding of the dCas9/sgRNA complex, via an effector domain, to the target region leads to transcriptional activation. Marks of transcriptionally active chromatin are shown. An example of H3K9ac is shown in HeLa cells studied by immunofluorescence and confocal microscopy (Leica SP5). These unpublished results, originate from my laboratory, and were obtained using IHC with the following antibody was used (06-942, Sigma-Aldrich). Used figure template "CRISPR Technology: Epigenome Editing" was assembled using BioRender software.

and thereby improve CRISP-Cas9 efficiency. Also, while CRISPR-Cas9 is a powerful tool for gene editing, it is not inherently designed for direct epigenetic modification. As mentioned above, epigenetic modifications involve changes in the chemical structure of DNA or histone proteins, influencing gene expression without altering the underlying DNA sequence (Fig. 3B, C). CRISPR-Cas9

is primarily used for precise targeting of DNA sequences by causing DNA breaks. There is no direct targeting of existing epigenetic marks, although sequences of genes encoding, for example, histone modifying enzymes, can be manipulated using the CRISPR-Cas9 technique. In addition to this, researchers have developed CRISPR-based technologies that can be specifically employed for epigenetic modifications. Instead of using the Cas9 nuclease to cut DNA, a mutated, catalytically inactive, version of Cas9 (dCas9) is employed (Fig. 3 Ab, C) [71, 72]. dCas9 contains an effector domain that can modify epigenetic marks without cleavage of DNA. For example, a CRISPR/dCas9-based system (CRISPR/dCas9-R2) can be applied to reduce DNA methylation levels by blocking the DNMT1 activity in the specific loci [73]. Furthermore, Saunderson et al. [72] developed methodologies that allow locus-specific epigenetic editing of the genome, using a dCas9-effector fusion in primary human hematopoietic stem and progenitor cells to analyze cancer-specific DNA methylation changes. Using these systems, researchers can induce specific changes in the epigenome, without causing damage to DNA.

Another possibility for gene manipulation is RNAi which is a natural cellular process regulating gene activity [60]. It is a biological mechanism through which small RNA molecules inhibit the expression of specific genes by either degrading the messenger RNA (mRNA) molecules or blocking their translation into proteins. RNAi plays a crucial role in various cellular processes, including defense against viral infections or maintenance of genome stability. The key players in RNAi are small RNA molecules, including small interfering RNAs (siRNAs) or microRNAs (miRNAs). These molecules are typically 20–25 nucleotides in length and are involved in post-transcriptional gene silencing [74].

The last-mentioned miRNAs are formed by transcription from coding sequences, but these transcripts are not subsequently translated into proteins. The primary transcript is called pri-miRNA, which forms hairpins and is subsequently processed into pre-miRNAs. This process is mediated by a protein complex composed of a nuclease called Drosha and a protein called Pasha, capable of binding double-stranded RNA. Subsequently, the pre-miRNA enters the cytoplasm, where it interacts with an endonuclease called Dicer to form a single-stranded miRNA that binds to the RISC complex (RNA-induced silencing complex). RISC is essential for RNAi because it has a catalytic component, Argonaute, which is an endonuclease capable of degrading messenger RNA (mRNA). The miRNA or siRNA guides the RISC to its target mRNA through base pairing. The specificity of the interaction is determined by complementary base pairing between the small RNA and the target mRNA [74]. If there is perfect base pairing between the small RNA and the target mRNA, the mRNA is cleaved and degraded, preventing translation into a functional protein. In the case of imperfect base pairing, translation is typically blocked without mRNA degradation. RNAi has become a powerful tool in molecular biology research and holds therapeutic potential for treating various diseases. Researchers can use synthetic siRNA or designed miRNAs to selectively silence specific genes that are manipulated for experimental purposes or the development of potential therapeutic strategies.

An example of an epigenetic process affecting physiological functions: the epigenetics of milk production and consumption

Epigenetics plays a significant role in regulating various biological processes, and milk production in mammals is not an exception. Specific epigenetic modifications are crucial in regulating the development of the mammary glands. During pregnancy and lactation, the mammary gland undergoes complex changes, leading to milk synthesis and secretion. Epigenetic processes help control the activation or suppression of gene expression in the mammary glands [26]. Epigenetic processes also influence the composition of milk, including its nutritional content and quality of milk protein, fat, or carbohydrate synthesis [75, 76]. Some of these processes are inherited from one generation to the next. This means that the epigenetic landscape in lactating mammals, including humans, could potentially impact the offspring. Understanding the epigenetic regulation of milk production has implications for improving human and animal healthcare.

It is very likely that not only some external epigenetic factors, including epigenetic diet, can affect milk production, but also maternal milk serves as an epigenetic regulator of mammalian development [77]. This process is an example of an epigenetic programming system affecting newborn individuals. For instance, milk exosome-derived miRNAs, secreted by mammary gland epithelial cells, suppress DNA methyltransferases (DMNTs), thus activating metabolically essential genes, including FTO (a gene encoding a fat mass and obesity-associated protein), INS (insulin gene), and IGF1 (a gene encoding an insulin-like growth factor 1) [78, 79]. These observations suggest the functional role of milk as an epigenetic regulator of gene expression in milk recipients, not only during lactation but for the whole life of the organism. For instance, human milk is abundant in miRNAs, including miRNA-148a, miR-152, miR-29b, and miR-21, which cause genome-wide DNA hypomethylation, which changes gene expression [80, 81]. Notably, the expression of specific miRNAs in human mothers also significantly increases during lactation [82]. Based on this fact, it seems very likely that miRNAs present in maternal milk significantly affect the epigenome of newborn individuals and can therefore affect the predisposition of offspring to diseases via regulating tissue-specific genes.

Epigenetics in veterinary science and medicine

Epigenetics in veterinary medicine is an emerging field of science that explores how environmental factors and gene expression patterns can impact the health and development of domestic animals. It focuses on understanding how epigenetic modifications in DNA, including DNA methylation and its associated histone and non-histone proteins, can influence gene activity without altering the underlying genetic code. This can have profound effects on an animal's susceptibility to diseases, their response to treatments, and even how specific traits are passed down to future generations. Epigenetic therapies in veterinary medicine are still in their early stages, and much research is being conducted to understand how epigenetic modifications can be targeted to improve animal health.

In normal cells, specific epigenetic modifications maintain the physiological function of proto-oncogenes that are, under physiological conditions, responsible for physiological cell proliferation in both humans as well as domestic animals. However, mutations may convert proto-oncogenes into oncogenes through their overexpression or changes in their protein product function. This process in turn leads to oncogenic cell transformation which is not only associated with the appearance of an aberrant genome but also an aberrant epigenome, both of which are associated with uncontrolled cell proliferation [83]. In comparison with normal cells, tumor cells are also characterized by an aberrant function

of tumor suppressor genes, e.g. TP53. This gene is considered a guardian of the genome, keeping cell division and apoptotic processes under control [83, 84]. However, in tumor cells, both oncogenes and tumor suppressor genes have characteristic changes in epigenetic marks that result in non-physiological gene expression. To reverse the aberrant epigenome in tumor cells, including DNA hypermethylation in promoters of tumor suppressor genes or histone hyperacetylation in oncogenes, epigenetic-based therapies could potentially be useful in both humans and domestic animals [85].

Changes in epigenetic modifications also accompany the process of aging and age-related diseases. Therefore, therapies using epigenetic drugs might offer possibilities to slow down the aging process and increase the lifespan of domestic animals. It is important to note that while there is potential for epigenetic therapies in veterinary medicine, there are still many challenges to overcome. The use of an epigenetic diet can be a promising step. In this case, favorable nutrition-like epigenetic factors are HDAC inhibitors, compounds affecting gene expression by mediating a more open chromatin structure. In human medicine, HDAC inhibitors have been studied extensively for their potential therapeutic applications, particularly in the field of cancer treatment, where they have been investigated for their ability to reactivate silenced tumor suppressor genes or induce apoptosis in cancer cells [86]. It is important to note that HDAC inhibitors are typically used as pharmaceutical agents, including, for example, Vorinostat (SAHA), Romidepsin, Panobinostat, and Belinostat, which have been approved by the US Food and Drug Administration (FDA) to treat T-cell lymphoma [87]. The use of HDAC inhibitors in veterinary medicine is still an evolving area and more research is needed to establish their safety and efficacy in different animal species. In the future, it is likely that veterinary science will benefit from the use of epigenetic drugs, including HDAC inhibitors in the therapy of domestic animals.

Many dietary components can have effects on the epigenome. For example, methyl-donating vitamins like folate (B9) and cobalamin (B12), and methyl-donating cofactor S-adenosyl-L-methionine (SAM), all of which are involved in methylation processes in DNA, RNA, and proteins [88]. Additionally, certain phytochemicals contained in fruits, vegetables, and other foods have been studied for their potential epigenetic effects. The understanding of the mutual link between dietary compounds and epigenetic modifications is still an evolving field of research. For example, folate is involved in one-carbon metabolism, which provides methyl groups for DNA methylation. Adequate folate intake is essential for physiological DNA methylation patterns. Good dietary sources of folate include leafy green vegetables, legumes, fortified cereals, and curcumin [89, 90]. Certain polyphenols found in fruits, vegetables, and beverages like tea and red wine have been studied for their potential epigenetic effects. For example, resveratrol, found mainly in red grapes and wine, has been associated with the modulation of DNA methylation and histone acetylation [91].

Focus on HDAC inhibitor curcumin and its use in epigenetic diet

As mentioned above, curcumin is a natural compound found in the rhizome of the turmeric plant (Curcuma longa). It is known for its striking yellow color and has been used for centuries in traditional medicine, particularly in Ayurveda and traditional Chinese medicine, for its potential health benefits. Curcumin regulates the epigenome at the level of DNA methylation, via inhibition of DNA methyltransferases (DNMTs). It also regulates miRNAs, and its most well-known effect is the regulation of histone acetylation [92]. The anti-inflammatory properties of curcumin are thought to be relevant for the treatment of various chronic diseases. The antioxidant properties of curcumin mean that it can neutralize harmful free radicals in the body and reduce oxidative stress. This effect may inhibit the growth and dissemination of cancer cells. Curcumin is an attractive candidate for an epigenetic diet, leading to cancer prevention and treatment [93–96]. Also, it is suggested that curcumin might have neuroprotective properties, potentially benefiting brain health and reducing the risk of neurodegenerative diseases like Alzheimer's disease [95]. Some studies showed that curcumin has positive effects on the cardiovascular system, including the ability to improve blood vessel function, reduce cholesterol levels, and reduce the risk of heart disease. Notably, the effect of curcumin can be improved by combining it with piperine (a compound from black pepper) [39]. All the above-mentioned factors mean that consuming natural products that affect the epigenome, including curcumin, can benefit physiological functions and general health in both humans and domestic animals.

Environmental epigenetics

Environmental epigenetics is a field of study that explores how environmental factors affect the epigenome. These factors can cause phenotypic variation leading to changes in the physiological processes of organisms. The environment, including factors such as diet, exposure to toxins, water pollutants, stress factors, and lifestyle, has a profound impact on the epigenome of not only animals and humans but also the epigenome of plants [97]. These changes can influence gene expression regulating cellular function and subsequently affecting health conditions. It is likely that exposure to environmental factors may lead to epigenetic changes that persist across generations. This transgenerational transmission of epigenetic information, called epigenetic memory, is an area of active research and has implications for understanding the long-term effects of the environment [98]. Environmental epigenetics is particularly relevant to understanding the link between environmental exposures and increased susceptibility to diseases, including cancer, neurodevelopmental disorders, and metabolic pathophysiologies. Studying environmental epigenetics provides insights into how external factors can influence molecular mechanisms within cells, potentially contributing to health and disease. It also raises important questions about the plasticity and adaptability of the epigenome in response to environmental stimuli and how changes in the epigenome might be targeted in the case of disease prevention or therapeutic interventions.

Another important area of research is how climate changes affect the epigenomes of organisms. Climate change refers to long-term changes in the temperature and other atmospheric conditions on Earth. It is primarily driven by human activities such as the burning of fossil fuels, deforestation, and industrial processes, leading to an increase in greenhouse gas concentrations and subsequent changes in the climate [97]. Studies have investigated how environmental stressors, including those associated with climate change, can influence the epigenetic regulation of genes, where aberrant function causes respiratory diseases, cardiovascular diseases, and neurological disorders. However, the understanding of how environmental factors affect the genome and epigenome needs ongoing research uncovering specific mechanisms in plants, animals, and humans. From this point of view, processes in the plant epigenome are also worth mentioning. For

example, plants are particularly sensitive to environmental inputs evolved intriguing epigenetic mechanisms to cope with various abiotic stresses, including DNA hypermethylation of heterochromatin in salt-stressed plants, hypermethylation of histone H3K4 during adaptation processes to drought, changes in chromatin condensation in response to heat stress, or alteration of H3K9ac levels following exposure of plants to UV light [99–103].

Concluding remarks

It is important to note that the concept of epigenetic therapy, the consumption of an epigenetic-based diet, and the potential analysis of epigenetic marks as diagnostic tools are promising in both human and veterinary medicine. Translating basic epigenetic research findings into clinical applications, such as diagnostic and therapeutic approaches, poses challenges. Understanding how to harness epigenetic information for personalized medicine and how to develop targeted interventions in epigenome is an ongoing area of research. Addressing these challenges requires collaborative efforts across disciplines, including molecular biology, biochemistry, biomedicine, nutrition therapy, and technological advancements. Also, it is essential to establish ethical guidelines in the field of epigenetics gene manipulation and therapy.

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