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THE INFLUENCE OF LACTOFERRIN ON THE EPIGENETIC CHARACTERISTICS OF MAMMALIAN CELLS OF DIFFERENT TYPES

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Despite the huge amount of accumulated data, the study of the main mechanisms of interaction between proteins and epigenetic mechanisms in health and various pathologies remains one of the most important problems of molecular biology. The search for various endogenous and exogenous factors affecting the epigenome of eukaryotes continues to be relevant. Lactoferrin is the second most abundant milk protein and has proven to be a very promising anti-inflammatory, antifungal, antibacterial, and anti-cancer agent. This protein can act as a transcription factor regulating the expression of some genes. However, little attention has been paid to the use of lactoferrin as an epigenetic modulating factor. This review demonstrates that lactoferrin can directly and/or indirectly influence epigenetic mechanisms (DNA methylation, histone modification, chromatin compaction, and microRNA pathways) in different types of cells, in particular cancer cells.

Keywords: lactoferrin; DNA methylation; miRNA; chromatin; epigenetics; epi-miRNA; TET enzymes; ER; HIF.

ВЛИЯНИЕ ЛАКТОФЕРРИНА НА ЭПИГЕНЕТИЧЕСКИЕ ХАРАКТЕРИСТИКИ КЛЕТОК МЛЕКОПИТАЮЩИХ РАЗНОГО ТИПА

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Несмотря на огромное количество накопленных данных, изучение особенностей взаимодействия между белками и эпигенетическими механизмами в норме и при различных патологиях остается одной из важнейших задач молекулярной биологии. Поиск эндогенных и экзогенных факторов, влияющих на эпигеном эукариот, по-прежнему актуален. Лактоферрин является вторым по распространенности белком молока, который обладает противовоспалительными, противогрибковыми, антибактериальными и противораковыми свойствами. Этот белок может действовать как фактор транскрипции, регулирующий экспрессию некоторых генов. Однако мало внимания уделяется использованию лактоферрина в качестве фактора, модулирующего эпигенетические модификации (механизмы). В данном обзоре представлены данные, указывающие на то, что лактоферрин может прямо и/или косвенно влиять на эпигенетические механизмы (метилирование ДНК, модификация гистонов, компактизация хроматина и микроРНК-пути) в различных типах клеток, в частности в опухолевых клетках.

Ключевые слова: лактоферрин; метилирование ДНК; миРНК; хроматин; эпигенетика; эпи-миРНК; ТЕТ-ферменты; рецепторы эстрогена; факторы, индуцируемые гипоксией.

Introduction

In the past decade, epigenetics has been taking a central role in explaining the relationships between behavior, stress exposure, and health. Inherited or acquired epigenetic changes affect gene expression status without modifying the DNA sequence itself. DNA methylation and post-translational modification of histones are the two most studied epigenetic events. Other potential epigenetic modifications are those mediated by non-coding RNAs, especially microRNAs.

List of abbreviations

DNMT — DNA methyltransferase; Lf — lactoferrin; ΔLf — delta-lactoferrin; miRNA — micro-RNA; EZH2 — enhancer of zeste 2; PRC — polycomb-repressive complex; Lfcin B — lactoferricin B; HIF — hypoxia-inducible factor; JMJD2C — jumonji domain containing protein 2C; TET — ten-eleven translocation enzymes; ER — estrogen receptor.

DNA methylation involves the addition of a methyl group to the 5-carbon position of cytosine bases through the action of a family of DNA methyltransferases (DNMT). The cytosine bases are most susceptible to methylation and are often found in the cytosine-phosphate-guanine (CpG) dinucleotide sequences of DNA, referred to as CpG islands [1]. DNA methylation can directly inactivate genes by preventing the binding of transcriptional machinery or most mammalian transcription factors with methylated promoter DNA [2]. Methylated CpGs can also affect nucleosome positioning or stability and core histone access, thereby modifying access of transcription factors to promoter regions [1].

Histone post-translational modifications include acetylation, methylation, phosphorylation, sumoylation, and ubiquitination. Histone acetylation and histone methylation are covalent post-translational modifications by which acetyl or methyl groups are transferred to amino acids on the histone tails, altering gene accessibility and therefore expression by modification of the chromatin structure [3]. Notably, acetylation is associated with an open chromatin state marking an active region of transcription, whereas methylation can be present both in actively transcribed and in repressed regions [4].

Non-coding RNAs have an essential role in the molecular mechanisms of epigenetics. Indeed, several micro-RNAs (miRNAs) have an active role in the epigenetic machinery, creating highly controlled feedback circuits that accurately tune gene expression. These subgroups of miRNAs, called "epi-miRNAs", target specific epigenetic regulators, such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) [3].

Lactoferrin (Lf) belongs to the transferrin (Tf) family and is a non-heme iron-binding glycoprotein with a molecular weight of 78 kDa that contains around 690 amino acid residues [5]. Lf was firstly identified by Sorensen and Sorensen in 1939 in bovine milk as a red protein in whey [6], and later in 1960, it was isolated from human milk by Johansson [7]. Interestingly, Lf from different mammalian species has a similar amino acid sequence. For example, human Lf and bovine Lf share approximately 68% sequence identity whereas human and chimpanzee Lf share almost 97% sequence identity [8]. This protein is also found in mucosal secretions, including plasma, saliva, tears, vaginal fluids, semen, nasal, gastrointestinal fluids, and urine [9]. Besides its role as an iron transporting protein, lactoferrin also plays a role as an innate host defense system against infection from a variety of bacteria, fungi, viruses, and even some parasites [10]. Additionally, Lf has antioxidant and anticancer activities [11].

There are two forms of Lf, the iron-free form (apo-Lf) and the iron-containing form (holo-Lf) [12]. Lf has also three different isoforms: Lf-α, Lf-γ, and Lf-β. Lf-α is the iron-binding form, while Lf-γ and Lf-β have a ribonuclease activity, and these two isoforms do not bind iron [13]. Lf is also able to bind to a wide range of compounds, including DNA, lipopolysaccharides, heparin, and many metal ions [14]. Human *Lf* gene possesses two promoter regions P1 and P2 [15]. Transcription from P1 promoter leads to the production of the secreted Lf and transcription from P2 leads to the production of delta-Lf (ΔLf). ΔLf is an intracellular protein that acts differently from Lf and shows anti-proliferative properties and induces cell cycle arrest. It is an efficient transcription factor interacting via a ΔLf response element found in the *Skp1*, *Bax*, *SelH*, and *DcpS* promoters [16]. Although the plasma membrane acts as an impermeable barrier to most macromolecules, Lf can reach the cytosol of living cells and then is transported into the nucleus, where it binds to DNA [17, 18].

In 2014 Verduci et al. [19] suggested that a direct relationship of some components of human breast milk with epigenetic changes could exist. Taking into consideration the fact that Lf can be transported into the nucleus of living cells, it is reasonable to investigate the effect of Lf on epigenetic mechanisms in wide range of many cell types. Impressively, Lf can directly and/or indirectly affect epigenetic mechanisms in different cell types, and some of these mechanisms are related to its effect and role in these cells.

Effect of lactoferrin on chromatin structural organization

Using small-angle neutron scattering (SANS) Lebedev et al. [20] studied a possible effect of the interaction of human Lf with oleic acid complexes (ChLfOA) in the model system, isolated HeLa nuclei. Their results revealed that complexes of Lf with oleic acid influence chromatin structure following penetration into nuclei. Accordingly, they reported that studied complexes caused chromatin compaction (Fig. 1). Chromatin compaction can lead to a decrease in the expression of genes in compacted regions, and thus interfere with the functioning of tumor cells, and can determine the antitumor effect of Lf. Significantly, they mentioned that the presence of oleic acid (OA) micelles or OA molecules is not the main reason of the effect of ChLfOA complexes on chromatin organization. This can suggest that Lf is the main cause of this effect.

Effect of lactoferrin on miRNA profile

Considering the importance of epigenetic modifications in the degree of malignancy, Zadvornyi et al. [21] investigated the effect of recombinant

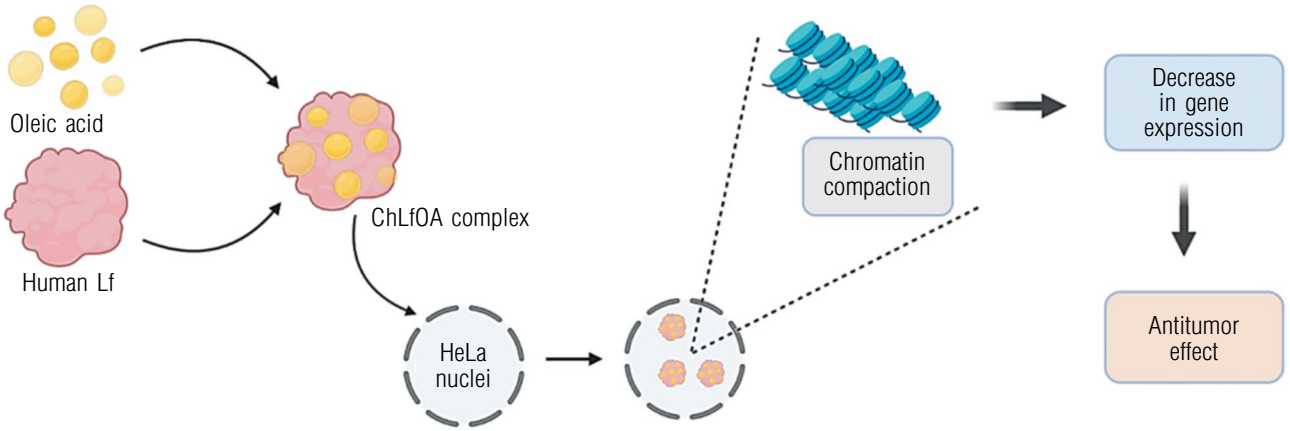

Fig. 1. Effect of lactoferrin complexes with oleic acid on chromatin compaction in isolated HeLa nuclei. Lf — lactoferrin; ChLfOA — human lactoferrin with oleic acid

human Lf on miRNA profile in two human prostate cancer cell lines DU145 and LNCaP. Results revealed that under the action of exogenous Lf in both cell lines there was an increase in the expression of miRNA-155 and miRNA-205. miRNA-155 regulates the synthesis of such pro-inflammatory cytokines such as IL-1 and IL-6 which lead to a decrease in the expression of ERα and progesterone receptor (PR) [22]. Moreover, estrogen receptor alpha promotes malignancy and osteoblastic tumorigenesis in prostate cancer cells [23]. Thus, inhibition of ERα signaling in prostate cancer cells may reduce its malignancy. Furthermore, it is important to mention that physiologically DNMT activity is under hormonal control, and DNMT1 levels vary with menstrual cycle phase and with estrogen and progesterone secretion in endometrial explant tissues [24] (Fig. 2).

Liganded estrogen receptor alpha (ERα) with 17β-estradiol promotes DNA methylation, regulates passive and active DNA demethylation, and cooperates with different histone modifying enzymes and chromatin remodeling complexes (Fig. 2, *a*). ERα recruits co-repressor proteins such as HDAC1 from nucleosome remodeling and deacetylase (NuRD) complex and EZH2 from the PRC2 complex [25]. At first the HDAC deacetylates the histone 3's 27th lysine residue (H3K27), and then EZH2 places three methyl groups on H3K27. After that DNMT3B recognizes the methylated H3K27 and methylates the cytosine in a CpG island that represents a repressive mark on the DNA [26] (Fig. 2, *b*).

Liganded ERα with 17β-estradiol also blocks DNMT1 expression and forms complexes with active demethylation proteins such as TET2 [27, 28].

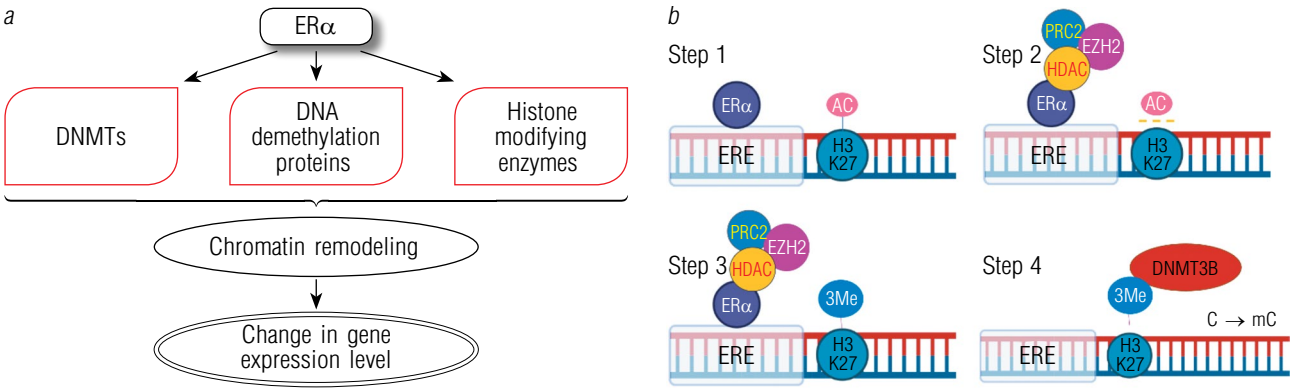

Fig. 2. Effects of estrogen receptor alpha on epigenetics mechanisms. (*a*) Estrogen receptor alpha has a regulatory effect on DNA methyltransferses, DNA demethylation proteins, and histone modifying enzymes, so that estrogen receptor alpha indirectly could affect chromatin status and genes expression levels. (*b*) Liganded estrogen receptor alpha-induced methylation mechanism. Step 1: Liganded estrogen receptor alpha binds to the estrogen responsive element in the DNA. Step 2: Estrogen receptor alpha recruits polycomb repressive complex 2, histone deacetylase 1, and enhancer of zeste homolog 2. Step 3: Histone deacetylase removes acetyl groups from the histone 3's 27th lysine residue, and then EZH2 places three methyl groups on H3K27. Step 4: DNA methyltransferase 3B recognizes the methylated H3K27 and methylates the cytosine in a CpG island. ERα — estrogen receptor alpha; DNMT — DNA methyltransferase; HDAC — histone deacetylase 1; PRC2 — polycomb repressive complex 2; EZH2 — enhancer of zeste homolog 2; H3K27 — histone 3's 27th lysine residue; AC — acetyl groups; 3Me — three methyl groups

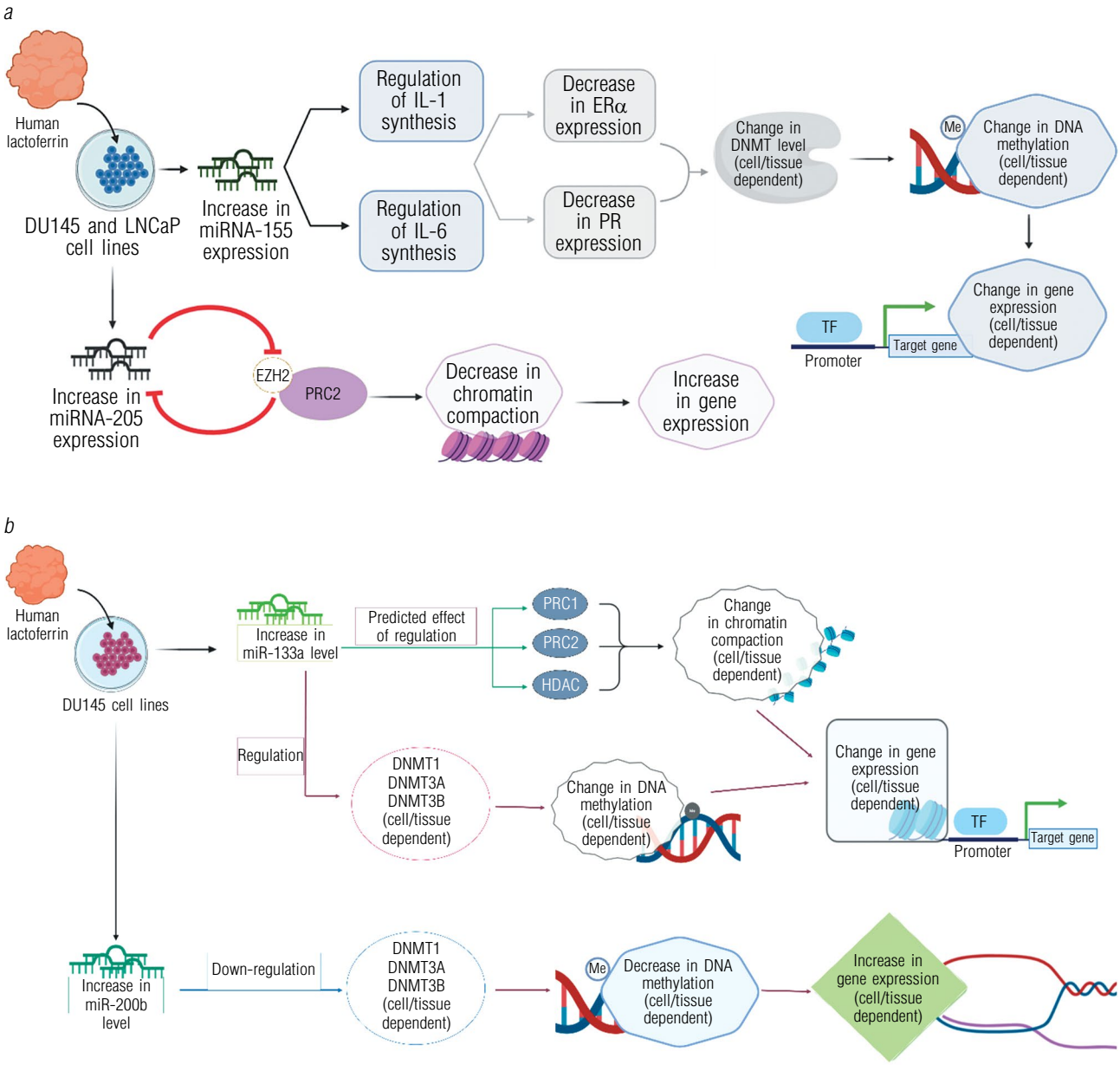

Fig. 3. Effect of lactoferrin on human prostate cancer cell lines DU145 and LNCaP (based on the results of Reale, Di Croce, Nuytten, Zadvornyi, Chavali, Liu and their colleagues [29–31, 21, 34, 35]). (*a*) Recombinant human lactoferrin causes an increase in the expression of miRNA-155 and miRNA-205 in the DU145 and LNCaP cell lines. These miRNAs were involved in the change of epigenetic status of cells. (*b*) miR-133a and miR-200b up-regulation after lactoferrin exposure in DU145 cell line leads to many changes in epigenetic statues. Lf — lactoferrin; ERα — estrogen receptor alpha; PR — progesterone receptor; DNMT — DNA methyltransferase; PRC2 — polycomb repressive complex 2; EZH2 — enhancer of zeste homolog 2; HDAC — histone deacetylase

These proteins remove the repressive methyl mark from the DNA and thereby promote gene expression. Furthermore, ERα interacts with histone acetyl transferases and with ATP-dependent chromatin remodelers that alter and regulate gene transcription [25].

At the end of 2019 Reale et al. [29] were the first to report miR-205 as an epi-miR, because there is evidence of a double inhibitory feedback loop with enhancer of zeste 2 (EZH2). EZH2 is a histone methyltransferase — the main component of the polycomb-repressive complex 2 (PRC2) [30]. PRC2 is a transcriptional-repressor complex, which mediates methylation of histone H3 lysine 27 (H3K27) that leads to chromatin compaction [31] (Fig. 3, *a*).

Zadvornyi and colleagues [21] also reported that exogenous Lf increases the levels of miR-133a and miR-200b only in Lf-treated DU145 cells. Both miR-133a and miR-200b function as tumor suppressors. miRNA-200b is involved in regulation the expression of the intercellular adhesion molecule

E-cadherin, which in turn decreases the invasive activity of the cells [32], and miRNA-133a is an inhibitor of the proliferative activity [33]. Noteworthy, miR-133a was classified as a candidate as an epi-miR by Reale and colleagues [29] by mentioning that miR-133a could be associated with polycomb-repressive complex 1 (PRC1), polycomb-repressive complex 2 (PRC2), and histone deacetylase (HDAC) pathways. miR-133a was also reported to play key role in the regulation of DNMT-1, DNMT-3A and DNMT-3B in diabetic cardiomyocytes, and so acts as an epi-miRNA [34]. It is also important to mention that Liu et al. [35] reported miR-200b as an epi-miR, because miR-200b directly down regulates DNMT-3A/DNMT-3B and indirectly down-regulates DNMT-1 by targeting the transcription factor sp1 in ovarian cancer cells (Fig. 3, *b*).

Effect of lactoferrin on DNA methylation

In addition to Lf effects on chromatin compaction and miRNA profile, human Lf showed the ability to affect indirectly DNA methylation. For example, human Lf indirectly affects DNA methylation at a subset of genomic loci by targeting β-amyloid generation (Fig. 4). This conclusion is based on a study aimed at investigating the effect of exogenous human Lf as a neuroprotective agent in APPswe/PS1dE9 transgenic mice, the model of Alzheimer's disease (AD) [36]. APPswe/PS1dE9 mice are characterized by overexpression of the Swedish mutation of amyloid precursor protein (APP) and β-amyloid (Aβ) accumulation in the brain [37]. After intranasal administration of human Lf, stably transfected mouse neuroblastoma 2a (APPsw N2a) cells were isolated from the brains of APPswe transgenic mice. Results indicated that human Lf promoted the non-amyloidogenic metabolism of APP processing through activation of α-secretase a-disintegrin and metalloprotease10 (ADAM10), resulting in enhanced cleavage of the α-COOH-terminal fragment of APP and the corresponding elevation of the NH2-terminal APP product, soluble APP-α (sAPPα), which consequently reduced Aβ generation [36]. Another study revealed a subset of genomic loci that shows a significant change in DNA methylation following β-amyloid treatment [38]. Authors mentioned that these significantly changed loci were associated with genes involved in neuronal differentiation, neurogenesis, and apoptosis control, which in turn may contribute epigenetically to AD progression by propagating neuronal loss of function and death. These results provide a basis for a possible protective mechanism of Lf in AD, as Lf has also a protective role against neurodegeneration in rodents after its intraperitoneal and nasal administration [39, 40].

Currently, the participation of lactoferrin in cell hypoxia has been established [41, 42]. At the same time, the role of hypoxia in the regulation of gene expression and epigenetic mechanisms has been established [43–46]. Hypoxia-inducible factors (HIFs) are heterodimeric transcription factors consist of α and β subunits that activate the transcription of genes necessary to circumvent to hypoxic (low oxygen level) environments [47]. Three α subunits (HIF-1α, HIF-2α, and HIF-3α) and one β subunit (HIF-1β) have been identified [48]. It is worth mentioning that the participation of Lf in iron regulation is also mediated via stabilization of iron-sensitive HIF-1α and HIF-2α, as well as induces HIF-signaling system in neonate animals [42, 49].

Luo et al. [43] reported that the histone demethylase jumonji domain containing protein 2C (JMJD2C) selectively interacts with HIF-1α and that HIF-1α mediates recruitment of JMJD2C to the hypoxia response elements of HIF-1 target genes in breast cancer cells. Furthermore, JMJD2C decreases trimethylation of histone H3 at lysine 9, and enhances HIF-1 binding to hypoxia response elements, thereby activating transcription of *LOXL2* and *L1CAM* genes, which are involved in lung metastasis, as well as *BNIP3*, *LDHA*, *PDK1*, and *SLC2A1* genes, which encode proteins that are required for metabolic reprogramming.

Hypoxia in tumor cells can lead to many events related to the epigenetic status in some specific sites of the genome (Fig. 4). An interesting study of Zalutski et al. [41] was performed on hormone receptor-positive (MCF-7, T47D) and hormone receptor-negative (MDA-MB-231, MDA-MB-468) human breast cancer cell lines. Upon treatment with exogenous Lf, results showed that exogenous Lf causes a violation of an antioxidant balance by increasing the level of reactive oxygen species (ROS), "free" iron, and nitric oxide (NO) generation rate, resulting in a blocking of cell cycle at G2/M-phase and apoptosis of malignant cells. Moreover, Lf treatment caused a decrease in the content of reduced glutathione [41].

Under hypoxia in human colorectal cancer (HCT116, 379.2) cell lines, down regulation of DNMT1 and DNMT3A was also reported, which contributes to DNA hypomethylation [44]. In contrast, hypoxia induces promoter CpG methylation of Protein kinase C gene to decrease its expression in rat embryonic ventricular myocyte cell lines H9c2 and fetal rat hearts [45]. Furthermore, tumor hypoxia in human and mouse cells reduces the activity of oxygen-dependent ten-eleven translocation (TET) enzymes–enzymes catalyze DNA demethylation through 5-methylcytosine oxidation, and thus hypoxiainduced loss of TET activity increases hypermethylation of

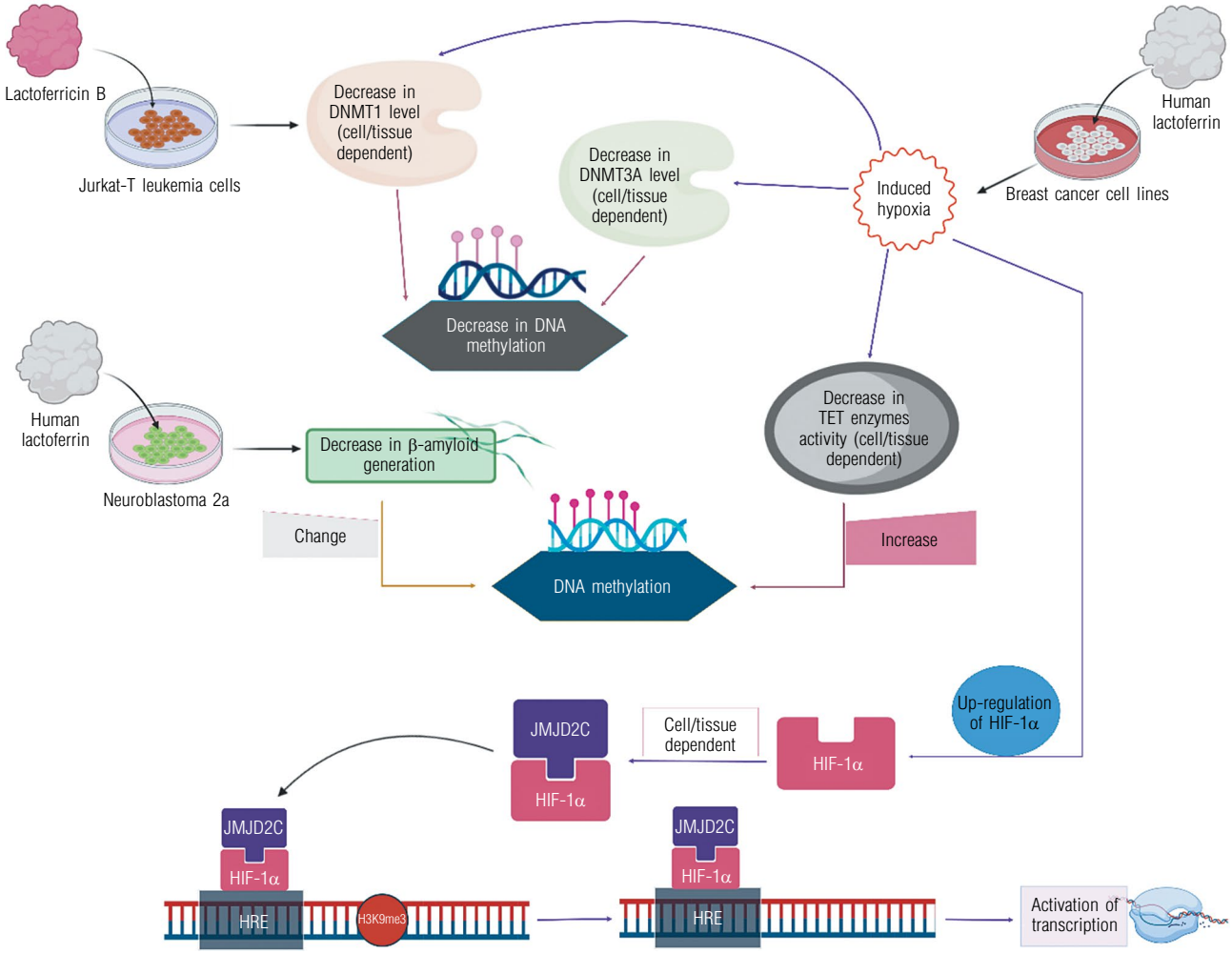

Fig. 4. Effect of lactoferrin on DNA methylation in Jurkat-T leukemia cells, neuroblastoma 2a cells, and breast cancer cell lines. Jurkat-T leukemia cells exposure to lactoferricin B leads to reducing the half-life, expression, and stability of DNMT1. Human lactoferrin reduces β-amyloid generation in neuroblastoma 2a cells, which in turn significantly affects DNA methylation in certain loci. Hypoxia mediated by human lactoferrin exposure in breast cancer cell lines triggers many mechanisms related to epigenetic means (depending on cell/tissue type). Hypoxia down regulates DNMT1, DNMT3A and TET enzymes, and which in the end will affect DNA methylation. Hypoxia-inducible factor 1α mediates recruitment of jumonji domain containing protein 2C to the hypoxia response elements of HIF-1 target genes that decreases trimethylation of histone H3 at lysine 9, and enhances HIF-1 binding to hypoxia response elements, thereby activating transcription of these genes. DNMT — DNA methyltransferase; TET enzymes — ten-eleven translocation enzymes (DNA demethylation enzymes); HIF-1α — hypoxia-inducible factor 1α; JMJD2C — jumonji domain containing protein 2C; HRE — hypoxia response element

the promoters of tumor suppressor genes *in vitro* [46].

It should be noted that DNA methylation seems to be influenced not only by the full-length form of Lf, but also by lactoferricin B, a fragment derived from bovine Lf by acid-pepsin hydrolysis of bovine Lf [50]. Lfcin B consists of 25 amino acid residues (17 to 41 proximal to the NH2 terminus of bovine Lf) [51]. It has been revealed that this peptide, leads to a reduction in stability of DNMT-1, also decreases the half-life of DNMT-1 mRNA and down modulated the expression of DNMT-1 protein in Jurkat T-leukemia cells (Fig. 4) [52].

Conclusion

Although practically all cells in an organism carry the same genetic information, not all genes are expressed simultaneously by all cell types. In a broader insight, epigenetic mechanisms mediate the diverse gene expression profiles in different cells and tissues of multicellular organisms. Epigenetic control of gene expression is a common process that acts throughout the differentiation of somatic cells, as well as in response to environmental stresses and cues. Furthermore, passing on these modulations to the offspring establishes epigenetic inheritance. Although several

epigenetic modifications are maintained throughout the lifetime of the organism, some epigenetic marks can easily change over time at particular genomic loci. This "epigenetic drift" is thought to depend on both intrinsic and environmental factors. Since alterations in epigenetic marks have been associated with a variety of human diseases, the investigation of possible roles of nutrition, behavior, stress, and physical activity is outstanding research. Human exposure to Lf starts from his early life, thus, investigating the role of Lf on epigenetic control and regulation is necessary to research since many questions about epigenetic control remain. Lf showed a wide range of effects on different cell types, affecting many mechanisms related to epigenetic means including chromatin compaction, micro RNA, and DNA methylation. Further studies investigating the relationship between epigenetics and Lf are required to expand the exciting hypotheses that are starting to emerge.

Additional information

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All authors have read and agreed to the published version of the manuscript.

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