DERLEME REVIEW

Med J SDU / SDÜ Tıp Fak Derg ▶ 2022:29(2):273-283 doi: 10.17343/sdutfd.1090522

WHAT IS EPIGENETIC CHANGE AND WHAT DO WE KNOW ABOUT ITS IMPACT ON MOLECULAR PATHOLOGIC MECHANISMS OF THE DISEASES?

EPİGENETİK DEĞİŞİKLİK NEDİR VE HASTALIKLARIN MOLEKÜLER PATOLOJİK MEKANİZMALARI ÜZERİNDEKİ ETKİSİ HAKKINDA NE BİLİYORUZ?

Kemal Kürşat BOZKURT[1,2], Ayça TAN[1,3], Onur ERTUNÇ[1,2], Rafet Güneş ÖZTÜRK[1,4], Yasemin Çakır[1,5], Zeynep SAĞNAK YILMAZ[1,6], Şadiye Mehtat ÜNLÜ[1]

[1] Dokuz Eylül University, Graduate School of Health Sciences, Department of Molecular Pathology, İzmir, TÜRKİYE
[2] Süleyman Demirel University, Faculty of Medicine, Department of Pathology, Isparta, TÜRKİYE
[3] Manisa Celal Bayar University, Faculty of Medicine, Department of Pathology, Manisa, TÜRKİYE
[4] University of Health Sciences, Bozyaka Education and Research Hospital, Department of Pathology, İzmir, TÜRKİYE
[5] Simav Doç. Dr. İsmail Karakuyu State Hospital, Department of Pathology, Kütahya, TÜRKİYE
[6] Karadeniz Teknik University, Faculty of Medicine, Department of Pathology, Trabzon, TÜRKİYE

Cite this article as: Bozkurt KK, Tan A, Ertunç O, Öztürk RG, Çakır Y, Sağnak Yılmaz Z, Ünlü ŞM. What is Epigenetic Change and What Do We Know About its Impact on Molecular Pathologic Mechanisms of the Diseases? Med J SDU 2022; 29(2): 273-283.

Öz

Epigenetik değişiklik, kromatin modifikasyonu, DNA metilasyonu, histon modifikasyonu, kromatin düzenleyici proteinler ve kodlamayan RNA'lar yoluyla meydana gelmekte olup, kalıcı genotipik değişiklik olmaksızın gerçekleşen fenotipik bir değişikliği ifade eder. Transkripsiyon sonrası m6A RNA metilasyonu da yeni tanımlanmış bir epigenetik mekanizma olup, yeni bir tanısal biyobelirteç ve potansiyel terapötik hedef olduğuna inanılmaktadır. Epigenetik değişikliklerin birçok nonneoplastik ve neoplastik hastalığın gelişiminde ve ilerlemesinde önemli bir rol oynadığı iyi bilinen bir gerçektir. Bu nedenle epigenetik değişiklikler tanısal ve prognostik açıdan değerlidir. Öte yandan kişiselleştirilmiş tıp ve hedefe yönelik tedavi yaklaşımlarının gelişmesiyle birlikte epigenetik değişiklikleri hedefleyen tedavi stratejileri birçok hastalık için umut verici bir alan haline gelmektedir. Bu derlemenin amacı, epigenetik değişikliklerin mekanizmaları ve neoplastik / nonneoplastik hastalıkların gelişimindeki rolleri hakkında klinisyenlere ve laboratuvar tıbbı uzmanlarına daha sonraki araştırmalar için yardımcı olabilecek bilgiler sağlamaktır.

Anahtar Kelimeler: Epigenetik, Hastalık, Nonneoplastik, Neoplastik

Abstract

Epigenetic change refers to a phenotypic alteration without permanent genotypic change, which occurs through chromatin modification, DNA methylation, histone modification, chromatin-regulating proteins and non-coding RNAs. Post-transcriptional m6A RNA methylation is also a newly described epigenetic mechanism and believed to be a new diagnostic biomarker and potential therapeutic target. It is a well-

Sorumlu yazar ve iletişim adresi /Corresponding author and contact address: K.K.B. / kemalbozkurt@sdu.edu.tr
Müracaat tarihi/Application Date: 21.03.2022 • **Kabul tarihi/Accepted Date:** 06.05.2022
ORCID IDs of the authors: K.K.B: 0000-0003-1522-9388; A.T: 0000-0003-4450-5425; O.E: 0000-0002-4159-1711; R.G.Ö: 0000-0002-6252-5668; Y.Ç: 0000-0002-1394-6474; Z.S.Y: 0000-0002-3225-2486; Ş.M.Ü: 0000-0002-7170-7594

known fact that epigenetic changes play a significant role in the development and progression of several nonneoplastic and neoplastic diseases. Therefore, epigenetic changes are of value in diagnostic and prognostic terms. On the other hand, with the development of personalized medicine and targeted treatment approaches, treatment strategies targeting the epigenetic changes are becoming a promising area for many diseases. The aim of this review is to provide information about the mechanisms of epigenetic changes and their role in the development of neoplastic and nonneoplastic diseases, which may be helpful for the clinicians and laboratory medicine experts for further researchs.

Keywords: Epigenetic, Disease, Nonneoplastic, Neoplastic

Epigenetic Change

Conrad Waddington proposed the concept of "epigenetics" in 1942 and this term expresses the phenotypic change without genotypic alteration [1]. Epigenetic changes consist of numerous chemical arrangements that can tell the genome what to do and what not to do. When the function of DNA changes epigenetically, the genome is marked and the DNA sequence does not change. These changes can be inherited through mitosis and meiosis [1, 2]. Expression of the gene appears to be more important rather than which genes are inherited [3]. Epigenetic modification mechanisms include; chromatin modification, DNA methylation, histone modification, chromatin regulating proteins and non-coding RNAs [2]. Recently, post-transcriptional modification of RNA is shown to play an important role in the development of several diseases as an epigenetic change mechanism. N6-methyladenine (m6A) RNA modification is the most investigated mechanism, and is involved in physiological conditions. Its dysfunction is thought to be involved in the development of various neoplastic and nonneoplastic diseases. More than 60% of all RNA modifications occur via methylation and m6A is the most abundant chemical modification in eukaryotic messenger RNA, which acts in regulation of cell fate, proliferation, metabolism and biogenesis of several tumor types [4, 5].

The Difference Between Epigenetic Change and Mutation

Epigenetic change is a mechanism that alters the expression of a gene without an alteration in the nucleotide sequence as opposed to mutations in which the nucleotide sequence is permanently altered [6]. Our genetic code is permanently determined, but acquired epigenetic traits are plastic and partially reversible. Epigenetic changes can occur due to the environmental exposure, but they do not occur equally in all periods of life. The most critical life periods are known as preconception, early development, pregnancy and early life periods [7]. Epigenetic changes play a key role in the control of cellular processes such as differentiation, embryogenesis, X chromosome inactivation and genomic suppression by regulating the expression of genes and changing protein levels. In many studies it has been shown that epigenetic regulations cause susceptibility to diseases. Errors in these mechanisms can cause cancer, neurological diseases, autoimmune diseases and various developmental disorders [8].

Mechanisms of the Epigenetic Change

Chromatin modification

Chromatin is a complex architectural chromosome unit consisting of DNA and proteins. It forms the physical basis of epigenetic changes. Chromatin modification is an important mechanism, which affects transcription factor binding as an important component of epigenetic modification, and differential gene expression between cell types [9]. The complex structure of chromatin is divided into two categories as heterochromatin and euchromatin. Heterochromatin has a condensed chromatin structure (30 nm chromatin fibril) and is inactive for transcription while euchromatin has a loose chromatin structure (11 nm chromatin fibril) and is active for transcription [10]. The location of the heterochromatin and euchromatin structure within the nucleus is also different. While the periphery of the nucleus is enriched for heterochromatin, euchromatin is located in the center of the nucleus, suggesting that the location of a gene within the nucleus is important for its epigenetic function [1].

The transcription initiating region called promoter and the regions that increase the speed of transcription, called enhancer, are the functional regions of our genome. Chromatin acts as a filter in terms of binding transcription factors to these functional regions. In order to activate a gene and copy it into mRNA, the chromatin in both the promoter and enhancer regions must be accessible. Therefore, in most

circumstances gene activation requires the transition from heterochromatin to euchromatin [11]. Chromatin remodeling factors play an important role in this transition by binding to transcription activators (Figure 1). Meanwhile, the opposite of these processes occur if these factors are linked to transcription suppressors to inhibit the transcription [2, 12]. While some of the epigenetic mechanisms enable genes to be silenced by converting chromatin into the form of heterochromatin, some of them enable genes to be activated by converting it into euchromatin form. Mechanisms of chromatin modification that can cause epigenetic changes include DNA methylation/unmethylation, nucleosome arrengement, histone methylation, dense/loose nucleosome packaging, and regulation of the nuclear organisation [1].

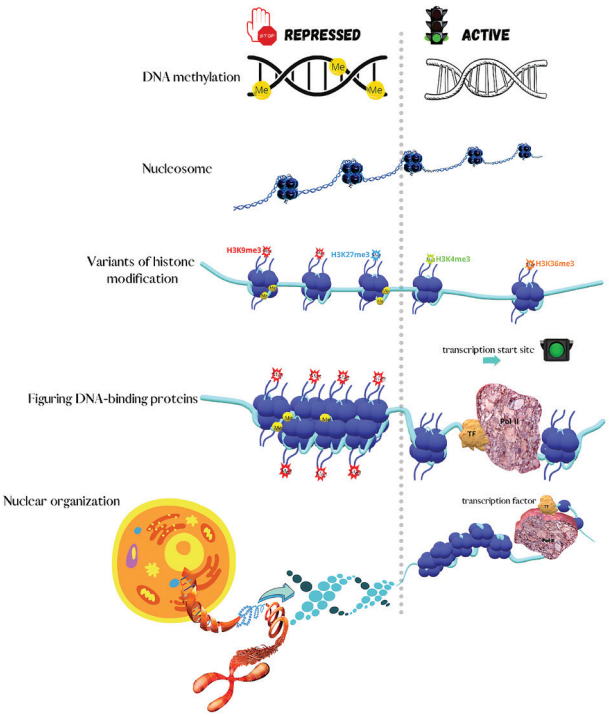

Figure 1
Mechanisms of the epigenetic remodeling of chromatine-associated with active or inactive gene expression.

DNA methylation

DNA methylation, an important epigenetic control mechanism involved in the protection of genome integrity, transcriptional regulation and developmental processes, is a covalent modification formed by the attachment of a methyl group to the carbon atom in the 5' position of the cytosine-guanine (CpG) dinucleotides [13]. DNA methyltransferase enzymes (DNMT) are responsible for this chemical reaction. This enzyme enables the methyl group transfer from S-adenosyl-methionine, which is the source of the methyl group, to the cytosine ring [14]. Although DNA methylation shows a conserved epigenetic inheritance in newly formed DNA strands after replication, it can be reversed through ten-eleven translocation (TET) enzymes [2].

Methylated cytosines constitute approximately 1% of the nucleotides in the whole genome and approximately 75% of the CpG dinucleotides. The regions including dense CpG dinucleotides throughout the genome are called CpG islands [15]. Approximately 60% of gene promoter regions in the human genome are associated with CpG islands. CpG islands in these regions are mostly unmethylated, except for some special tissues that show differentiation. CpG island methylation often leads to transcriptional suppression, which plays an important role in physiological processes such as determining which allele (maternal or paternal) to be expressed in a diploid cell (genomic imprinting or X chromosome inactivation) [13, 16]. DNA methylation-mediated gene silencing can occur directly by preventing binding of transcription factors or indirectly by binding methyl-CpG binding proteins to methylated DNA [17, 18].

In addition to the CpG islands, DNA methylation also occurs in CpG shores (regions containing less dense CpG dinucleotides), gene bodies and non-coding intragenic regions and act in transcriptional regulation. Methylation of the CpG shores leads to transcriptional suppression, and the methylation status in these regions in particular is thought to cause different DNA methylation patterns. In contrast, DNA methylation in gene body regions is usually observed in highly expressed genes and is associated with increased gene expression. DNA methylation in non-coded intragenic regions is predominantly seen in repetitive elements such as satellite DNA, SINE, LINE, and contributes to the protection of genome integrity [16, 19].

Histone modification

The DNA is organized around an octameric structure called nucleosome core particle, which consists of H2A, H2B, H3, H4 histone proteins. DNA fragments consisting of 145-147 bps are wrapped around this structure 1.65 times. H1 has a histone binding feature and contributes to chromosome structure outside the nucleosome (Figure 2). The histone structure is globular except for the N-terminal tail protruding from the nucleosome to communicate with other nucleosomes. This tail contains 130 amino acids.

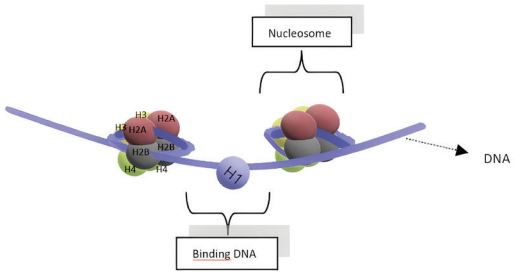

Figure 2
The structure of the Histone.

Histone modification processes neutralize acidic residues, weaken the connection between DNA and chromatin, and facilitate chromatin's accessibility [20]. The main post-translational modifications in the histone tail are acetylation, methylation, phosphorylation, ubiquitination, sumoylation and ADP-ribosylation [21].

Histone acetylation is a mechanism that provides transcriptional activity to the gene by neutralizing the positive charge of histone in the lysine tail and weakening the histone-DNA link. Histone acetylation is regulated by two antagonist enzymes, histone acetyl transferase (HAT) and histone deacetylase (HDAC). The HAT enzyme acetylates the lysine tail of the histone, weakening the histone – DNA connection. HDAC, on the other hand, reverses this mechanism and suppresses transcription by stabilizing the chromatin structure [20]. Histone methylation takes place in the lysine or arginine residue, causing condensation or relaxation of the chromatin relative to the modified residue site. Two antagonist enzymes, histone methyl transferase and histone demethylase, are available for histone methylation. The exact position of the methylated domain and the degree of methylation differ in transcriptional effect [22]. Histone phosphorylation results in a negative charge to the histone by adding a phosphate group to the serine, threonine and tyrosine residue [23]. ADP Ribosylation is a reversible process that takes place in the form of poly-/mono-ADP ribosylation in glutamate and arginine residues. Ubiquitination is a broad type of covalent modification unlike other identified modifications. Sumoylation is a type of modification related to ubiquitination and antagonizes the acetylation and ubiquitination mechanism that takes place in the same lysine region [21].

Chromatin-regulating proteins and non-coding RNAs

Chromatin-regulating protein complexes can cause epigenetic changes by changing the interaction between DNA and histones. They shift the nucleosomes into new positions by catalyzing the movement of histone octamers on DNA to enable transcription factors reach the specific regions in DNA. They also enable the interaction of specific DNA regions with proteins that regulate transcription and form non-nucleosome regions. These protein complexes can be brought into DNA via transcription activators and repressors. Thus, the initiation of transcription can be achieved or prevented by changing the sequences of nucleosomes [2].

The newest class of molecules that contribute to epigenetic changes are non-coding RNAs (ncRNA). Non-coding RNAs can be divided into two categories according to their functions as regulator RNAs and housekeeping RNAs, while regulator RNAs are also divided into two categories according to their size. Those larger than two hundred nucleotides are called as long non-coding RNAs (lncRNA), while those shorter than 200 nucleotides are called short-chain non-coding RNAs (siRNAs, miRNAs and piRNAs) [24]. Recent studies have revealed that ncRNAs play an important role in epigenetic changes and can regulate expression at the gene or chromosome level [25]. Short, 19-25 nucleotides long, miRNAs partially or completely match with the 3' regions (3'UTR) of target mRNAs to regulate gene expression through post-transcriptional silencing and/or degradation [26]. It has been shown that more than 30% of human genes, which act in cell growth, cell cycle regulation, apoptosis, differentiation, and cellular response to the stress, are targeted by the miRNAs [25]. Expression of miRNA is tissue-specific, and thanks to its ability to target post-transcription gene silencing, it can cause epigenetic changes by directly regulating gene transcription [27]. It has been shown that the siRNA, produced from long double-stranded RNA molecules that can be cut into 19-24 nucleotide-long RNA fragments by the Dicer enzyme is capable of transcriptional gene silencing in cells through DNA methylation and histone modification [28]. LncRNAs are known as key players for the gene regulation in a variety of human pathologies due to their impact on regulating the heterochromatin formation, histone modifications, DNA methylation and gene silencing. LncRNAs act by binding to transcription regulating proteins, including histone modification enzymes and chromatin remodeling factors. However, they are also known to act by binding to miRNAs or regulate mRNAs by binding directly [26].

Epigenetic Changes in Nonneoplastic Diseases

Genetic and neurodegenerative diseases

Epigenetic changes can lead to genetic diseases, particularly through increased or decreased DNA methylations in related genes [29]. One of the best example of these diseases is Silver-Russell syndrome, which is associated with epigenetic changes in the region that includes the IGF2/H19 domain of the telomeric section (11p15.5) on chromosome 11. Silver-Russell syndrome presents with intrauterine and postnatal growth retardation, facial dysmorphism, body asymmetry and nutritional problems in affected patients. Beckwith-Wiedemann, Prader-Willi and Angelman syndromes are also associated with epigenetic changes [29].

Neurodegenerative diseases, including Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis, and Huntington's disease, are considered to be the second leading cause of death by replacing cancer around the world in 2050 [30]. It is not sufficient to explain the pathophysiology of neurodegenerative diseases with only genetic. In addition to genetic alterations, epigenetic changes appear to be involved in their pathogenesis. Although there are similarities among these diseases in terms of proteopathies formed by genetic and misfolded proteins, important epigenetic changes such as decreased DNA methylation in the temporal neocortex are also observed as in Alzheimer's [29-31]. Cytosine methylation and histone modification continue from early brain development to older age. Epigenetic changes in genes that initiate neurodegeneration in the substantial region include; hypomethylation, histone hypoacetylation and accompanying misfolded protein accumulation [29, 30].

Immunological diseases

The mechanisms of rearrangement of antigen receptors, allelic exclusion, and response to pathogens, which are characteristics of immune cells, are epigenetically controlled [32]. Internal and external environmental factors, such as smoking, nutrition, viral infection, and exposure to chemicals, contribute to the development of autoimmune diseases by regulating some genes through epigenetic mechanisms [33]. Various studies of systemic lupus erythematosus (SLE) have shown increased expression of integrin *ITGAL, CD40LG, Perforin 1, CD70, IFN gamma receptor 2, MMP14, Lipocalin 2*, and *rRNA* (18S and 28S) gene promoters by hypomethylation [34]. Hypomethylation and decrease in acetylation in synovial cells in rheumatoid arthritis (RA) cause excessive expression of inflammatory cytokines in synovial fluid. *IL-6* promoter gene hypomethylation in mononuclear cells in RA patients lead to the B cell response and increased inflammation [34]. In multiple sclerosis (MS), protein-arginine deaminase type 2 (*PAD2*) promoter region is hypomethylated. Overexpression of *PAD2* induces myelin imbalance and chronic inflammation [35].

Unlike SLE and RA in type 1 diabetes mellitus, hypermethylation activity is increased due to the changes in homocysteine metabolism. *CTLA4, TGF-ß, NF-κB, p38* mitogen-activated protein kinase, toll-like receptors and *IL-6* genes, which are associated with autoimmune mechanism and inflammation in lymphocytes, have been observed to increase H3K9me2. It is also known that the H3K4 and H3K9 modification is associated with hyperglycemia-associated gene expression [34]. Increased expression of miR-21, miR-34a and miR-146a in pancreatic islets increases the level of proinflammatory cytokines leading to beta cell failure [36].

Asthma and allergic diseases are characterized by an exaggerated immune reaction. Evidence about the efficacy of epigenetic mechanisms in this reaction is increasing. Various environmental factors such as air pollution, cigarette smoke, diet during pregnancy and vitamin D level also play a role in the development of these diseases by affecting epigenetic mechanisms. Atopy and asthma related genes (*IFN-γ, IL4, IL13, IL17*) and regulatory T cell related genes (*FOXP3, Arginase, iNOS*) are sensitive to epigenetic regulation. It has been observed that DNA demethylation in CpG regions of the *IFN-γ* gene induces IFN-γ. MiR-145 is also important for the proinflammatory process in patients with allergic respiratory tract [37].

Psychiatric diseases

In psychiatric disorders, DNA methylation and histone modifications have been shown to be important for neural and glial cell differentiation and gene regulation during brain development. They are also involved in the regulation of neuroplasticity, memory formation, emotional response, and neurogenesis in adulthood [38]. It is known that glucocorticoid hormone expression increases as a result of the stimulation of the hypothalamus-pituitary-adrenal gland (HPA) axis in response to stress in patients with depression. Overstimulation of the HPA axis is associated with glucocorticoid receptor down-regulation. DNA methylation in the glucocorticoid receptor gene was detected in postmortem studies. Increased brain-derived neurotrophic factor methylation

and increased H3K4me3 levels in synapsin genes in the prefrontal cortex have also been detected [38, 39]. GABAergic dysfunction, related to the basic cognitive symptoms, plays an important role in the pathogenesis of schizophrenia. The expression of *RELN* and *GAD1* genes (GABAergic genes) were shown to be decreased by hypermethylation and H3K4me3 modification [38, 40].

Epigenetic Changes in Neoplastic Diseases

Cancers of the gastrointestinal tract

In colorectal carcinogenesis, the silencing of tumor suppressor genes (TSG) such as *CDKN2A*, *MLH1* and *APC* by promoter methylation and activation of protooncogenes such as *HRAS* and *cMYC* by hypomethylation are the main epigenetic mechanisms [41]. Colorectal cancers are divided into three groups as chromosomal instable, microsatellite instable (MSI) and CpG islet methylator phenotype (CIMP). The most common mechanism in MSI tumors is the *MLH1* gene promoter methylation [42]. CIMP tumors develop as a result of inactivation by CpG islet methylation in the TSG promoter. LncRNA also affects cancer-related genes such as *WNT, TGF-B, EGFR* and *TP53* by different mechanisms. MiR-200, miR-143, mirRNA-145, miRNA-34a and let7 family have been reported as tumor suppressor miRNAs, while miR-21, miR-31, miR-34b and miR-34c have been reported as miRNAs with oncogenic effects [43].

DNA hypermethylation is also seen in EBV-associated gastric cancers, which are also defined as the CIMP phenotype in the stomach, and MSI tumors. DNA methylation affects the pathogenesis of gastric carcinoma through extrinsic (Helicobacter Pylori, inflammation, smoking, diet, age and physical activity) and intrinsic mechanisms. Helicobacter pylori inflammation has been associated with hypo- and hypermethylation of the gastric mucosa. EBV causes hypermethylation due to its pathogenic effect. Additionally, demethylating loss of TET1 is often present in MSI tumors exhibiting the gastric CIMP phenotype [44].

Many epigenetic mechanisms, including miRNA and DNA methylation, effect the esophageal carcinogenesis. Thirty-eight miRNAs were reported to be upregulated, while 74 were reported to be downregulated in esophageal adenocarcinomas [45]. Many studies have shown that miR21 has an effect on *PTEN* in esophageal squamous cell carcinomas and Barret adenocarcinomas. *CDX2* methylation has also been reported to effect the carcinogenesis [46].

Malignancies of the central nervous system

Among the central nervous system tumors, glioblastomas and ependymomas constitute the group of tumors whose epigenetic mechanisms are more elucidated. An epigenetic classification was made based on DNA methylation profiles in these two tumor groups. According to this classification, higher DNA methylation rates have been detected in tumors with the CIMP phenotype [47]. Global DNA hypomethylation and gene-specific hypermethylation, generally lead to genomic instability and silencing of TSGs in gioblastoma [48]. Global DNA hypomethylation occurs due to the decreased expression of DNMT3B in glioblastomas and is thought to contribute to tumorigenesis by silencing some genes. O6-methyl guanine-DNA methyl transferase (*MGMT*), is the most frequently suppressed gene in this way. Decreased MGMT levels, have been associated with 1p/19q codeletion, *IDH* and *TP53* mutations, and is blamed for shorter disease-free survival and resistance to treatment [47, 49].

Tumor suppressor genes such as *RB, CDKN2A, PTEN, TP53* and genes involved in apoptosis such as Ras association domain family 1A (*RASSF1A*) and *CASP8* are the other hypermethylated genes [48]. In addition, increased levels of miR-21 and miR-26a silence the TSGs, while decreased levels of miR-124, miR-128 and miR-451 contribute to tumorigenesis by stimulating proliferation and invasion ability [48].

Endocrine system malignancies

It is known that many genes related to regulation of cell proliferation and differentiation contain epigenetic changes in thyroid tumors, which are the most studied tumors in terms of epigenetic mechanisms among endocrine system tumors. Studies examining methylation profiles have found differences in gene methylation patterns in different thyroid carcinoma groups [50].

It has been reported that the *PTEN* gene, which inhibit the PI3K/Akt pathway, is frequently hypermethylated in papillary thyroid cancers (PTC) and follicular thyroid cancers (FTC). Coexistence of *BRAF* mutation in PTCs with hypermethylation of TSGs such as tissue suppressor of metalloproteinase enzyme (TIMP3) and death-associated protein kinase (DAPK) has been observed [50]. This association was found to be associated with aggressive clinicopathological parameters such as extrathyroidal spread, presence of lymph node metastasis and advanced stage [51]. Hypermethylation of the *RASSF1A* gene has mostly been reported in FTCs and anaplastic thyroid

carcinomas (ATC), leading to uncontrolled cell proliferation by stimulating the MAPK pathway, which is an important pathway in thyroid carcinogenesis. However, in studies examining the status of DNA methylation in the whole genome, it has been reported that global hypomethylation in gene promoters in ATCs is a more common epigenetic change than hypermethylation [52].

Non-coding RNAs also play a role in the tumorigenesis in thyroid carcinomas. MiR-21, miR-146b and miR-204 levels found to be associated with the degree of differentiation in thyroid tumors. There are studies reporting that increased miR-6 levels in PTCs are associated with advanced stage and aggressive course [51]. Decreased levels of miR-200 and miR-30 were found in ATCs in relation to epithelial mesenchymal transition and increased invasiveness [53].

Melanoma

It has been shown that a large group of genes are methylated in melanomas [54]. Among the TSGs that are reported to be hypermethylated most frequently in the process of melanoma development and progression are retinoic acid receptor-beta2 (*RAR-beta 2*), *RASSF1A, CDKN2A, PTEN* genes [55]. The transformation of 5 methyl cytosine to 5-hmc by TET enzymes (basic DNA demethylation mechanism) is an important epigenetic process affecting melanoma progression. Decreased levels of TET enzymes are also a more common finding in melanomas than in benign nevi [56]. Histone hypoacetylation is another epigenetic mechanism that leads to suppression of the TSGs in melanomas. Levels of EZH2 protein, a subunit of histone modifying enzymes, increase in the melanocytic nevus-melanoma spectrum [56]. In recent studies, it has been shown that increased levels of miR-221 and miR-137 are responsible for stimulation of cell proliferation, while miR-204 and let-7a are responsible for cell migration and invasion in melanomas [57].

Lung cancer

Epigenetic changes are responsible for silencing of TSGs and activation of oncogenes in lung cancer [58]. Smoking causes DNA methylation changes. Hypermethylation is observed in CpG islands, which constitute approximately 75-80% of the promoter regions of the genes in lung cancers. *MLH1* hypermethylation, most commonly defined in colorectal cancers, has also been identified in non-small cell lung cancer. *DAPK1* and *CDKN2A* promoter hypermethylation are common changes in lung carcinomas. Hypermethylation has been identified in more than 700 genes in lung cancers. Among these; *APC, PTEN, RASSF1A, MGMT, SHOX2, SEPT9, RARB2* and *E-cadherin* are the most frequently hypermethylated genes [19]. Histone modifications have been found more frequently in the *EGFR, KRAS, NRAS, MYC, ERBB2* and *MET* genes in lung cancer [59]. Studies have shown that a large number of miRNAs play a role in the development and progression of lung cancer. MiR-21, one of the most well-regulated miRNAs, inactivates oncogenes such as *RAS* and *MYC*. On the other hand, miR-34 plays a role in gene expression by creating tumor suppressing effect through p53. In addition, miR-21, miR-183, miR-126 and miR-155 were found to be associated with poorer prognosis in lung cancers [60]. Metastasis-associated lung carcinoma transcript 1 (MALAT1) lncRNA was found to be upregulated in lung cancers. It has been reported that TINCR lncRNA is down-regulated in lung adenocarcinoma and squamous cell carcinoma (SCC) when compared to normal tissues, while SNHG1 is upregulated in SCCs. The absence of SNHG1 has been found to inhibit tumor invasion and metastasis [61].

Head and neck cancers

The best defined epigenetic changes in head and neck SCCs is DNA methylation. Promoter hypermethylation has been detected in many genes in these tumors, and the most known ones are the genes that affect the *APC, MGMT, DAPK1, CDKN2A, RASSF1, EDNRB, Cadherin* family and the WNT signaling pathway. In these genes, methylation contributes to tumor development by causing loss of expression [19, 62]. Athough histone modifications are rare in head and neck cancers, H3K4, H3K9 and H3K27 methylation has been reported in oral SCCs [63]. Numerous miRNAs with increased or decreased expressions in tumors of different localization in the head and neck region have been reported [64].

Breast cancer and gynecological malignancies

A relatively small number of genes are frequently hypomethylated in breast tumors. In contrast, more than 100 genes have been shown to be hypermethylated in the CpG promoter region, and they play critical roles in apoptosis, cell cycle regulation, angiogenesis, invasion, metastasis, and hormonal signaling [65]. *CCND2* and *CDKN2A*, which act as cell cycle regulators, have been found to be widely methylated. *APC, TWIST* and *HOXA5*, which play a key role in the apoptosis, are silenced by DNA hypermethylation. *Estrogen receptor alpha* and progesterone receptor (*PgR*) are also frequently methylated. In addition to protein-encoding genes, it has been shown that tumor

suppressor miRNAs can also be silenced by DNA methylation in breast cancer cells [27]. It has also been shown that histone modification by demethylases play a role in the development of breast cancer through the Wnt1/Beta-catenin pathway [66]. The reduction of H3K9 trimethyl demethylase JMJD2B (component of the H3K4-specific methyltransferase) inhibits tumor growth by preventing estrogen-induced G1/S transmission [67].

MiRNAs are generally down-regulated in breast cancer. Depletion of the let-7 miRNA family in breast cancer leads to increased tumor development. MiRNAs, which are associated with high proliferative activity index (let-7c and let-7d), PgR status (let-7c), and positive lymph node status (let-7f-1, let-7a-3 and let-7a-2) have been defined [68]. In addition, miR-15/16 has been shown to be downregulated in breast cancer, leading to abnormal expression of *BCL2* [69]. However, amplification of some miRNAs, such as increased invasiveness and lung metastasis associated miR-21 overexpression, have also been identified in breast cancer [27].

Epigenetic changes such as hypermethylation of specific gene promoters have also been described in ovarian and endometrial cancers, which are the most common gynecological malignancies. Promoter hypermethylation of TSGs, such as *BRCA1* and *RASSF1A* is more frequent in ovarian cancers than they are in non-neoplastic tissues, causing genomic instability by inhibiting *BRCA1* function. In addition, chromatin regulating proteins also cause epigenetic changes in ovarian cancers [70]. Promoter hypermethylation is the most common epigenetic mechanism in endometrioid endometrial cancers. Epigenetic changes in TSGs cause microsatellite instability in 20-35% of endometrioid cancers, leading to alterations in the DNA repair, apoptosis, transcriptional regulation and signal transduction associated genes. The silencing of TSGs usually occur via *MLH1* promoter hypermethylation in endometrioid cancers. Epigenetic changes are less significant in non-endometrioid endometrial cancers [71].

Prostate cancer and malignancies of the urinary system

DNA hypomethylation, which can lead to structural and functional changes in the genome, has been observed in prostate cancer cells. Gene-specific hypomethylation has a role in invasion, metastasis and cell cycle control in prostate cancer. DNA hypermethylation is the most common and well-known epigenetic change in prostate cancer as well as in other cancers. Hypermethylated genes play critical roles in various biological processes, including DNA damage repair, signal transduction, adhesion, hormonal transmission, apoptosis, invasion, metastasis, and cell cycle control [27]. Changes in histone modifications have been shown to play an important role during prostate carcinogenesis by facilitating the activation of genes that enable cell growth and survival, and by silencing TSGs. Prostate cancer cells are enriched with H3K4me3, which is associated with the activation of genes such as BCL2 [72].

A large number of oncogenic miRNAs, such as miR-15a/16, miR-21, miR-125b, miR-32, miR-26a, miR-196a, miR-181a, miR-25, miR-92/-93, miR-221/-222, miR-488 and let-7i were found to be upregulated in prostate cancer. On the other hand, various tumor suppressor miRNAs, such as miR-101, miR-126, miR -205, miR-31, miR-146a, miR-330, miR-34 set, miR-218, miR-128, miR-203, and miR-200 family were found to be abnormally regulated and silenced [73, 74]. Additionally, miR-34 activation reduce the effect of proteins such as CDK4, CDK6, cyclin D1, cyclin E2, E2F3, BCL2 to increase cell cycle arrest and apoptosis [27].

Mechanisms of epigenetic changes have also been investigated in urinary tract malignancies such as kidney and bladder cancers. In clear cell renal cell carcinomas, it has been shown that abnormal DNA methylation can cause transcriptional defects in related genes, leading to some gene expression errors and cell differentiation errors. It has also been demonstrated that TSGs and DNA repair genes are silenced by hypermethylation [75]. In bladder cancers, the abnormal promoter methylation level was found to correlate with the clinicopathological profile, and hypermethylation in four genes (*RASSF1A, CDH1, CDH13* and *APC*) was found to be associated with more aggressive features [76].

Detection of the Epigenetic Changes

Epigenetic changes, caused by DNA methylation, can be detected by molecular pathologic methods such as polymerase chain reaction (PCR), next generation sequencing (NGS) and DNA microarray analysis. Selection of a specific method to detect the methylated CpG sequences depends on the objectives of the study. Bisulfite conversion - followed by sequencing or microarray analysis can be employed to uncover newly methylated sites. Bisulfite conversion - followed by qPCR / PCR and sequencing can be used to detect the extent of known methylated genes. Bisulfite conversion changes unmethylated cytosines

to uracil during library preparation process of NGS. Converted bases are identified (after PCR) as thymine in the sequencing data, and read counts are used to determine the % methylated cytosines [77, 78].

Conclusion

The mechanisms of epigenetic change, including recently identified m6A RNA methylation are believed to be diagnostic biomarkers and potential therapeutic targets for several nonneoplastic and neoplastic diseases. Therefore, they should be investigated in a wide variety of diseases to understand how they affect the development and progression of these diseases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors Contributions

KKB: Supervision; Writing-original draft

AT: Writing-review & editing

OE: Visualization; Validation; Writing-review & editing

RGÖ: Writing-review & editing

YÇ: Writing-review & editing

ZSY: Writing-review & editing

ŞMÜ*:* Conceptualization; Supervision

References

1. Carlberg C, Molnar F (Eds.). Human Epigenetics: How Science Works. Springer Nature Switzerland; 2019. ISBN:978-3-030-22907-8.
2. Cooper GM (Ed.). The cell: a molecular approach. Eighth edition. Oxford; New York: Sinauer Associates, an imprint of Oxford University Press; 2019. ISBN:9781605357461.
3. Kaminsky ZA, Tang T, Wang SC, Ptak C, Oh GHT, Wong AHC, Feldcamp LA, Virtanen C, Halfvarson J, Tysk C, McRae AF, Visscher PM, Montgomery GW, Gottesman II, Martin NG, Petronis A. DNA Methylation Profiles in Monozygotic and Dizygotic Twins. Nat Genet 2009;41(2):240-245. DOI:10.1038/ng.286.
4. Zhang Y, Geng X, Li Q, Xu J, Tan Y, Xiao M, Song J, Liu F, Fang C, Wang H. m6A modification in RNA: biogenesis, functions and roles in gliomas. J Exp Clin Cancer Res 2020;39:192. DOI:10.1186/s13046-020-01706-8.
5. Yang C, Hu Y, Zhou B, Bao Y, Li Z, Gong C, Yang H, Wang S, Xiao Y. The role of m6A modification in physiology and disease. Cell Death Dis 2020;11:960. DOI:10.1038/s41419-020-03143-z.
6. Burns SN. Gene Expression, Epigenetic Regulation and Cancer. In: Bishnupuri KS, Mishra MK (Eds.). Epigenetic Advancements in Cancer. 1st ed. Cham: Springer International Publishing; 2016:79-94. ISBN:978-3-319-24951-3.
7. Lassi M, Teperino R. Introduction to Epigenetic Inheritance: Definition, Mechanisms, Implications and Relevance. In Teperino R (Ed.). Beyond Our Genes. Pathophysiology of Gene and Environment Interaction and Epigenetic Inheritance. Switzerland: Springer Nature AG, 2020:159-161. ISBN:978-3-030-35213-4.
8. Heard E, Martienssen RA. Transgenerational epigenetic inheritance: Myths and mechanisms. Cell 2014;157(1):95-109. DOI:10.1016/j.cell.2014.02.045.
9. Klemm SL, Shipony Z, Greenleaf WJ. Chromatin accessibility and the regulatory epigenome. Nat Rev Genet 2019;20(4):207-220. DOI:10.1038/s41576-018-0089-8.
10. Murakami Y. Heterochromatin and Euchromatin. In: Encyclopedia of Systems Biology. New York, NY: Springer New York; 2013:881-884. DOI:10.1007/978-1-4419-9863-7_1413.
11. Whalen S, Truty RM, Pollard KS. Enhancer–promoter interactions are encoded by complex genomic signatures on looping chromatin. Nat Genet 2016;48(5):488-496. DOI:10.1038/ng.3539.
12. Calo E, Wysocka J. Modification of Enhancer Chromatin: What, How, and Why? Mol Cell 2013;49(5):825-837. DOI:10.1016/j.molcel.2013.01.038.
13. Skvortsova K, Stirzaker C, Taberlay P. The DNA methylation landscape in cancer. Essays Biochem 2019;63(6):797-811. DOI:10.1042/EBC20190037.
14. Kanwal R, Gupta S. Epigenetic modifications in cancer. Clin Genet 2012;81(4):303-311. DOI:10.1111/j.1399-0004.2011.01809.x.
15. Camprubí C, Blanco J (Eds.). Epigenetics and assisted reproduction: an introductory guide. Boca Raton, FL: CRC Press/Taylor & Francis Group; 2019. ISBN:9781138633094.
16. Portela A, Esteller M. Epigenetic modifications and human disease. Nat Biotechnol 2010;28(10):1057-1068. DOI:10.1038/nbt.1685.
17. Ferreira HJ, Esteller M. CpG Islands in Cancer: Heads, Tails, and Sides. Methods Mol Biol 2018;1766:49-80. DOI:10.1007/978-1-4939-7768-0_4.
18. Radford EJ. An Introduction to Epigenetic Mechanisms. Prog Mol Biol Transl Sci Prog Mol Biol Transl Sci 2018;158:29-48. DOI:10.1016/bs.pmbts.2018.04.002.
19. Hesson LB, Pritchard AL (Eds.). Clinical Epigenetics. Singapore: Springer Singapore; 2019. ISBN:978-981-13-8958-0.
20. Steunou AL, Rossetto D, Côté J. Regulating chromatin by histone acetylation. In: Workman JL, Abmayr SM (eds.). Fundamentals of chromatin. Springer, New York, NY; 2014:147-212. ISBN:978-1-4614-8624-4.
21. Chang B, Chen Y, Zhao Y, Bruick RK. JMJD6 is a histone arginine demethylase. Science 2007;318:444-447. DOI:10.1126/science.1145801.
22. Di Cerbo V, Mohn F, Ryan DP, Montellier E, Kacem S, Tropberger P, Kallis E, Holzner M, Hoerner L, Feldmann A, Richter FM, Bannister AJ, Mittler G, Michaelis J, Khochbin S, Feil R, Schuebeler D, Owen-Hughes T, Daujat S, Schneider R. Acetylation of histone H3 at lysine 64 regulates nucleosome dynamics and facilitates transcription. eLife 2014;3:e01632. DOI:10.7554/eLife.01632.
23. Xhemalce B, Dawson MA, Bannister AJ. Histone modifications. In: Meyers R (ed.). Encyclopedia of Molecular Cell Biology and Molecular Medicine. John Wiley and Sons, 2011. ISBN:978-3527306534.
24. Mazzone R, Zwergel C, Artico M, Taurone S, Ralli M, Greco A, Mai A. The emerging role of epigenetics in human autoimmune disorders. Clin Epigenetics 2019;11:34. DOI:10.1186/s13148-019-0632-2.
25. Dykes IM, Emanueli C. Transcriptional and Post-transcriptional Gene Regulation by Long Non-coding RNA. Genom Proteom Bioinf 2017;15:177-186. DOI:10.1016/j.gpb.2016.12.005.
26. Panni S, Lovering RC, Porras P, Orchard S. Non-coding RNA regulatory networks. BBA - Gene Regulatory Mechanisms 2020;1863(6):194417. DOI:10.1016/j.bbagrm.2019.194417.

27. Chen QW, Zhu XY, Li YY, Meng ZQ. Epigenetic regulation and cancer (Review). Oncol Rep 2014;31:523-532. DOI:10.3892/or.2013.2913.
28. Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics (Review). Oncol Rep 2017;37:3-9. DOI:10.3892/or.2016.5236.
29. Neidhart M (Ed.). DNA Methylation and Complex Human Disease. Translational Epigenetics. San Diego, CA, 2015: Academic Press. ISBN:9780127999203.
30. Lovrečić L, Maver A, Zadel M, Peterlin B. The Role of Epigenetics in Neurodegenerative Diseases In: Uday K (Ed.). Neurodegenerative Diseases. Rijeka, 2013: IntechOpen. DOI:10.5772/45957.
31. Xylaki M, Atzler B, Outeiro TF. Epigenetics of the Synapse in Neurodegeneration. Curr Neurol Neurosci Rep 2019;19(10):72. DOI:10.1007/s11910-019-0995-y.
32. Moosavi A, Ardekani AM. Role of Epigenetics in Biology and Human Diseases. Iran Biomed J 2016;20(5):246-258. DOI:10.22045/ibj.2016.01.
33. Zhang Z, Zhang R. Epigenetics in autoimmune diseases: Pathogenesis and prospects for therapy. Autoimmun Rev 2015;14(10):854-63. DOI:10.1016/j.autrev.2015.05.008.
34. Quintero-Ronderos P, Montoya-Ortiz G. Epigenetics and Autoimmune Diseases. Autoimmune Dis 2012;2012:593720. DOI:10.1155/2012/593720.
35. Musse AA, Boggs JM, Harauz G. Deimination of membrane-bound myelin basic protein in multiple sclerosis exposes an immunodominant epitope. Proc Natl Acad Sci 2006;103(12):4422-4427. DOI:10.1073/pnas.0509158103.
36. Roggli E, Britan A, Gattesco S, Lin-Marq N, Abderrahmani A, Meda P, Regazzi R. Involvement of MicroRNAs in the Cytotoxic Effects Exerted by Proinflammatory Cytokines on Pancreatic -Cells. Diabetes 2010;59(4):978-986. DOI:10.2337/db09-0881.
37. Lovinsky-Desir S, Miller RL. Epigenetics, asthma, and allergic diseases: A review of the latest advancements. Curr Allergy Asthma Rep 2012;12(3):211-220. DOI:10.1007/s11882-012-0257-4.
38. Kundakovic M. Epigenetics of Psychiatric Disorders. In: Grayson D (Ed.). Medical Epigenetics. Elsevier; 2016:335-350. ISBN:9780128135662.
39. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;12(3):342-348. DOI:10.1038/nn.2270.
40. Huang H-S, Matevossian A, Whittle C, Kim SY, Schumacher A, Baker SP, Akbarian S. Prefrontal Dysfunction in Schizophrenia Involves Mixed-Lineage Leukemia 1-Regulated Histone Methylation at GABAergic Gene Promoters. J Neurosci 2007;27(42):11254-11262. DOI:10.1523/JNEUROSCI.3272-07.2007.
41. Luo J, Qu J, Wu DK, Lu ZL, Sun YS, Qu Q. Long non-coding RNAs: a rising biotarget in colorectal cancer. Oncotarget 2017;8(13):22187-22202. DOI:10.18632/oncotarget.14728.
42. Pussila M, Törönen P, Einarsdottir E, Katayama S, Krjutškov K, Holm L, Kere J, Peltomäki P, Mäkinen MJ, Linden J, Nyström M. Mlh1 deficiency in normal mouse colon mucosa associates with chromosomally unstable colon cancer. Carcinogenesis 2018;39(6):788-797. DOI:10.1093/carcin/bgy056.
43. Jung G, Hernández-Illán E, Moreira L, Balaguer F, Goel A. Epigenetics of colorectal cancer: biomarker and therapeutic potential. Nat Rev Gastroenterol Hepatol 2020;17(2):111-130. DOI:10.1038/s41575-019-0230-y.
44. Padmanabhan N, Ushijima T, Tan P. How to stomach an epigenetic insult: The gastric cancer epigenome. Nat Rev Gastroenterol Hepatol 2017;14:467-478. DOI:10.1038/nrgastro.2017.53.
45. Liu H, Zhang Q, Lou Q, Zhang X, Cui Y, Wang P, Yang F, Wu F, Wang J, Fan T, Li S. Differential Analysis of lncRNA, miRNA and mRNA Expression Profiles and the Prognostic Value of lncRNA in Esophageal Cancer. Pathol Oncol Res 2020;26:1029-1039. DOI:10.1007/s12253-019-00655-8.
46. Guo M, House MG, Suzuki H, Ye Y, Brock MV, Lu F, Liu Z, Rustgi AK, Herman JG. Epigenetic silencing of CDX2 is a feature of squamous esophageal cancer. Int J Cancer 2007;121:1219-1226. DOI:10.1002/ijc.22828.
47. Karajannis MA, Zagzag D (Eds.). Molecular Pathology of Nervous System Tumors: Biological Stratification and Targeted Therapies [Internet]. New York, NY: Springer New York; 2015. ISBN:978-1-4939-1830-0.
48. Dubuc AM, Mack S, Unterberger A, Northcott PA, Taylor MD. The Epigenetics of Brain Tumors. Methods Mol Biol 2012;863:139-153. DOI:10.1007/978-1-61779-612-8_8.
49. Suter RK, Rodriguez-Blanco J, Ayad NG. Epigenetic pathways and plasticity in brain tumors. Neurobiol Dis 2020;145:105060. DOI:10.1016/j.nbd.2020.105060.
50. Rodríguez-Rodero S, Delgado-Álvarez E, Díaz-Naya L, Nieto AM, Torre EM. Epigenetic modulators of thyroid cancer. Endocrinol Diabetes Nutr 2017;64(1):44-56. DOI:10.1016/j.endinu.2016.09.006.
51. Asa SL, Ezzat S. The epigenetic landscape of differentiated thyroid cancer. Mol Cell Endocrinol 2018;469:3-10. DOI:10.1016/j.mce.2017.07.012.
52. Ahmed AA, Essa MEA. Potential of epigenetic events in human thyroid cancer. Cancer Genet 2019;239:13-21. DOI:10.1016/j.cancergen.2019.08.006.
53. Catalano MG, Fortunati N, Boccuzzi G. Epigenetics Modifications and Therapeutic Prospects in Human Thyroid Cancer. Front Endocrinol 2012;3:40. DOI:10.3389/fendo.2012.00040.
54. Guo W, Xu T, Lee JJ, Murphy GF, Lian CG. Epigenetic markers in melanoma. Melanoma Manag 2015;2(4):367-382. DOI:10.2217/mmt.15.30.
55. Micevic G, Theodosakis N, Bosenberg M. Aberrant DNA methylation in melanoma: biomarker and therapeutic opportunities. Clin Epigenetics 2017;9:34. DOI:10.1186/s13148-017-0332-8.
56. Sarkar D, Leung EY, Baguley BC, Finlay GJ, Askarian-Amiri ME. Epigenetic regulation in human melanoma: past and future. Epigenetics 2015;10(2):103-121. DOI:10.1080/15592294.2014.1003746.
57. Mannavola F, D'Oronzo S, Cives M, Stucci LS, Ranieri G, Silvestris F, Tucci M. Extracellular Vesicles and Epigenetic Modifications Are Hallmarks of Melanoma Progression. Int J Mol Sci 2019;21(1):52. DOI:10.3390/ijms21010052.
58. Ansari J, Shackelford RE, El-Osta H. Epigenetics in non-small cell lung cancer: from basics to therapeutics. Transl Lung Cancer Res 2016;5(2):155-171. DOI:10.21037/tlcr.2016.02.02.
59. Suzuki A, Makinoshima H, Wakaguri H, Esumi H, Sugano S, Kohno T, Tsuchihara K, Suzuki Y. Aberrant transcriptional regulations in cancers: genome, transcriptome and epigenome analysis of lung adenocarcinoma cell lines. Nucleic Acids Res 2014;42(22):13557-13572. DOI:10.1093/nar/gku885.
60. Vosa U, Vooder T, Kolde R, Vilo J, Metspalu A, Annilo T. Meta-analysis of microRNA expression in lung cancer. Int J Cancer 2013;132(12):2884-2893. DOI:10.1002/ijc.27981.
61. Wu X, Gao Y, Bu J, Deng L, Zhang P, Chi M, Jiang L, Shi X, Ning S, Wang G. Identification of Potential Long Non-coding RNA Expression Quantitative Trait Methylations in Lung Adenocarcinoma and Lung Squamous Carcinoma. Front Genet 2020;11:602035. DOI:10.3389/fgene.2020.602035.
62. Weeramange CE, Tang KD, Vasani S, Langton-Lockton J, Kenny L, Punyadeera C. DNA Methylation Changes in Human Papillomavirus-Driven Head and Neck Cancers. Cells 2020;9:1359. DOI:10.3390/cells9061359.
63. Le JM, Squarize CH, Castilho RM. Histone modifications: Targeting head and neck cancer stem cells. World J Stem Cells 2014;6(5):511-525. DOI:10.4252/wjsc.v6.i5.511.
64. Nowicka Z, Stawiski K, Tomasik B, Fendler W. Extracellular miRNAs as Biomarkers of Head and Neck Cancer Progression and Metastasis. Int J Mol Sci 2019;20:4799. DOI:10.3390/ijms20194799.

65. Wu Y, Sarkissyan M, Vadgama JV. Epigenetics in Breast and Prostate Cancer. Methods Mol Biol 2015;1238:425-466. DOI:10.1007/978-1-4939-1804-1_23.
66. Chen J, Luo Q, Yuan Y, Huang X, Cai W, Li C, Wei T, Zhang L, Yang M, Liu Q, Ye G, Dai X, Li B. Pygo2 associates with MLL2 histone methyltransferase and GCN5 histone acetyltransferase complexes to augment Wnt target gene expression and breast cancer stem-like cell expansion. Mol Cell Biol 2010;30:5621-5635. DOI:10.1128/MCB.00465-10.
67. Shi L, Sun L, Li Q, Liang J, Yu W, Yi X, Yang X, Li Y, Han X, Zhang Y, Xuan C, Yao Z, Shang Y. Histone demethylase JMJD2B coordinates H3K4/H3K9 methylation and promotes hormonally responsive breast carcinogenesis. Proc Natl Acad Sci USA 2011;108:7541-7546. DOI:10.1073/pnas.1017374108.
68. O'Day E, Lal A. MicroRNAs and their target gene networks in breast cancer. Breast Cancer Res 2010;12:201. DOI:10.1186/bcr2484.
69. Walter BA, Gomez-Macias G, Valera VA, Sobel M, Merino MJ. miR-21 expression in pregnancy-associated breast cancer: a possible marker of poor prognosis. J Cancer 2011;2:67-75. DOI:10.7150/jca.2.67.
70. Moufarrij S, Dandapani M, Arthofer E, Gomez S, Srivastava A, Lopez-Acevedo A, Villagra A, Chiappinelli KB. Epigenetic therapy for ovarian cancer: promise and progress. Clin Epigenetics 2019;11(1):7. DOI:10.1186/s13148-018-0602-0.
71. Stampoliou A, Arapantoni-Dadioti P, Pavlakis K. Epigenetic mechanisms in endometrial cancer. J Buon 2016;21:301-306. PMID:27273937.
72. Muller I, Wischnewski F, Pantel K, Schwarzenbach H. Promoter- and cell-specific epigenetic regulation of CD44, Cyclin D2, GLIPR1 and PTEN by methyl-CpG binding proteins and histone modifications. BMC Cancer 2010;10:297. DOI:10.1186/1471-2407-10-29.
73. Sikand K, Slaibi JE, Singh R, Slane SD, Shukla GC. miR 488* inhibits androgen receptor expression in prostate carcinoma cells. Int J Cancer 2011;129:810-819. DOI:10.1002/ijc.25753.
74. Majid S, Dar AA, Saini S, Yamamura S, Hirata H, Tanaka Y, Deng G, Dahiya R. MicroRNA-205-directed transcriptional activation of tumor suppressor genes in prostate cancer. Cancer 2010;116:5637-5649. DOI:10.1002/cncr.25488.
75. Hu M, Xie J, Hou H, Liu M, Wang J. Prognostic Value of DNA Methylation-Driven Genes in Clear Cell Renal Cell Carcinoma: A Study Based on Methylation and Transcriptome Analyses. Dis Markers 2020;2020:8817652. DOI:10.1155/2020/8817652.
76. Luo Q, Vögeli TA. Methylation-Based Reclassification of Bladder Cancer Based on Immune Cell Genes. Cancers 2020;12:3054. DOI:10.3390/cancers12103054.
77. Harrison A, Parle-McDermott A. DNA methylation: a timeline of methods and applications. Front Genet 2011;2:74. DOI:10.3389/fgene.2011.00074.
78. Singer BD. A Practical Guide to the Measurement and Analysis of DNA Methylation. Am J Respir Cell Mol Biol 2019;61(4):417-428. DOI: 10.1165/rcmb.2019-0150TR.