



## Review Article

## Epigenetics of human diseases and scope in future therapeutics



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## الملخص

علم التخلُّق هو دراسة التعديلات النوكليوتيدية الموروثة التي تعمل كآلية تنظيمية دون تغيير التسلسل النيوكليوتيدي للجينوم. تؤثر إشارات خارجية مثل البيئة، ونمط الحياة، والتغذية، والإجهاد والعوامل النفسية على آليات التخلُّق. وتتوافق هذه الآلية مع المعلومات الجينية التي تلعب دوراً مهماً في حياة الفرد قبل الولادة وبعدها. لقد كشفت الدراسات الأخيرة في علم التخلُّق إمكانات علم التخلُّق في توضيح آليات أمراض مختلفة لم يتم فهمها سابقاً بشكل كامل.

ناقشنا في هذا الاستعراض آليات التخلُّق الأساسية ودورها في الصحة والمرض. إضافة إلى ذلك فقد تم وصف الانحرافات في التنظيم التخلُّقي التي تم تسجيلها لبعض الأمراض البشرية الشائعة. وأخيراً، نتناول الورقة بعض الأساليب في علم التخلُّق، التي تكمن بها القدرة على العلاج الموجه للأمراض.

**الكلمات المفتاحية:** علم التخلُّق؛ داء السكري؛ السرطان؛ اضطراب الطبع؛ داء الزهايمر

## Abstract

Epigenetics is the study of nucleotide modifications that are heritable and act as regulatory mechanisms without changing the nucleotide sequence of the genome. Exogenous cues such as environment, lifestyle, nutrition, stress, and psychological factors affect epigenetic mechanisms. This mechanism is in concordance with the genetic information that plays an important role during

prenatal and postnatal life of an individual. Recent epigenetic studies have revealed the potential of epigenetics in elucidating the mechanisms of different diseases. In this review, we discuss basic epigenetic mechanisms and their roles in health and disease. In addition, reported aberrations in epigenetic regulation for some common human diseases are described. Finally, we address some epigenetic approaches that have shown potential for targeted treatment of diseases.

**Keywords:** Alzheimer's disease; Cancer; Diabetes; Epigenetics; Imprinting disorders

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## Introduction

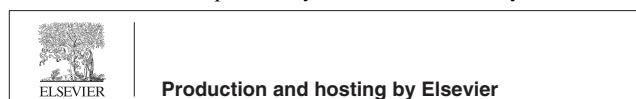
The term 'epigenetics' means 'on top' or 'in addition' to genetics. Epigenetic processes include mitotically and/or meiotically heritable alterations to genetic information without changing the DNA sequence.<sup>1</sup> Thus, the genome refers to the entire set of genetic information as nucleotide sequence within the DNA, whereas the epigenome refers to complex modifications within genomic DNA.

Genetics studies have been widely conducted and have contributed greatly to our understanding of human diseases; however, epigenetics has recently provided new information to decipher the causative mechanisms of many diseases. Epigenetics not only considers the genomic constitution, but also integrates the social and natural environment, influence of everyday routine, dietary habits, and stresses to biological

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systems. The epigenome integrates information encoded in the genome with molecular and chemical cues of cellular, extracellular, and environmental origin to define the functional identity of each cell type during development or disease.<sup>2</sup> These stimuli-initiated modulations of the epigenome contribute to embryo development, cell differentiation, and responses to exogenous signals.<sup>3</sup> Thus, in contrast to the consistency of the genome, plasticity in the epigenome is characterized by dynamic and flexible responses to intracellular and extracellular stimuli including those from the environment.

Predominantly, epigenetic modifications include DNA methylation, histone modifications, and RNA-associated silencing. These modifications in the genome regulate numerous cellular activities, and disruption of these activities may cause abnormal expression or silencing of genes. Aberrations in the epigenome contribute to the aetiology of numerous diseases during both prenatal and postnatal life. Unlike most genetic defects, epigenetic defects are reversible. This reversibility is an important aspect of the epigenetic contribution to diseases and makes such diseases amenable to therapeutics.

This review describes the most widely studied epigenetic mechanisms and epigenetic aberrations in some common human diseases. The contribution of epigenetics in human diseases and new treatment options currently being explored are also discussed.

### Mechanisms underlying epigenetics

The genome within each cell is identical; however, the terminal phenotype is contributed by manifestations of epigenetic markers in the genome that lead to deviations in their gene expression profiles. These deviations are regulated mainly by DNA methylation, as well as modifications of histone and RNA-associated silencing.

#### DNA methylation

DNA methylation takes place at the 5' position in the pyrimidine ring to covalently link a methyl group ( $-CH_3$  moiety) to the cytosine. A cytosine located prior to guanine in the genome forms CpG sites, which are abundantly present in the promoters of protein-coding genes. Methylation and demethylation of these CpG sites regulate transcription and gene expression. DNA methylation is maintained by a variety of DNA methyltransferases (DNMTs) that are present in biological systems. DNA methyltransferase 1 (DNMT1) maintains normal methylation markers during the trans-generational copying of the methylation pattern from one cell generation to another during cell division. DNMT2 is associated with potential RNA methylation and embryonic stem cells. *De novo* methylation at CpG sites involves DNMT3A and DNMT3B.<sup>4,5</sup>

The 'methylome', i.e. the genomic arrangement of a methylated DNA sequence in a cell, may change in response to environmental stimuli, disease, and developmental stage. 5-Methylcytosine is highly prone to mutations; C:G to T:A transitions lead to CpG methyl acceptor site suppression. Approximately 40% of mammalian genes have stretches of CpGs within their promoter regions; methylation of these

sites leads to heritable transcriptional silencing. *De novo* methylation errors at CpGs in the promoter region are indicators of human diseases and have been detected during early tumorigenesis.<sup>6</sup>

#### Histone modifications

Histones are core proteins that wrap around DNA to function as a structural backbone at regular intervals during formation of a chromatin complex. The first level of chromatin organization, referred to as the nucleosome, includes histones H2A, H2B, H3, and H4 structured as an octameric core with DNA wrapped tightly around the octamer.<sup>7</sup>

Acetylation and methylation of conserved lysine residues at the amino-terminal tail domains of histone are epigenetic modifiers. Epigenetic regulation through histones is mediated by the degree of DNA compaction, which influences transcriptional activity.

Histone acetyltransferases and histone deacetylases add/remove acetyl groups on lysine residues in histone tails, as a part of epigenetic regulation. Generally, lysine acetylation on histone tails promotes transcriptional activation by chromatin relaxing, whereas deacetylation promotes chromatin compaction and transcriptional inactivation.

Depending upon which amino acid is methylated, histone methylation can activate or inactivate chromatin expression. If lysine 9 in the N-terminus of histone H3 (H3-K9) is methylated, gene expression is suppressed. Heterochromatic regions such as telomeres and centromeres, repressed promoters, and inactive X chromosome are regulated by this mechanism. However, for lysine 4, methylation at histone H3 (H3-K4) promotes gene expression mostly in the promoters of active genes.<sup>8</sup>

#### RNA-associated silencing

MicroRNAs (miRNA) and small interfering RNAs play important roles in RNA-associated silencing, during which they downregulate gene expression at the post-transcriptional modification stage. Post-transcriptional binding of non-coding RNA to 3'-untranslated regions of target mRNAs acts as a putative RNA silencing mechanism.<sup>9</sup> Approximately 30% of genes are targeted by miRNA, representing just 1% of the genome.<sup>10</sup> These RNAs act as switches and modulators to fine-tune gene expression during normal development and in diseases.<sup>11-13</sup> Additionally, miRNAs play an important role in tumour suppression, apoptosis, cellular proliferation, and cell movement.<sup>14</sup>

### Epigenetic influences and human diseases

Epigenetic abnormalities such as aberrant DNA methylation, histone modifications, or RNA silencing are found in numerous human diseases. Gene mutations that alter the epigenetic profile may also cause pathologies, which can be inherited or acquired somatically.

Throughout life, DNA accessibility is epigenetically regulated. In early embryonic stages, histone modifications and demethylation occur in the paternal genome.<sup>15</sup> The

maternal genome also undergoes demethylation, after which embryonic re-methylation is initiated, contributing to the epigenetic profile of the developing embryo. The newly established epigenetic profile must be maintained for efficient gene regulation. Any error in maintenance may contribute to congenital disorders and paediatric syndromes or predispose people to acquired diseases.

### Epigenetics of cancer

Global DNA hypomethylation and gene-specific hypermethylation have been observed in human cancer cells obtained from clinical tissue biopsies.<sup>16</sup> During initial studies of cancer epigenetics, the genome of patients with colorectal cancer was reported to be hypomethylated.<sup>17</sup> In these patients, regions that are hypermethylated under normal conditions and silent regions of the genome were found to be demethylated. In contrast, aberrant gene activity such as repression of tumour-suppressor genes has been associated with hypermethylation of CpG islands in certain cancers.<sup>18</sup> DNA repetitive sequences such as microsatellites become functionally aberrant and induce tumourigenesis by hypermethylation of DNA.<sup>19</sup> Jones and Baylin reported that microsatellites in colorectal and ovarian cancers are distorted by abnormal epigenetic modulations in the *MLH1* promoter (a DNA repair gene).<sup>6</sup>

In many human cancers, the CpG islands in the promoters of tumour-suppressor genes such as *CDKN2A*, *CDKN2B*, *TP73*, *MLH1*, *APC*, *BRCA1*, *MGMT*, *VHL*, *GSTP1*, *CDH1*, and *DAPK1* have been observed to be hypermethylated.<sup>16</sup> Promoter hypermethylation<sup>20</sup> and heterochromatinization<sup>21</sup> in patients with cancer suggests that epigenetics play a critical role in tumourigenesis.

In a study by Kim and Sharpless, *INK4* (a cyclin-dependent kinase inhibitor), was transcriptionally inactivated by hypermethylation at the promoter region.<sup>22</sup>

*INK4* encodes several proteins that are frequently targeted during early tumourigenesis, including *p14*, *p15*, and *p16*. Carcinogenic changes have also been reported in abnormal histone modifications. Witcher and Emerson reported that the loss of chromatin domains and discrete histone structures are associated with dysregulation of transcriptional control of *p16* in breast cancer cells.<sup>23</sup>

miRNAs, which are short non-coding RNAs (~21 nucleotides), induce translational repression when they imperfectly align with the 3'-untranslated regions of target mRNAs. Many tumour-suppressive microRNAs such as miR-34a and 34b/c, miR-124, miR-137, miR-152, miR-218, and miR-345 are suppressed by DNA hypermethylation.<sup>24</sup>

### Epigenetics of neurological disease

Recent studies have suggested that neurological diseases are also caused by epigenetic anomalies. Evidence suggests that *de novo* methylation and DNMT maintenance is critical for neuronal function and neurological behaviour. In patients with schizophrenia and bipolar disorder, elevated DNMT1 levels were found in GABAergic neurons.<sup>25</sup> Further, hypermethylated *GAD67* and *RELN* associated with low transcript levels were observed in cells from patients with neurological diseases.<sup>25</sup>

It has been reported that hereditary sensory neuropathy due to *DNMT1* gene mutations are associated with dementia and hearing loss.<sup>26</sup> Mutations in *DNMT3B* are commonly reported in immunodeficiency-centromeric instability-facial anomalies.<sup>27</sup> In this condition, hypomethylation at *LHX2*, loss of tri-methylation at histone H3K27 causing gene repression, and gain of H3K9 acetylation and H3K4 trimethylation causing gene activation have been observed<sup>27</sup>.

In Alzheimer's disease, significant DNA hypomethylation in the temporal neocortex has been observed.<sup>28</sup> In brain tissues from patients with Alzheimer's disease, DNA methylation markers were significantly reduced.<sup>29</sup> However, a study of blood samples from patients with Alzheimer's disease showed elevated *LINE-1* methylation compared to samples from age-matched controls.<sup>30</sup>

In autism, a cumulative effect of genetics (mutations in synaptic factors) and the environment has been suggested. Epigenetics may connect these two contributory factors leading to disease development.<sup>31</sup> Environmental factors such as stress, maternal care, dietary insufficiencies, drugs, and mental and neuronal stimulation may affect brain function by altering the epigenetic profile of genes.<sup>32-37</sup>

### Epigenetics of autoimmune disorders

Studies have confirmed that epigenetic anomalies are also important contributors to autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). SLE is a chronic autoimmune disorder.<sup>38</sup> Epigenetic changes are influenced by the environment, and dysregulation of related genes may stimulate autoimmunity.<sup>38,39</sup> The disease severity of SLE has been reported to be inversely associated with 5-methylcytosine from CD4<sup>+</sup> T lymphocytes of patients.<sup>40,41</sup> Similar observations for altered DNA methylation profiles were observed in SLE mouse models. Animal models with mutations affecting the epigenome showed reduced DNA methylation and suppressed *DNMT1* expression in T-cells, which directly correlates with aging and SLE progression.<sup>42,43</sup>

However, little is known regarding the role of histone acetylation abnormalities in SLE. In CD4<sup>+</sup> T lymphocytes of patients with SLE, global histone H3 and H4 hypoacetylation has been reported.<sup>44</sup> In contrast, histone H4 hyperacetylation at gene promoters was observed in monocytes from patients with SLE.<sup>45</sup>

The affected joints of patients with RA contain hyper-reactive synovial cells because of elevated levels of pro-inflammatory cytokines.<sup>46</sup> Additionally, osteoclasts and rheumatoid arthritis synovial fibroblasts (RASf) in the joints break down bone and cartilage tissues.<sup>47</sup> In patients with arthritis, global DNA hypomethylation is found in the blood, synovial mononuclear cells, and synovial tissue.<sup>48</sup> Neidhart et al. reported hypomethylation of RASf in patients with arthritis.<sup>49</sup> Similar findings were reported by Karouzakis et al., who observed that healthy controls had higher levels of DNMT1 than did patients with arthritis.<sup>50</sup> Further, they found that the severity of phenotypes of RASf was correlated with DNMT1 and global DNA methylation. In RASfs, *MMP1* promoter hyperacetylation leads to overexpression of this gene.<sup>51</sup>

### Epigenetics of diabetes

Insufficient secretion of insulin from the pancreas results in abnormal blood glucose levels, leading to type 2 diabetes. The findings of numerous studies emphasize the critical role of epigenetic errors in type 2 diabetes. Intrauterine stress prior to or during pregnancy has been reported to increase the susceptibility to diabetes during postnatal life.<sup>52–55</sup> Intrauterine stress that may adversely affect adaptive physiological and cellular responses in key organs may be attributed to nutritional, environmental, maternal, placental, or genetic factors.<sup>56</sup> It has been suggested that the susceptibility to metabolic disease during adult life involves *in utero* epigenetic mechanisms influenced by intrauterine stress factors.<sup>57,58</sup>

Kuroda et al. observed that as compared to non-insulin expressing cell types, the promoter region of insulin-producing beta cells is hypomethylated.<sup>59</sup> Further, they demonstrated that expression of the insulin gene is negatively associated with DNA methylation at a CpG site located at 182 base pairs upstream of the insulin promoter. Further, H4 hyperacetylation and H3 dimethylation at lysine 4 were reported in patients with type 2 diabetes.<sup>60,61</sup> Thus, the expression of epigenetic changes in pancreatic islets and beta cells significantly affects diabetes risk in individuals.

### Imprinting disorders

The epigenetic mechanism regulating gene expression in a parent of origin-specific manner is referred as genomic imprinting. During imprinting, one allele from either parent is expressed while the other is silent (imprinted). Imprinting errors are critical in numerous developmental and paediatric disorders.<sup>62–65</sup> DNA methylation and histone modifications regulate the imprinting processes.<sup>66</sup> Angelman, Prader–Willi, and Beckwith–Wiedemann syndromes are the most common and widely studied imprinting disorders. Epigenetic abnormalities at chromosome 15 on the paternal allele lead to Prader–Willi, whereas epigenetic abnormalities at the same locus on the maternal allele of chromosome 15 cause Angelman syndrome.<sup>62,63</sup> The clinical features of Prader–Willi syndrome include developmental delay, neonatal hypotonia, hyperphagia, and hypogonadism. Patients with Prader–Willi syndrome were reported to have maternal uniparental disomy 15q11.2 and hypermethylation of the paternal allele for small nucleolar ribonucleoprotein polypeptide N.<sup>67–69</sup>

The clinical features of Angelman syndrome includes developmental delay with absent or nearly absent speech, ataxic gait, and seizures. Patients with Angelman syndrome show suppressed maternally expressed ubiquitin-protein ligase E3A and paternal uniparental disomy 15q11.2.<sup>70,71</sup>

### Future perspectives

Various studies and clinical trials have examined epigenetic therapies which shown the potential to decrease the burden of diseases in which abnormal epigenetic mechanisms play a critical role. Numerous therapeutic agents that can modulate epigenetic mechanisms in various disease conditions are under consideration for clinical use. Azacitidine, a

nucleoside analogue that can be incorporated into DNA during replication, inhibits methylation and reactivates a previously silenced gene<sup>72</sup> and is the compound of choice in most studies. It has been reported to be effective in clinical trials for treating myelodysplastic syndrome and leukaemia.<sup>73</sup> MG98, an antisense oligonucleotide, was reported to be effective for treating solid tumours and renal cancers<sup>74</sup> by downregulating DNMT1. Another class of molecules used to treat epigenetic diseases are the histone modifiers ‘histone deacetylase (HDAC) inhibitors’. These molecules inhibit HDAC activity and prevent the removal of acetyl groups from DNA to maintain active gene expression active. Phenylbutyric acid, SAHA, depsipeptide, and valproic acid are the most common HDAC inhibitors.<sup>75</sup> Amalgamating different epigenetic therapy strategies as demethylating agents and HDAC inhibitors or a combination of epigenetic therapy and chemo- or immunotherapy may have greater efficacy. Such combinations will help to synergistically kill cancer cells by reactivating silenced tumour-suppressor genes and re-sensitizing cells that are resistant to drugs and therefore enhance the response to conventional therapies.<sup>75–77</sup> Additional studies of the therapeutic approach to epigenetic therapy are required, as the procedure is not selective for target cells and activating gene expression in normal cells may make them cancerous. Further insight into the molecular mechanisms governing these epigenetic modulators will facilitate the design of more specific and effective drugs. The development of more specific HDAC inhibitors has shown great promise. Increasing target specificity will also significantly affect the development of more effective treatment options. The approval of two epigenetic drugs (Vidaza and romidepsin, HDAC inhibitors) by the US Food and Drug Administration has supported their use in disease treatment. Additionally, epigenetic profiling of patients may have predictive or prognostic value for epigenetic therapy. Thus, epigenetic biomarkers can be used to complement current strategies for diagnosis, prognosis, and prediction of drug responses and assist with therapeutic decision-making.

### Conclusion

The findings from various studies clearly suggest that aberrations in the epigenome are critical factors in the initiation and progression of many diseases. Although progress has been made in understanding epigenetic abnormalities, further large-scale epigenetic profiling will lead to a comprehensive and clear understanding of how lifestyle factors, social and psychological attributes, and various other dynamics interact with the naturally inherited genome to affect the predisposition to diseases.

### Conflict of interest

The authors have no conflict of interest to declare.

### Authors' contribution

MBS and ASF conceived, designed and carried out the literature study and wrote the full manuscript. MBS, ASF,

SNI, NA and MAS critically reviewed and approved the initial submission and the revisions of the manuscript. The authors are responsible for the content of the manuscript.

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