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Review Article

# Epigenetics of human diseases and scope in future therapeutics

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**الملخص**

علم التخَلّق 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 التخَلّق. وتتوافق هذه الآلية مع المعلومات الجينية التي تلعب دورا مهما في حياة الفرد قبل الولادة وبعدها. لقد كشفت الدراسات الأخيرة في علم التخَلّق إمكانات علم التخَلّق في توضيح آليات أمراض مختلفة لم يتم فهمها سابقا بشكل كامل.

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

**الكلمات المفتاحية:** علم التخَلّق؛ 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.[1] 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.[2] These stimuli-initiated modulations of the epigenome contribute to embryo development, cell differentiation, and responses to exogenous signals.[3] 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.[4,5]

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 tumourigenesis.[6]

### *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.[7]

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.[8]

### *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.[9] Approximately 30% of genes are targeted by miRNA, representing just 1% of the genome.[10] These RNAs act as switches and modulators to fine-tune gene expression during normal development and in diseases.[11–13] Additionally, miRNAs play an important role in tumour suppression, apoptosis, cellular proliferation, and cell movement.[14]

## 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.[15] The

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