

Epigenetics

Abstract

Historically, cancer is known to be a genetic disease. It is now realized that it involves epigenetic abnormalities along with genetic alterations. Epigenetics is an extra layer of instruction that lies upon DNA and controls how the genes are read and expressed. It simply means changes in phenotype without a change in genotype. In this review we aim to discuss the fundamentals of epigenetics, role of these alterations in carcinogenesis and its implications for epigenetic therapies.

Keywords: *Epigenetics, histone deacetylase, myelodysplastic syndrome*

Introduction

Darwin's theory of evolution is driven by genetic variation and natural selection, whereas Lamarck's theory is based on the inheritance of acquired characteristics. Conrad Waddington explained these concepts and coined the term epigenetics in 1942, to illustrate the interactions between genes and the environment. The term "Epi" comes from the Greek word meaning "upon or above." Therefore, epigenetics is an extra layer of instruction that lies upon DNA and controls how the genes are read and expressed. This explains why, despite having same genetic code, cells from different tissues behave differently and also the fact that identical twins are not actually identical!

Epigenetic changes alter gene expression or phenotype without changing the primary DNA sequence and are heritable.^[1] Their implications include normal development, disease pathophysiology (including cancers), and therapies for cancer. In contrast to genetic alterations, epigenetic changes are relatively stable and reversible.

Cancer Epigenetics

Broadly, epigenetic information falls into three categories: DNA methylation, histone modification, and microRNA (and chromatin) regulation.

Epigenetic modifications involve either covalent attachment (or removal) of a

methyl or acetyl group to a DNA base or a histone (DNA-binding proteins), leading to DNA methylation of promoter region (CpG island) and histone modification,^[2] which inactivate selected tumor suppressor genes causing loss of expression [Figure 1].^[3] DNA methylation is the best understood epigenetic modification for several reasons as it can be copied, interpreted, and erased as required. It is stable over a period of decades making it the most useful epigenetic marker. Histone methylation differs from DNA methylation as the methyl groups are added to lysine and arginine, instead of cytosine and guanine pairs of DNA.

MiRNAs are small noncoding RNAs of 19–25 nucleotides that bind to the areas on target mRNAs and affect gene expression by inhibiting the translation of the specific mRNA. MiRNAs are implicated in the carcinogenesis of APL and many solid tumors.

Few examples of common epigenetic signatures include:

1. Global hypomethylation, e.g., hypomethylation of RAS oncogenes
2. Promoter hypermethylation, e.g., CpG island methylator phenotype in colorectal cancer
3. Inactivation of VHL gene in RCC by hypermethylation of VHL promoter
4. Mutations affecting the isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) in malignant gliomas and AML
5. Hematologic malignancies:
 - Mutations in genes that control histone modifications - MLL, EZH2

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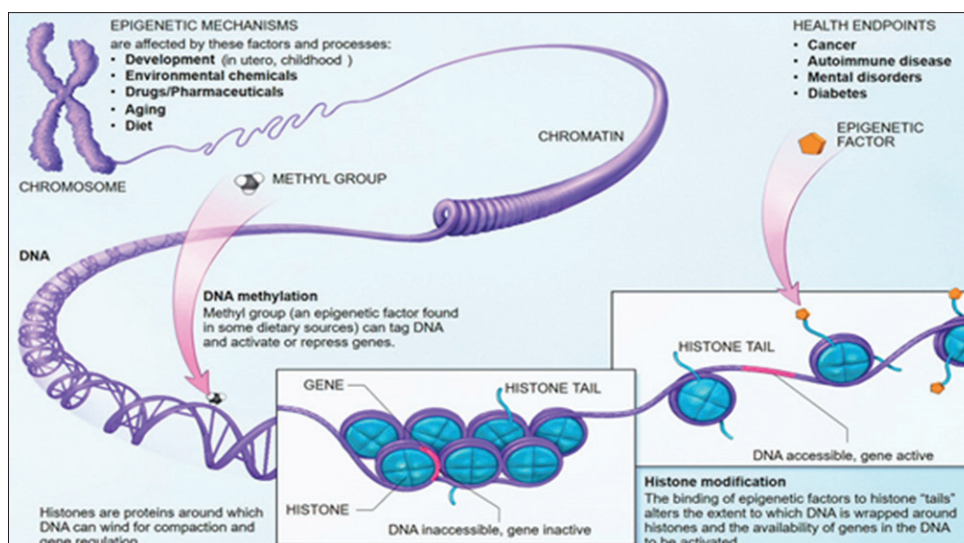


Figure 1: Epigenetic mechanisms

Table 1: Various epigenetic techniques

Epigenetic techniques	Tools for studying
1. DNA methylation analysis	
Bisulfite conversion	PCR, qPCR, and sequencing
High-resolution melt analysis	PCR
Methylated DNA immunoprecipitation	DNA microarrays or NGS
2. Analysis of DNA/histone	
ChIP	PCR, qPCR, sequencing, and microarray hybridization
3. Chromatin accessibility and conformation assays	
EpiQ™ chromatin analysis kit	PCR, qPCR
Digital DNase and DNase Seq	NGS
3C	PCR

PCR – Polymerase chain reaction; qPCR – Quantitative PCR; ChIP – Chromatin immunoprecipitation; 3C – Chromosome conformation capture; NGS – Next generation sequencing

- Mutations in genes that control DNA methylation - TET2, IDH1, IDH2, and DNMT3
- Mutations in genes that control nucleosome position - SNF5, ARID1A.

Techniques Used for Studying or Detecting Epigenetic Changes

Various techniques used for studying epigenetics have been summaries in Table 1.^[4]

Epigenetic Therapies

Why do we need to target epigenetic mechanisms?

The central feature to cancer is a disruption and instability of epigenome, which apart from mutations is caused by epigenetic changes as a result of aging and tissue injury. This epigenetic instability leads to chemoresistance, impairs DNA repair, drives metastasis, and death.^[1]

Hypomethylating agents

DNA-demethylating drugs are modified forms of cytidine and work by incorporating into replicating DNA and covalently binding to the catalytic sites of DNA methyltransferases (DNMTs). The DNA methyltransferase inhibitors irreversibly inhibit the enzymatic activities of DNMTs and trigger their proteasomal degradation. Azacitidine and decitabine are nucleoside analogs that inhibit DNMTs and are approved for the use in myelodysplastic syndrome (MDS). Meta-analysis of these agents in MDS has shown improved overall survival and improved time to AML transformation or death. In a subgroup analysis, the survival benefit was limited to azacitidine.^[5] Azacitidine can be given subcutaneously at 75 mg/m² for 7 consecutive days every 4 weeks as an outpatient therapy in low-intermediate- and high-risk (transplant ineligible or unfit) MDS.

Histone deacetylase inhibitors

DNA is associated with histone and nonhistone proteins to form chromatin. Condensation (tight coiling) of the DNA suppresses gene expression. Histone deacetylase (HDAC) inhibition facilitates chromatin decondensation and histone acetylation, leading to activated gene expression. This subsequently results in cell cycle arrest and apoptosis, inhibition of angiogenesis, and alteration of immune response.

Romidepsin, vorinostat, and belinostat are approved for patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease. Vorinostat is an oral drug which is started at 400 mg/day, while the other two are administered intravenously.^[6] Panobinostat is approved for multiple myeloma patients who have progressed on two regimens containing bortezomib and an immunomodulatory agent. Patients on HDAC inhibitors are monitored for myelosuppression, hepatotoxicity, and QTc prolongation.

Isocitrate dehydrogenase inhibitors

IDH1 and IDH2 are enzymes which catalyze the conversion of isocitrate to alpha-ketoglutarate and are part of the citric acid cycle. IDH1 or IDH2 mutations are present in about 20% of patients with AML. IDH inhibitors also called “sidenibs” target cancers with these mutations. Enasidenib and ivosidenib are the FDA-approved oral drugs for IDH2- and IDH1-mutated patients, respectively, with relapsed/refractory AML.^[7]

Other therapeutic strategies targeting epigenetics in cancer and future directions

Clustered, regularly interspaced, short palindromic repeats-associated protein 9 is an enzyme which inserts break in DNA and is used to edit genes targeting molecules involved in epigenetic modifications. Similarly, newer drugs such as zebularine, a DNMT inhibitor is found to be more stable and less toxic than azacytidine and decitabine. There are ongoing clinical trials which are exploring combination of epigenetic or “immune-sensitizing” therapeutic agents, such as the DNA methyltransferase inhibitors, with immune-checkpoint inhibitors, such as those that block CTLA-4 and programmed death 1 for the treatment of multiple cancers.^[8] Thus, cancer epigenetics is an area of ongoing research that has led us to an era of comprehensive medical understanding of complex molecular pathogenesis and identifying novel therapeutic targets.

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Conflicts of interest

There are no conflicts of interest.

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