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Effects of Epigenetic Regulation on Cancer

Epigenetik Düzenlemenin Kanser Üzerine Etkileri

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Abstract

Epigenetics is the science of biology that studies gene expression changes, which are not caused by changes in DNA sequence, but are also inherited. The molecular basis of epigenetics is a complex phenomenon and determines when and how certain genes are activated. Cancer is characterized as a disease in which cells reproduce uncontrollably and then spread. Cancer is a multifactorial complex disease caused by the accumulation of genetic and/or epigenetic changes. Epigenetic mechanisms include DNA methylation, histone modifications, and noncoding ribonucleic acid regulation. Epigenetic mechanisms affect the tumor behavior and thus the clinical course. Being a biomarker that will determine the diagnosis, treatment and prognosis will enable its use in the diagnosis and treatment of many cancers in the future. We believe that future studies on the relationship between epigenetic mechanisms and cancer will be hope for cancer treatment.

Keywords Epigenetic, Cancer, DNA Methylation, Histone Modifications, Non-coding RNAs

Öz

Epigenetik DNA dizisindeki değişikliklerden kaynaklanmayan, ama aynı zamanda kalıtsal olan gen ekspresyon değişikliklerini inceleyen biyoloji bilim dalıdır. Epigenetiğin moleküler temeli karmaşık bir olaydır ve belli genlerin ne zaman ve nasıl aktive edileceğini belirler. Kanser, hücrelerin kontrolsüz bir şekilde çoğaldığı ve daha sonra yayıldığı bir hastalık olarak karakterize edilir. Kanser, genetik ve / veya epigenetik değişikliklerin birikmesinin neden olduğu multifaktöryel bir hastalıktır. Epigenetik mekanizmalar, DNA metilasyonu, histon modifikasyonları ve kodlanmayan ribonükleik asit regülasyonunu içerir. Epigenetik mekanizmalar tümör davranışını ve dolayısıyla klinik seyri etkiler. Tanı, tedavi ve prognozu belirleyecek bir biyobelirteç olması ileride birçok kanserin tanı ve tedavisinde kullanılmasını sağlayacaktır. Epigenetik mekanizmalar ile kanser arasındaki ilişkiye yönelik ileride yapılacak çalışmaların kanser tedavisi için umut olacağına inanıyoruz.

Anahtar Kelimeler *Epigenetik, Kanser, DNA Metilasyonu, Histon Modifikasyonları, Kodlanmayan RNA'lar*

INTRODUCTION

As a science of biology, epigenetics studies gene expression changes, which are not caused by changes in DNA sequence, but are also inherited. In other words, it examines inherited and non-genetic phenotypic variations. Epigenetics was defined in 1942 by Conrad Waddington. The molecular basis of epigenetics is a complex phenomenon and determines when and how certain genes are activated. If we imagine an orchestra conductor playing the right instruments at the right time for a good musical performance to emerge, the epigenetic process can be compared to this conductor. In this process, while events such as cell renewal, gene imprinting and X chromosome inactivation are taking place, the disruption of the process causes health problems such as cancer, autoimmune and neurological diseases.[1-8]

Cancer is characterized as a disease in which cells reproduce uncontrollably and then spread. Cancer is a multifactorial complex disease caused by the accumulation of genetic and/or epigenetic changes. Disruption of epigenetic regulation occurs early in cancer. Activation of oncogenes and/or loss of function of tumor suppressor genes play a role in cancer formation. As a result of these genetic and/or epigenetic changes, it leads to change in gene function, malignant transformation and plays an important role in the progression of cancer.[9]

Quite a few reports have been published on the relationship between epigenetics and cancer. In this review, we will discuss the effect of epigenetic regulation on cancer in the light of current literature data.

RESEARCH METHODS

Literature was searched using the keywords "Epigenetic, Cancer, DNA Methylation, Histone Modifications, Non-coding RNAs" in English databases including PubMed / Medline, ISI Web of Science, SCOPUS, Google Scholar etc. Relevant parts of the appropriate articles were used for the writing of the manuscript.

Epigenetic Mechanisms and Cancer

Epigenetic mechanisms are essential for normal development and maintenance of tissue specific expression. Tissue-specific epigenetic mechanisms are variable, adapted to specific cellular events not only during development but throughout life. It is possible to explain how cells and organisms with the same genome have different phenotypes with epigenetics.[10-11]

Epigenetic mechanisms include DNA methylation, histone modifications, and noncoding ribonucleic acid regulation. Collectively, epigenetic mechanisms determine chromatin architecture, accessibility of genetic loci to transcriptional machinery, and gene expression levels.

1. DNA Methylation

DNA methylation is an epigenetic mechanism that is effective in the triggering, progression and metastasis process of the cancer mechanism. It is effective in cancer in two ways: global DNA hypomethylation and promoter DNA hypermethylation. Global hypomethylation was discovered in the 1980s and can be defined as a decrease in 5-methylcytosine content in the whole genome. Whole genome hypomethylation is mainly seen in repetitive sequences such as Alu, LINE-1 and Sata, which make up more than 40% of the genome and are normally highly methylated. Whole genome hypomethylation is detected in almost all cancers and increases the progression of cancer by causing genomic instability.[5,12-14]

DNA methylation is observed in regions where CpG sequences are dense, which are formed by sequencing of cytosine (C) and guanine (G) pairs in the genome. CpG islets are regions with greater than 500 base pairs and a GC content of more than 55%. CpG islets are usually located in the promoter regions of genes. CpG islets in housekeeping and regulatory genes that must be constantly expressed in the organism are regions resistant to DNA methylation. However, CpG sequences in heterochromatin regions such as repeat sequences and transposons have a high DNA

methylation rate. With the methylation of these regions, the transcription event is suppressed and the intra-genome movement of such structures is prevented and the stable structure of the chromosome is preserved. Changes in the methylation level of CpG islets may be associated with cancer.[15,16]

DNA methylation plays a role in many biological events such as physiological embryonic development in the genome, inactivation of transposable elements, regulation of chromatin structure, genomic imprinting, X chromosome inactivation, regulation of gene expression. This covalent modification is catalyzed by DNA methyltransferase (DNMT) enzymes. DNMT1 is required for the continuity of methylation present in DNA, while DNMT3A and DNMT3B are essential for de novo DNA methylation.[17]

Global DNA hypomethylation has been associated with the occurrence of prostate, head-neck, hepatocellular and brain cancer in particular. Methylation is one of the main mechanisms that inactivate tumor suppressor genes. Hypermethylation of the promoter region in tumor suppressor genes has been shown in the literature as von Hippel-Lindau (VHL) in renal cell carcinoma, Retinoblastoma (Rb) in sporadic retinoblastoma and Cadherin-1 (CDH1) in hepatocellular carcinoma.[18-21]

Let's review some of the studies on this subject in recent years. Liu and colleagues tried to identify DNA methylation markers to distinguish cancer samples from corresponding normal samples in pan-cancers. In this study, full genome methylation data of 27 cancer types containing 10,140 cancer samples and 3386 normal samples were collected. In cell-free DNA methylation data of 163 prostate cancer samples, the CpG markers achieved the sensitivity as 100%, and the promoter markers achieved 92%. For both marker types, the specificity of normal whole blood was 100%. In summary, as a result of this study, methylation markers were determined to diagnose pan cancers that can be applied to liquid biopsy of cancers.[22] Parashar et al., In their study on DNA methylation signatures of breast cancer in peripheral T-cells, point to the possibility of using DNA methylation signatures as a non-invasive method for the early diagnosis of breast cancer and its progression.[23] Zhang et al. investigated specific prognosis subtypes based on DNA methylation status using 669 breast cancers in their study on specific breast cancer prognosis-subtype distinctions based on DNA methylation patterns. As a result of the study, these specific classifications by DNA methylation can explain the heterogeneity of previous molecular subgroups in breast cancer and will help in the development of personalized treatments for the new specific subtypes.[24]

The role of DNA hypermentilation in cancer diagnosis and treatment;[25-28]

- As hypermentilation occurs in the early stages of carcinogenesis, it can be used for early diagnosis in cancer.
- It can be used to evaluate response to chemotherapeutic agents.
- Because methylation is rare in normal cells and is reversible, unlike mutations, it has come to the fore in cancer treatment.
- DNA methyltransferase (DNMT) inhibitors, called demethylated agents, cause demethylation of the genome, leading to a decrease in tumor formation and an increase in the expression of tumor suppressor genes.
- DNMT inhibitors are used in the treatment of solid tumors and hematological malignancies.

2. Histone Modifications

The DNA molecule is surrounded by histone and non-histone proteins in the cells and is found in the nucleoprotein structure called chromatin. In 1964, Vincent Allfrey prophetically surmised that histone modifications might have a functional influence on the regulation of transcription. Histone modification plays an important role in the post-translational regulation of a gene. These post-trans-

lational modifications include methylation, acetylation, ubiquitination, phosphorylation, glycosylation, sumolation and the like reactions. Histone modifications are involved in epigenetic mechanisms such as DNA repair and replication during cell division, gene transcription, heterochromatin formation, and X chromosome inactivation.[10,29-31]

The great variety in histone modifications reveals considerable complexity that is slowly beginning to be explained. Histone modifications are reversible and dynamic. In all genome studies carried out so far, it has been revealed that various histone modifications in a specific genome region play a role in the active or suppressed chromatin structure. Many of the proteins that modify or bind these histone modifications are misregulated in cancer.[8,32]

The most studied histone modification is acetylation and methylation. Hyperacetylation is found in actively transcribing euchromatin. Hypoacetylation is found in heterochromatin and transcriptionally located in silent genomic regions. Histone acetylation and deacetylation are processes in which lysine residues protruding from the histone core of the nucleosome in the N-terminal tail are acetylated and deacetylated as part of gene regulation. Histone acetylation and deacetylation are essential parts of gene regulation. Histone acetylation is catalyzed by histone acetyltransferase (HAT), deacetylation histone deacetylase (HDAC) enzymes.[33-34]

As a result of advanced technological applications made today, it has been shown that chromatin changes occur during tumor initiation and progression. Loss of acetylation and increase in methylation in H4 histone protein is a common change observed in the early stages of carcinogenesis. The reduction of histone acetylation is important in carcinogenesis. This situation is associated with low HAT activity or increased HDAC activity. Molecular changes that occur with the disruption of the balance between HAT and HDAC activities are observed at the basis of many cancers. HDAC enzymes show pro-oncogenic effects by protecting genes that are effective in differentiation, apoptosis and transcriptional silent cell cycle. The increasing in HDAC activity occurs by multiple mechanisms. Global histone hypoacetylation as a result of HDAC overexpression is characteristic of many cancers. Mutation and/or aberrant expression of HDAC subtypes have been detected in many diseases, including cancer. In studies conducted in the literature, an increase in HDAC expression has been found in cancer cell lines in colon, gastric, renal, prostate, neuroblastoma, breast and cervical cancer.[10,21,35,36]

"HDAC inhibitors" effective on epigenetic mechanisms have begun to be used as cancer treatment agents. HDAC inhibitors increase the acetylation of histones by disrupting the vicious cycle that occurs in cancer, it allows the genes that become silenced in cancer to be expressed again and the malignant phenotype to return.[8,34,37]

3. Non-coding RNAs

The information in the genetic material of developed living cells is transferred as messenger RNA (mRNA). It is then transported to the ribosome as mRNA and protein synthesis takes place. But not every RNA synthesized from DNA can be converted into protein, these RNAs that cannot be translated into protein are called "non-coding RNAs" (ncRNA). With the development of next generation sequencing techniques, surprising data have been found as a result of whole genome sequencing. The finding of approximately 20.000 protein-coding genes, corresponding to less than 2% of the total genome of the human genome, has supported that most of the transcriptome is constructed with ncRNA. It is now known that RNAs, which were seen as a simple information carrier between the information store and DNA-protein before, play a very important role in the development of organisms. NcRNAs are RNAs that cannot be translated into protein and they are a new class of RNA molecules that perform many basic regulatory functions in eukaryotes.[38-39]

RNA sequencing studies have shown that the origin of ncRNAs are anti-sense transcripts of protein-encoding genes, bidirectional promoter transcripts, intronic transcripts, enhancer in transcription, and repetitive sequences. ncRNAs are involved in many biological events such as cellular defense, transcriptional gene silencing, and chromosome remodeling. Short ncRNAs refer to ncRNAs that are shorter than 50 nucleotides in length, while long ncRNAs (lncRNAs) refer to ncRNAs longer than 200 nucleotides. The most studied and known group of short ncRNAs are miRNAs. Disruption of miRNA regulation has been shown in all human malignancies. There are miRNAs that act as oncogenics (oncomir) as well as those that act as tumor suppressors. LncRNAs are known to have important roles in many biological events such as stress response, development, embryonic stem cell potential, chromatin remodeling, cell cycle, migration and metabolism. Its contribution to cancer formation is different. The data obtained show that the main role of lncRNAs guides the chromatin modifying complex. LncRNAs are known to have important roles in many biological events such as stress response, development, embryonic stem cell potential, chromatin remodeling, cell cycle, migration and metabolism. Its contribution to cancer formation is different. The data obtained show that the main role of lncRNAs guides the chromatin modifying complex. LncRNAs can function as oncogene or tumor suppressors during cancer progression. Further studies on the roles and mechanisms of LncRNAs in cancer have identified new lncRNA-based treatment strategies in the treatment of human cancers.[40-45] Let us examine in detail two of the studies in the literature on non-coding RNAs. Song et al reached some conclusions in their study on non-coding RNAs. These results suggest that non-coding RNAs can alter the expression of proteins in cancer networks. Here, the authors reveal a regulatory network in gastric cancer; thereby klaudin-4 expression is reduced by specific miRNAs, which then bind by specific lncRNAs acting as competitive endogenous RNAs (ceRNAs) resulting in increased expression of klaudin-4.[46] Smolander et al conducted a study comparing biological information contained in mRNA and non-coding RNAs for classification of lung cancer patients. As a result of this study, the authors underline the importance of general ncRNAs in understanding the complex etiology of lung cancer and recommend similar studies for other types of cancer and possibly other complex disorders.[47]

Nucleosome Remodeling and Epigenetics

Recognized roles for nucleosome remodeling elements involve local nucleosome remodeling at regulatory factors to affect specific gene expression programs, as well as assuring the completeness of the chromatin fibre by nucleosome formation and spacing, and lastly their role in the changing of histone versions. Remodeling elemets may have other, less reconnoitered functions as well. Remodelers have been shown to use ATP-dependent DNA translocase activities to modulate the chromatin assembly of non-histone substrates. As a result, nucleosome remodeling enzymes are involved in the assembly and propagation of epigenetic chromatin states.[48] Studies on nucleosome remodeling and epigenetics are few. In February 2021, Feng et al's article on nucleosomes and epigenetics from a chemical perspective was published. In this article, it was mentioned that with the continuous development of research approaches such as Cryo-EM, FRET and next-generation sequencing for genome-wide analysis of nucleosomes, understanding of nucleosomes is getting deeper and deeper.49 More precise information will be obtained as a result of future studies on this subject.

Epigenetics in Nnutrigenomics

Today, due to the change in lifestyle and eating habits, people are more at risk for diet-related diseases and cancers. Studies have found that dietary changes significantly reduce the risk of disease. Nutrigenomics is a relatively new discipline, but it has enormous potential that may apply to the prevention and management of some carcinomas and diseases. Omega 3 fatty acids are the best example of nutrient and gene interaction that do not involve DNA methylation; Some bioactive food compounds have a proven role

in cancer prevention through an epigenetic mechanism. Folate, zinc, and selenium have anticancer properties that are involved in DNA repair. In addition, consumption of multivitamins has been shown to inhibit methylation of cancer cells. As a result, nutrigenomic status has an effect on cancer by affecting epigenetic modifications.[50]

Let's review some of the researches and articles in the literature on epigenetics in nutrigenomics. In an article by Dadon et al on-vitamin A and epigenetics, they found that retinoic acid is a powerful agent that can induce changes in epigenetic modifications that produce various effects on the phenotype[51]. Bakulski et al examined the data of 249 families on prenatal multivitamin use and MTHFR genotype are associated with newborn cord blood DNA methylation in their study. Health history and biological samples were collected from the mothers, fathers, older probands with autism spectrum disorder, and baby siblings. Families were followed from pregnancy until the subsequent child was 36 months of age. Multivitamin intake before maternal pregnancy was found to be associated with cord blood methylation depending on the maternal MTHFR genotype[52]. Levine et al.'s study on the relationship between the maternal use of folic acid and multivitamin supplements before and during pregnancy and the risk of autism spectrum disorder in children, the data of 45,300 children were analyzed. Maternal exposure to folic acid and multivitamin supplements before and during pregnancy was associated with a reduced risk of ASD in offspring compared to offspring of mothers without such exposure[53].

CONCLUSION

Understanding the importance of epigenetic mechanisms in cancer as a result of the studies carried out has brought cancer diagnosis and treatment to a different dimension. Although it passes the replication, transcription and translation stages in protein formation, the answer to when, where, how and to what extent these stages are hidden within epigenetic mechanisms. Epigenetic mechanisms affect the tumor behavior and thus the clinical course. Being a biomarker that will determine the diagnosis, treatment and prognosis will enable its use in the diagnosis and treatment of many cancers in the future. Since multivitamin consumption inhibits methylation of cancer cells, nutrigenomine's effect on cancer by affecting epigenetic modifications is promising. We believe that future studies on the relationship between epigenetic mechanisms and cancer will be hope for cancer treatment.

Conflict of Interest

None declared by the authors.

Financial Disclosure

None declared by the authors.

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