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Review Article

Role of epigenetic mechanisms in various cancer therapies

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ABSTRACT

Epigenetics play a role not just in the normal functioning of the cell and its development, but also in diseases like neurological diseases and cancer. Epigenetic therapies can help to resolve non-identical problems of these pathophysiological conditions. Cancer is a complex disease with both genetic and epigenetic origins. The importance of epigenetics in cancer has been identified, and the field has emerged rapidly in recent years. Epigenetic and genetic alterations contribute to the initiation and progression of cancer. Epigenetic modifications introduced genetic changes, and usually occur at an early stage in development of a neoplasm, but may also be involved in its invasion and spread. Recent technological advances in genetics and epigenetics offer a better understanding of the underlying epigenetic alterations during initiation and in the progression process of the human tumors.

Keywords: Epigenetic, Cancer, Histone, DNA-Methylation

Introduction

The term epigenetics currently refers to the mechanisms of temporal and spatial control of gene activity that do not depend on the DNA sequence, influencing the physiological and pathological development of an organism. The molecular mechanisms by which epigenetic changes occur are complex and cover a wide range of processes including paramutation, bookmarking, imprinting, gene silencing, carcinogenesis progression, and most importantly regulation of heterochromatin and histone modifications. The term 'epigenetic' was coined by the developmental biologist, Conrad Hal Waddington, in 1942.[1] Robin Holliday defined epigenetics as the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms. One of the best examples of epigenetic changes in eukaryotic biology is the different developmental stages from the single fertilized egg, the zygote, to a fully grown organism. Modern biology uses epigenetic changes as molecular tools for finding and treating various diseases including cancer.[2]

Cancer is a multi-step process derived from combinational crosstalk between genetic alterations and epigenetic influences through various environmental exposures. Moreover, it has been well documented that environmental exposure to nutritional, dietary, physical, and chemical factors could alter gene expression and modify individual genetic susceptibility through changes in the epigenome (Figure 1).[3] Several distinct but intertwined mechanisms are known to be part of the epigenome which includes DNA methylation, histone acetylation, poly-ADP ribosylation and ATP-dependent chromatin remodeling.[3,4-7]

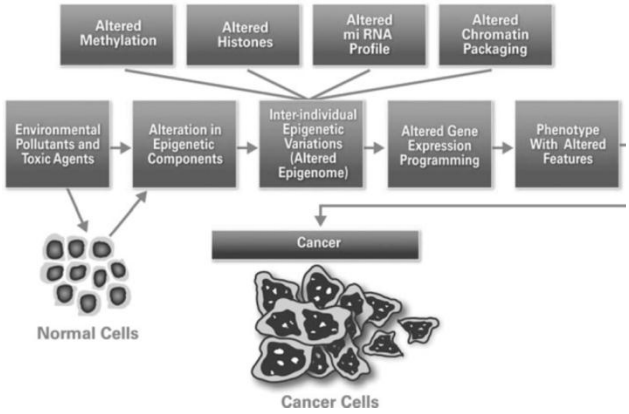

Figure 1: Factors contributing to carcinogenesis.[3]

Epigenetic mechanisms controlling gene transcription are frequently involved in cell proliferation, differentiation, and survival and are casually linked with malignant development. Alterations in epigenetic processes including chromatin modifications such as DNA methylation and histone acetylation are common targets studied in cancer epigenomics. It has been shown that half of all tumor suppressor genes are inactivated in cancers more often by epigenetic, than by genetic, mechanisms. Growing evidence suggests that bioactive dietary components impact epigenetic processes often involved with reactivation of tumor suppressor genes, activation of cell survival proteins, and induction of cellular apoptosis in many types of cancer. In addition to transcriptional silencing of tumor suppressor genes and protein expression, noncoding microRNAs can regulate expression of a myriad of cellular proteins by affecting mRNA stability and translation by epigenetic processes in cancer progression. Interestingly, these miRNAs can control the expression of various epigenetic modifying enzymes such as DNA methyltransferases (DNMTs), histone methyltransferases (HMTs), and histone deacetylases (HDACs) involved in carcinogenesis processes. Recent evidence suggests that bioactive dietary components can also target various oncogenic or tumor suppressive miRNAs to alter the gene expression profile in cancer prevention. In fact, miRNA profiles are now being used to classify human cancers. Further, miRNAs can directly or indirectly regulate cancer progression either by acting as cancer suppressors or by altering epigenetic modifying enzymes, respectively. In particular, miRNA-221 and miRNA-222 target, an oncogene, and therefore function as tumor suppressors in erythroblastic cells and other human solid tumors. Furthermore, the miRNA-29 family can directly regulate the expression of DNMTs and increase expression of DNMT thereby causing a global genomic hyper methylation and silencing of methylation sensitive tumor suppressor genes such as FHIT and WWOX.[1,5,8-11]

Epigenetic mechanisms related to cancer

DNA methylation

DNA methylation plays a well-defined role in both development and disease, including cancer.[4] First identified in 1975, CpG island (CGI) methylation was shown to function as a relatively stable alteration on DNA that can serve to silence gene transcription. We now understand that DNA methylation is much more dynamic and complex, with diverse epigenetic consequences linked to varied genomic locations of where this mark occurs. For example, DNA methylation at gene promoter CGIs potently blocks the initiation of transcription, whereas methylation within CpG-poor gene bodies may actually facilitate elongation and influence patterns of alternate splicing. In addition, DNA methylation is frequently found in repeat-rich areas of the genome and is vital for both chromosomal and genomic stability, possibly through the repression of retroviral transposons. Still, the role for this epigenetic mark at other regulatory regions, such as enhancers and insulators, has yet to be determined. Regardless, aberrant methylation in human cancer is a defining feature, with global promoter CGI hypermethylation and non-CGI hypomethylation widely reported. Furthermore, local variations in methylation at only several key loci have been shown to be sufficient for carcinogenesis. Importantly, these altered patterns of DNA epigenetic marks are frequently accompanied by a critical imbalance in transcriptional programs involving differentiation and stem cell

maintenance, thereby initiating carcinogenesis and sustaining growth. DNA methylation can function to silence tumor suppressor genes along with genetic mutations. For example, in the case of hereditary gastric cancer, methylation of CDH1 (which encodes the E-cadherin tumor suppressor) can function as a "second hit" and cause gastric cancer when the first allele is mutated. In sporadic cancers, tumor suppressor genes that are mutated in hereditary versions of the disease are frequently silenced by DNA methylation instead. For example, in hereditary nonpolyposis colon cancer (HNPCC), MLH1 inactivation via mutation can lead to microsatellite instability (MSI) and tumorigenesis, whereas in sporadic colon cancers, MLH1 is frequently silenced by methylation. These data and others indicate that aberrant DNA methylation can work along with genetic alterations to promote tumorigenesis (Figure 2).[12,13]

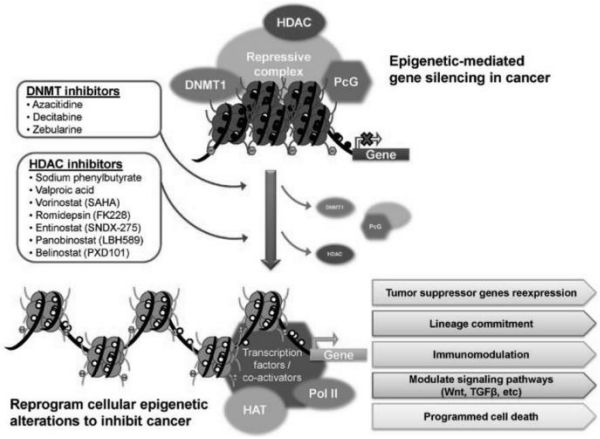

Figure 2: DNA methylation-mediated aberrant gene silencing in cancer involves transcriptional repressive complexes in the gene promoter region and interactions between DNA methylation machinery, chromatin modifiers (such as histone deacetylase, HDAC) and polycomb (PcG) proteins. HAT: histone acetylase. Pol II: RNA polymerase II.[12,13]

Pharmacological inhibition of individual components in the repressive complex with DNMT inhibitors and HDAC inhibitors, either alone or in combination, may result in DNA demethylation and complex disintegration leading to reactivation of critical genes and reversal of genome-wide epigenetic alterations in cancer through resetting multiple cellular processes, including lineage commitment, immunomodulation, major cell signaling pathways, programmed cell death, and others.

Histone acetylation and methylation

In 1964, Vincent Allfrey prophetically surmised that histone modifications might have a functional influence on the regulation of transcription. Many histone modifications play important roles in epigenetic alterations, and acetylation and methylation are the two main histone modifications that have been clinically linked as predictors for cancer progression.[14] These histone modifications induce chromatin alterations that allow access to the various transcriptional activators and/or repressors at gene promoters, and they therefore play an important role in gene regulation and carcinogenesis. Histones are subject to different types of reversible covalent posttranslational modifications including, but not limited to, lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation. These modifications occur primarily within the histone amino-terminal tails protruding from the surface of the nucleosome as well as on the globular core region and regulate key cellular processes such as transcription, replication, and repair. Specific histone modifications appear to act as programmed "codes" which can be identified by specific proteins to bring about distinct downstream events such as transcriptional activation or repression. The mechanism of inheritance of this histone code, however, is still not fully understood (Figure 3).[15,16]

Chromatin remodeling

In addition to gene regulation via covalent histone tail modifications, the ATP-dependent chromatin remodelers also shape chromatin structure and thereby affect gene expression patterns. In the past several years, protein components of the SWI/SNF complex have been found to be frequently inactivated in cancer, and

subsequent work has solidified their status as bona fide epigenetic tumor suppressors.[17,18]

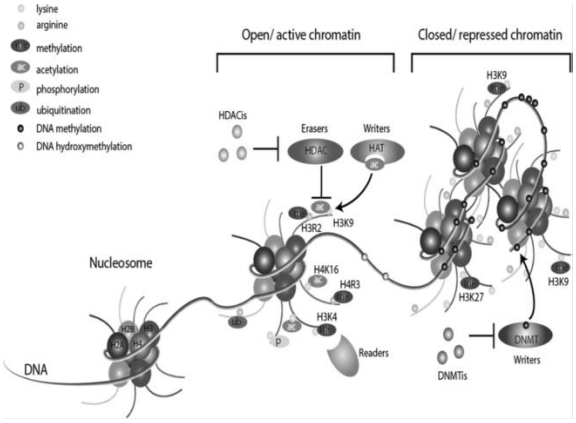

Figure 3: Epigenetic enzymes and their inhibitors. The figure shows the interactions between epigenetic enzymes (writers, erasers, readers) and nucleosomes. The nucleosome core consists of a histone octamer (mainly two copies each of H2A, H2B, H3 and H4) that is wrapped by a nuclear DNA strand of 147 bp. DNA methylation and hydroxymethylation are depicted as black and grey circles, respectively. DNA methylation is induced by DNA methyltransferases (DNMTs). To inhibit DNA methylation, DNMT inhibitors (DNMTis) are used to target and suppress DNMTs. Histone tales can be post-transcriptionally modified using enzymes such as histone acetyltransferases (HATs). Histone acetylation can be inhibited by histone deacetylases (HDACs), and HDAC inhibitors (HDACis) can be used as HDAC suppressors.[15]

Epigenetic in cancer diseases

Although in the last decade several cancer pathologies have been associated to specific epigenetic changes, the way in which epigenetic modifications are regulated is still largely unknown. In this section we describe the current knowledge linking various cancer types with epigenetic targets, considering that demonstrated cause-consequence might not necessarily indicate that these targets are validated for anticancer drug design purposes. In this review we summarized the connections between the most important cancer diseases and the various classes of epigenetic targets, associating them to relevant drug discovery information.[19-21]

Breast cancer

Epigenetic alterations such as DNA methylation and chromatin remodeling play a significant role in breast cancer development and, although extensive research has been done, the causes, mechanisms and therapies of breast cancer are still to be fully elucidated.[22-24] Epigenetic changes in different classes of this type of cancer have been studied, including: estrogen receptor positive (ER+), that are estrogen-level dependent; estrogen receptor negative (ER-), whose tumor cells are not responsive to estrogen thus resistant to antiestrogenic drugs such as tamoxifen and aromatase inhibitors; progesterone receptor (PR); and human epidermal growth factor 2 (HER2) related cancers. A number of genes have been identified to be aberrantly methylated in breast cancer and their number is rapidly growing. [25-29]

Lung cancer

Epigenetic changes in lung cancers contribute to cell transformation by modulating chromatin structure and specific expression of genes, these include DNA methylation patterns, covalent modifications of histone and chromatin by epigenetic enzymes, and micro- RNA. All these changes are involved in the silencing of tumor suppressor genes and enhance the expression of oncogenes. Genome-wide technologies and bioinformatics studies demonstrated that global alterations of histone patterns are linked to DNA methylation and are causal in lung cancer. These techniques were also used for the prediction of specific miRNAs targeting the epidermal growth factor receptor (EGFR) in lung cancer. Many genes were found to be silenced by methylation promoters in lung cancers in response to radiation stimuli. DNA methylation patterns may also predict early recurrence of stage I non-small-cell lung carcinoma (NSCLC).[23,30-32]

Pancreatic cancer

Pancreatic cancer (PC) is by far an incurable disease with an estimated 168,800 annual fatalities worldwide translating to approximately

20 deaths every hour. PC is often called 'the silent killer' because early stages of the disease often does not cause any symptoms so this leads to PC being diagnosed at a very late stage when it is not amenable to surgery or standard chemotherapy Emerging research in this area has led to the identification and characterization of deregulated miRNAs, which have generated a renewed interest and hope in that novel targeting of miRNAs may lead to a better clinical outcome for patients diagnosed with PC. However, recent evidence suggests that miRNAs are also under a highly coordinated system of epigenetic regulation emphasizing the fact that the design of miRNAs as targeted therapy may not be as simple as originally anticipated. For a successful miRNA-based therapeutic regimen, a holistic integrated approach may be required to take into account because of these emerging epigenetic regulatory mechanisms.[33,34]

Kidney cancer

Kidney cancer accounts for 2% of all adult cancer malignancies and the majority of them (80-85%) are renal cell carcinomas (RCCs) originated from the renal parenchyma. While the direct causes of this type of cancer are still vaguely defined, smoking and chemical carcinogens (e.g. asbestos and organic solvents) have been related to renal carcinogenesis. Furthermore pathologies like obesity, hypertension and the use of antihypertensive medications, have been reported as risk-factors for RCCs. Stepwise accumulation of DNA methylation has been observed by comparing normal renal tissues, renal tumor tissues and non-tumor renal tissues of patients with renal tumors.[35] These results highlighted that regional CpG patterns may participate in the early and precancerous stage of renal carcinogenesis. On the contrary, DNA hypomethylation does not seem to be a major event during renal carcinogenesis. DNA methylation alterations at a precancerous stage may further predispose renal tissue to epigenetic and genetic alterations, generating more malignant cancers and even determining the patient outcome. At present there are few clinical trials of Phase I/II for testing inhibitors of HDACs in advanced RCC.[23,36]

Gastric cancer

Gastrointestinal (GI) carcinogenesis causes some of the most common types of tumors worldwide, including esophagus, stomach, bowel, and anus. Even thought it has been recognized that the major reason for GI carcinogenesis resides in at least one genetic mutation that either activates an oncogene or inhibits the function of a tumor suppressor gene, recent data indicate that epigenetic abnormalities are critical in regulating benign carcinogenesis and eventual malignant transformation in gastorointestinal (GI) carcinogenesis. In particular aberrant histone acetylation regulated by HATs and HDACs have been linked to gastric cancer. Epigenetic alterations have also been identified in presence of Epstein-Barr virus, while *Helicobacter pylori*, which constitutes a main cause of gastric cancer, was shown to reduce HDACs activity. These data suggest that pharmacological actions of HDACi in GI might be detrimental or beneficial depending on the clinicopathological context. Despite the fact that various links between GI cancer and HATs and HDACs have been identified, comparing to other cancers, fewer progresses have been reported to treat GI carcinogenesis with epidrugs. A Phase I study has combined Vorinostat with radiotherapy in GI carcinoma. This, as well as other studies, created foundations for additional initiatives to improve the therapeutic potential of HDACi and other epigenetic enzymes for GI tumors.[23,37,38]

Hepatocellular carcinoma (liver cancer)

Hepatocellular carcinoma (HCC) originates from hepatocytes and is the most common liver cancer. Cancer rates and etiology of HCC vary considerably by age, gender, ethnic origin, lifestyle (in particular alcohol abuse and environmental pollution. Other factors include the infection by hepatitis B and C virus (HBV and HCV), exposure to aflatoxins, hypertension and diabetes. Both geetic and epigenetic factors form the molecular basis of HCC. Epigenetic alterations may predispose to genetic changes and, *vice versa*, genetic changes may also initiate aberrant epigenetic modifications. DNA methylation and various histone modifications,

as well as RNA interference, have been reported as epigenetic events contributing to HCC development. It should be remarked that the use of epigenetic biomarkers for detecting hepatocellular carcinoma has expanded the potential for non-invasive screening of high-risk populations. However, the road to develop small-molecule compounds targeting epigenetic enzymes for HCC cancer treatment is at its beginning. Presently only HDAC is have been studied for the treatment of HCC.[23,39]

Gynecologic cancer

Gynecologic cancer includes any cancer that occurs in the female reproductive organs. There are five frequently occurring gyne-cologic cancers: ovarian, cervical, endometrial (uterine), vaginal, and vulvar. Gynecologic cancers usually have high mortality rates, because it is difficult to detect the cancer in early stage. Ovarian cancer is the most lethal gynecologic cancer. In advanced ovarian and endometrial carcinomas, current therapies that are initially responsive evolve to a fully drug-resistant phenotype. Among the factors that contribute negatively to the progression and therapeutic resistance against ovarian and endometrial cancer, there are several genetic mutations and epigenetic anomalies which are frequent in both malignancies.[40,41]

Conclusions

In this review, we described the epigenetic mechanism that contributes to assets maintenance of self-renewal feature for cancer cell, which include change in DNA and histone-methylation, chromatin remodeling in many different condition. The development of small molecule inhibitors for specific methyl-transferases and methyl-readers has provided novel strategies to target the epigenetic processes that are disrupted in malignant cells. Sequence-specific, engineered proteins attached to chromatin remodeling enzymes have the pivotal advantage to target specific locus associated with malignant progression.

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