Review Article

Epigenetics and cancer

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ABSTRACT

The activation of oncogenes and/or the deactivation of tumor suppression genes involve uncontrolled cell growth which leads to the development of cancer. Downregulation of cell adhesion receptors necessary for tissue-specific, cell-cell attachment, as well as upregulation of receptors that enhance cell motility, is required for metastasis. These characteristics can be modified by epigenetic changes including histone modifications, DNA methylation, and DNA hydroxymethylation. Signaling pathways that regulate apoptosis and autophagy, as well as microRNA, include targets for these epigenetic changes. Predisposed normal cells change to cancer progenitor cells that, after growing, experience an epithelial-mesenchymal transition. Epigenetic medication seems to enhance the action of traditional medicine, usually by demethylating and reexpressing tumor suppressor genes to inhibit tumorigenesis. Adopting epigenetic alteration as a brand new hallmark of cancer could be a logical and necessary step that may additionally encourage the event of novel epigenetic biomarkers and therapeutics.

KEY WORDS: Apoptosis, Cancer, Demethylation, Epigenetics, Epithelial-mesenchymal transition, Hydroxymethylation, Metastasis, Methylation, MicroRNA, Therapeutics

INTRODUCTION

Cancer includes uncontrolled cell development, which pursues the enactment of oncogenes or potentially the deactivation of tumor suppressor genes which causes uncontrolled cell cycle progression and inactivation of apoptotic mechanisms.[1] As indicated by the hallmarks of cancer, self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion (metastasis), these abilities lead to the advancement and progression of cancer.[2] Improvements in the applied concept of cancer biology in the previous decade have directed to the current proposal that reprogramming of metabolism and evasion of immune destruction be accepted as additional hallmarks.[3] Thus, it is suggested that epigenetic alteration should be dignified another hallmark of cancer and thus a further emphasis for study for the next generation of cancer therapies. In this review, we will highlight the role of epigenetics in carcinogenesis and the possible therapeutics derived from this perspective.

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STATISTICS

Cancer is the second driving reason for death globally and is in charge of an expected 9.6 million deaths in 2018 [Figure 1]. Comprehensively, around one of six deaths is due to cancer. Around 70% of deaths from cancer occur in low- and middle-income countries.[4] Hence, the health of all human societies is affected due to cancer. Unfortunately, it is a variable disease at the tissue level and this variability is a major challenge for its specific diagnosis, followed by the efficacy of treatment.[5]

CAUSES

Cancer causes by a sequence of succeeding mutations in genes so that these mutations alter cell functions. Chemical compounds have an observable role of forming gene mutations and cancer cells. In addition, smoking consists of several carcinogenic chemical compounds that lead to lung cancer.[6] Remarkably, the cytoplasm and nucleus of cells are affected directly or indirectly by the environmental chemical substances with carcinogenic properties and lead to genetic disorders and gene mutations.[7-10] About 7% of all cancers comprise viruses, bacteria, and radiation rays are other carcinogenesis factors.[11]

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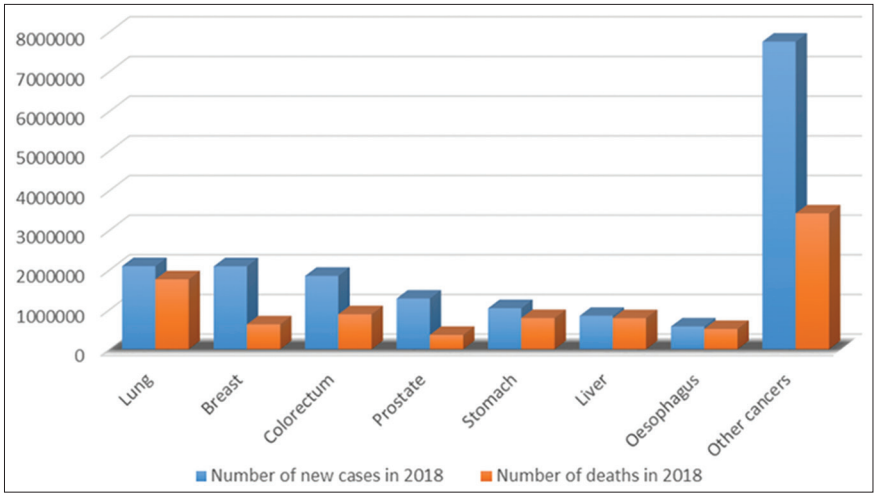

Figure 1: Statistics of cancer worldwide

EPIGENETIC

In general, cancer disrupts cellular relations and leads to the dysfunction of significant genes. This disturbance is affectional within the cell cycle and results in abnormal proliferation.[12,13] Proto-oncogenes are responsible for cell division and growth below traditional condition but become oncogenes all through genetic mutations that are most dangerous for cell existence.[14] In addition, the absence of tumor suppressor genes triggers uncontrolled cells division.[15] Epigenetics could be a dynamic scenario throughout the study of cell fate and epigenetic modifications such as deoxyribonucleic acid methylation, histone modifications, and nucleosome position that plays necessary roles in cancer development.[16,17] Cancer cells are characterized by an unlimited reduction in desoxyribonucleic acid methylation (about 5–6% reduction within the total amount of 5-methylcytosine).[18]

DNA METHYLATION

Epigenetic variations are modifications in gene expression, freelance of changes in deoxyribonucleic acid sequence. Numerous epigenetic modifications, such as deoxyribonucleic acid methylation and hydroxymethylation, simple protein acylation and methylation, and changes in little non-coding RNAs, have intense effects on gene expression. DNA methylation at CpG islands has been revealed to silence gene expression by officious with transcriptional machinery.[19,20] For decades, cancer development was attributed to strictly genetic mechanisms; however, a growing body of proof has discovered that a lot of its quality is often directly attributed to epigenetics.[21] Cell cycle progression and differentiation are firmly controlled procedures with advanced regulative mechanisms, and epigenetic changes will have profound effects on these processes.[22]

HYDROXYMETHYLATION

The current finding of 5-hydroxymethylcytosine (5 hmC) in human tissue has led to noteworthy attention in the potential functions of this novel DNA modification.[23] 5 hmC levels are found to be distinctly reduced in carcinomas of the prostate, breast, and colon. However, 5 mC levels were sole with modesty reduced, indicating that worldwide DNA hypomethylation could not account for the reduction in 5 hmC. Even low microscopic anatomy grade lesions confirmed a reduction in 5 hmC, probably revealing loss of 5 hmC as an early event in carcinogenesis.[24]

APOPTOSIS AND AUTOPHAGY

Tumor progression is encouraged by epigenetic silencing of tumor suppressor genes through inhibition of apoptosis in cancer cells. Apoptosis is an extremely controlled procedure of cell death in the growth and preservation of a typical cell population in mature organisms. Hence, a key feature of carcinogenesis is deregulation of apoptosis pathways. There are basically two pathways of apoptosis: Intrinsic and extrinsic. The intrinsic pathway includes a modest balance between antiapoptotic Bcl-2 and proapoptotic BAX; an excess of BAX permeabilizes the mitochondrial membrane to cytochrome c through Apaf-1 signaling.[25] Activating mass proteolysis and cell death, cytochrome c triggers caspase 3 through caspase 9. Regulators such as XIAP and Bcl-2 family proteins inhibit this pathway, which is upregulated in numerous forms of cancer.[26] Cell surface death receptors introduce the extrinsic pathway, the ligands for which are typically in the tumor necrosis factor-α family. The death receptors trigger caspase 8, which further activate caspase 3 through Jun kinase to cause apoptosis. This pathway is negatively regulated by the proteins FLIPL and FLIPS.[27] In cell death, an important role is also played by epigenetic control

of autophagy. In cancer cells, epigenetic alterations related to oncogenes negatively control the autophagy, demonstrating that autophagy is a tumor suppressive. These genes include Akt-1, Bcl-2, and Ras.[28,29]

MICRORNA

MicroRNAs (miRNAs) are non-coding forms of RNA contained around 20 nucleic acids, which purpose is to regulate messenger RNA (mRNA) by binding to the 3' untranslated region (3' UTR) of the mRNA and activating degradation or inhibiting translation.[30] MicroRNAs are involved in the growth and metastasis of the many cancers. Varied studies over the past decade have elaborated the association between expression levels of miRNA and carcinogenesis.[31] Epigenetic changes, notable alterations within the methylation standing of DNA coding for miRNA, are seemingly one of the important reasons behind altered miRNA expression levels in cancer cells.[32] Since then, aberrant methylation of DNA coding for specific miRNAs has been related to abnormal levels of these miRNAs in varied cancers, as well as each solid tumors and blood cancers.[33]

EPITHELIAL-MESENCHYMAL TRANSITION (EMT)

An EMT is accompanied by the development of precursor cells to mature cancer cells in epithelial cancers. EMT is categorized by a decrease in cell-cell adhesion and an increase in cell motility. The receptors needed for motility are upregulated and the cell-cell attachment receptors are downregulated. Few of the examples of such receptors are E-cadherin (E-cad), integrins, and their ligands. It has been assumed that EMT gives dispersed cancer cells with the capacity to overcome systemic dormancy and start off metastatic outgrowth. This is able to do by downregulating E-cad expression or activity, separating cell-cell junctions, invading the surrounding tissues, and intravasation the vasculature or lymphatic system.[34,35] In completely distinguished cells, E-cad functions to preserve cell-cell junctions, thus preventing aberrant cell proliferation and migration. Therefore, epigenetic silencing of E-cad is a common characteristic of systemically invasive cancer.[36]

Clinical Features of Cancer and Therapeutics

The new paradigm of drug development involves targeting multiple hallmarks of cancer at the same time. Epigenetic and non-epigenetic medicine that reexpresses tumor suppressor genes ought to sensitize the cancer cells to lower doses of ancient cytotoxic drugs.[37] Clinical studies recommend that combination treatment with epigenetic medicine and normal chemotherapy may be a powerful treatment paradigm that is capable of potentiating classical treatments and reducing relapse within the context of the many different kinds of cancer. It is probable that these styles of medical care are simpler as a result of they kill progenitor cancer cells.[1]

CONCLUSION

This review summarizes some current literature on epigenetics and cancer. Several epigenetic changes, such as hypomethylation of oncogenes, hypermethylation of tumor suppressor genes, depletion of hydroxymethylation, changes of histone acylation and methylation patterns, and miRNA expression level variations, are far-famed to be related to several cancers. Further studies are expected to elucidate; however, these variations are generated and, in turn, however, they mediate the growth of metastatic cancer progenitor cells. The information of this mechanism is not solely necessary to grasp; however, cancer cells rework and acquire resistance to therapy, however, are going to be priceless within the style of harder epigenetic medicine. These treatments, together with ancient therapies such as surgery, radiation, and ancient therapy, can allow targeting of cancer progenitor cells and sure cut back the many mortality related to cancer decline.

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