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Review Article

Review of cancer from perspective of molecular

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ABSTRACT

Cancer in the broader sense refers to more than 277 different types of cancer disease. Scientists have identified different stage of cancers, indicating that several gene mutations are involved in cancer pathogenesis. These gene mutations lead to abnormal cell proliferation. Genetic disorders caused by heritance or inheritance factors have a pivotal role in the increase of cell growth. With the assistance of technological advances in bioinformatics and molecular techniques, additional information has been obtained that can be useful for early diagnosis and proper treatment. The effects of drugs on patients with cancer can predict and even manage some aspects of side effects. In recent years, carcinogenesis mechanisms have been detected by molecular genetic studies. The results of these studies led to an improved understanding of the role of genetic disorders in cancer formation. In this study, our aim was to review molecular aspects of cancer.

1. Introduction

Cancer is the second leading cause of mortality worldwide. Overall, the prevalence of cancer has actually increased; just in the United States alone, approximately 1,665,540 people suffered from cancer, and 585,720 of them died due to this disease by 2014 [1]. Therefore, cancer is a serious problem affecting the health of all human societies. Unfortunately, it is a variety disease at the tissue level and this variety is a major challenge for its specific diagnosis, followed by efficacy of treatment [2,3]. In men, the highest percentages of cancer types occur in the prostate, lung and bronchus, colon and rectum, and urinary bladder, respectively. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid, respectively. This data indicates that prostate and breast cancer constitute a major portion of cancer in men and women, respectively [4]. For children, the highest percentage types of cancer disease are blood cancer, and cancers related to the brain and lymph nodes, respectively [5,6]. Cancer occurs by a series of successive mutations in genes so that these mutations change cell functions. Chemical compounds have an obvious role of forming gene mutations and cancer cells. In addition, smoking involves several carcinogenic chemical compounds that lead to lung cancer [7]. Interestingly, environmental chemical substances with carcinogenic properties influence directly or indirectly the cytoplasm and nucleus of cells, and lead to genetic disorders and gene mutations [8–11]. Viruses, bacteria and radiation rays are other carcinogenesis factors, comprising about 7% of all cancers [12]. In general, cancer disrupts cellular relations and results in the dysfunction of vital genes. This disturbance is affective in the cell cycle, and leads to abnormal proliferation [13,14]. Proto-oncogenes are responsible for cell division and growth under normal condition, but become oncogenes during genetic mutation, which are most dangerous for cell existence [15]. In addition, the lack of tumor suppressor genes triggers uncontrolled cells division [16]. Normally, repair genes translate to protein and enzymes that have repairing properties and more than 30 types of detected repair proteins [17]. Removing uracil from DNA bypasses the DNA damage and removes the main DNA lesions induced by ultraviolet light, which are essentially the functions of repair genes to successfully repair DNA [18].

Epigenetics is a dynamic situation during the study of cell fate and epigenetic modifications such as DNA methylation, histone modifications and nucleosome position, which play important roles in cancer formation [19,20]. Cancer cells are characterized by a vast reduction in DNA methylation (about 5–6% reduction in the total amount of 5-methyl cytosine) [21]. Overall reduction of monoacetylated H4K16 forms the majority of histone modifications in cancer cells [22]. All families of chromatin modifying proteins are associated with cancer, although in most cases, the molecular

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mechanisms underlying their functions remain unknown [23]. In this study, we reviewed cancer from the perspective of the molecular level, in order to get a closer look at this disease.

2. Review method

Initially, we searched research papers using keywords such as cancer and molecular process, cancer and treatment and molecular aspects. Subsequently, the papers that matched such word criteria were fully reviewed and their findings duly noted.

3. Cancer from the molecular prospective

Genetic changes that lead to oncogene generation and genetic disorders include chromosomal translocation (gene Bcr and oncogene Abl in chronic blood cancer), point mutation (Ras gene in colon cancer), deletion (Erb-B gene in breast cancer), amplification (N-myc in neuroblastoma), and insertion activation (C-myc in acute blood cancer). Chronic blood cancer often occurs in the elderly due to an exchange of genetic material between chromosomes 9 and 22. This condition leads to production of a biomarker called ph1, which is found in 95% of patients and can facilitate a correct diagnosis. The connection of Bcr gene to Abl oncogene results in creation of a gene new combination that translated to protein with kinase activity [24–27].

Mutation in the p53 gene leads to formation of an unusual protein that has a prominent role in disturbance of molecular process related to p53. Abnormality of these molecular and biological events leads to formation of cancer cells; therefore, the p53 gene has a complex relationship with cancer and it has been reported that p53 abnormality occurs in 60% of cancer cases. Under normal conditions, p53 plays an important role in cell division, cell death, senescence, angiogenesis, differentiation, and DNA metabolism. Additionally, the majority of mutations related to the p53 gene occur in the DNA-binding position, and the disability of genes is controlled by p53 for replication. Cooperation of p53 with CDK1-P2 and CDC2 keeps cancer cells in G1 and G2 phases of cell cycle [28,29]. In fact, p53 is either an inhibitor or a promoter of cancer cells. After DNA damage has been caused by other genes, the p53 protein binds to DNA and leads to stimulation of the WAF1 gene [30,31]. This event leads to connection of p53 with CDK2, and ultimately inhibits the effect of p21 for the next stage of the cell cycle. The anti-cancer action of p53 is active during three routes stimulating, for DNA repairing proteins, induction of apoptosis, and arresting of cell cycle in G1/S phase [16,32–38].

Overall, hypomethylation primarily occurs in repeated sequences and leads to an increase of movement, and deletion of genes as well as chromosomal instability [21,39]. L1 from the LINE family is a prime example of hypomethylation, which has been observed in a range of cancers including breast, lung, and bladder cancer [40]. Hypomethylation in specific promoters can activate the ectopic expression of oncogens; for example, this condition occurs for MASPIN as a tumor suppressor gene in breast and prostate cancer. Other examples include S100P in pancreatic cancer, SNCG in breast and ovarian cancer, MAGE and DPP6 in melanoma [41]. Unlike overall hypomethylation, hypermethylation occurs only in a specific CpG region. Transcription inactivation caused by hypermethylation of promoter influences genes involved in repair (Hmlh1, WRN and BBRCA1), response to vitamin (CRBP1, RARB2), cell cycle control (P16INK4b, P16INK4a) and apoptosis (TMS1, DAPK1, and WIF-1). These events have a pivotal role in the induction of cancer [42]. Therefore, hypermethylated promoters can be considered as novel biomarkers for the diagnosis and prognosis of cancer because most studies are focused on the CpG regions of promoters. In addition, it is an important option that frequently aberrant methylation such as hypermethylation in CpG region occurs during cancer (45–65%) [43,44]. Overall disturbance in DNA methylation patterns can be due to impaired regulation of DNMT, such that it has been determined that DNMT1 and DNMT3b have a high level of expression in many tumors. In addition, miRNA regulates DNMT expression, and it has been found that the MIR-29 family reduces expression of DNMT3a, DNMT3b (directly) and DMNT1 (indirectly) [45].

Deacetylation occurs by HDAC so that this condition is involved in different tumors. The Sirtuin family is a main class of HDAC enzymes [46]. The increase of SirT1 expression and activity has been shown to have various types. In addition, cooperation between SirT1 and DNMT1 affects DNA methylation [47]. HDAC expression can be regulated by microRNA; for example, miR-449a regulates cell growth and survival during prostate cancer through suppression of HDAC-1 expression. In addition to alteration of HDAC expression in many cancers such as colon cancer, lung and leukemia, disturbance in histone acetylation occurs through ectopic mutations and deletion in HAT and its related genes. These events can be a main reason for cancer formation [48]. Moreover, cancer cells lost H4K16ac, H3K4me3, H4K20me3 and H3K27me3 [49]. Change in the distribution of histone methylation is mainly due to expression of histone methyltransferases and histone demethylase. In addition, disabling mutations in SETD2 (a histone methyltransferase) and UTX (a histone demethylase) occurs during renal carcinoma [50]. In leukemia, MLL oncoprotein leads to abnormal patterns of H3K4 and H3K29 methylation, and ultimately changes in the expression of the target genes of MLL [51].

BRG1 and BRM (as subunits of ATPase related to SWI/SNF complex) are known as tumor suppressors that manifest a pivotal role in 15–20% of lung cancer. Interestingly, it has been reported that BRG1 is a destabilizing of p53 and SWI/SNF complex, and regulates gene expression as local. The SWI/SNF complex is involved in formation of many cancers through its reaction with RB, p53, MYC, MLL, and BRCA1. Therefore, disabling of the SWI/SNF complex disrupts cell growth. In addition, changes in the position of nucleosomes leads to suppression of transcription by promoter hypermethylation. Promoter hypermethylation causes TSS occupation by nucleosomes, and this issue has been reported involving MLH1 in colon cancer. Encoding genes related to subunits of changing complexes of chromatin such as CHD5 are the main target of CpG hypermethylation during cancer. This condition leads to a reduction of its expression and a disturbance in the normal structure of chromatin [52]. In addition to the situation associated with nucleosomes position, histone variants are also associated with cancer such as an increase of MacroH2A expression during the senescence process. Thus, lung tumors along with an increased MacroH2A expression have a better prognosis due to reduction of cell proliferation amount [53].

4. Conclusion

In the past three decades, researchers have reported a substantial volume of information about genes and proteins and their roles in the production of cancer cells. In fact, the role of mutated genes in cancer cells was one of the most important discoveries. Recently, environmental factors related to genetic mutations have been identified. With the help of different molecular methods, we are able to determine the potency of gene expression and defective proteins, as well as detecting novel cancer biomarkers. These findings can be useful to treat cancer and reduce cancer complications. In addition, various studies to explore the epigenetic mechanisms and their relationship together with the development, and progression of various diseases, especially cancer are continuing. Besides, it seems that many aspects of epigenetic

remain unknown. However, by identifying all environmental factors and pivotal genes, this gives us a comprehensive map for further efforts to reduce cancer in the future.

Conflict of interest

The authors declare that there is no conflict of interest regarding this paper.

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