A Mini Review of Cancer Treatment and Epigenetic

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Abstract

Unlike genetic mutations, epigenetic disruptions are reversible therefore, it can be a promising idea to treat cancer. This strategy can be a new view in order to management and treatment cancer however, understanding of this idea has dire require performing further studies. In addition, researcher should be considering that this idea has to not obvious side effect and it led not to prominent damage. In this study, we review effect of cancer treatment based on epigenetic strategy. Finally, we found the promising effect of this idea while other aspects of a useful therapy have to perform in further studies.

Keywords: Genetic mutations; Epigenetic disruptions; Cancer; Treatment

Introduction

Cancer is a genetic disease that include 277 disease type on the other hand there are about 100,000 chemical substances with inducing cancer activity [1,2]. Cancer results from uncontrolled proliferation due to interference of environmental compounds or genetic disorders particularly genes related to cancer such as oncogenes, genes of tumor inhibitor, genes related to repair and apoptosis. When a mutation occurs in DNA, normal cells become to cancer cells under a disrupted cell growth [3]. There is a positive correlation between cancer and age so that increase of age leads to cancer susceptibility in Individuals. In addition, smoking, diet habit, infection disease and ionize and unionize rays have pivotal role in cancer cells formation [2,4]. It has been described that epigenetic is studding temporary control mechanisms related to gene activity during evolution of organism indeed it is describing anything related to cell development apart from DNA [5]. Another researcher believe that it is changing in gene function with heritability without effect on DNA sequencing [6]. Based on definition of National Institutes of Health (NIH) epigenomics project; epigenetic besides heritability changing it include Long-term and fixed changes in cell replication that usually are not inheritable [7]. Generally, it consider as a stably inherited phenotype resulting from genetic modification without changing of DNA sequence [8]. DNA methylation, nucleosomal remodeling and histone covalent modifications are three pivotal processes associated with epigenetic, which regulate gene expression at the level of chromatin [9]. They can be important options for cancer treatment; For example; using histone deacetylase inhibitors lead to good results about cancer treatment [9]. Because it have been reported that cancer cells have either epigenetic disruption or genetic alterations [10,11]. Interestingly, these event occur in all stages of cancer development [12]. Nevertheless, it is an important point that epigenetic abnormalities are reversible unlike genetic mutations [13]. In fact, genetic alterations along with epigenetic changes are common reason of cancer as shown in Figure 1 [14]. In this study, we reviewed the role of cancer treatment based on epigenetic interference.

Review Method

We considered study related to cancer treatment according to epigenetic interference by searching keywords such as Histone deacetylases inhibitors and cancer, histone methyl transferase and cancer as well as DNA methylation inhibitors and cancer. Then the papers were read and summarized here.

Cancer Treatment by Epigenetic Interference

Histone deacetylases inhibitors (HDACi) wide number purified from natural sources or synthesized and many of them have gone to the clinical study. HDACi, mostly inhibit classes HDAC IV and II, I and specific groups of III. HDACi mediate anti-tumor effects with a number of biological responses such as induction of cell death, inhibition of cell growth, suppression of angiogenesis, increase immune response [15]. Studies show that HDACi have pivotal role in interference of many genes. The basic model to describe the biological effects of HDACi is including changes in gene expression as a direct result of hyper-acetylation at a specific locus [15]. Nevertheless, we know that HDAC enzymes targets not only histones but also range of non-histone chromatin proteins, which whose regulated by acetylation [16,17]. These proteins include transcription factors such as P53, NF-κB, E2F1, which have important role in tumor formation and anti-tumor responses [18,19]. In addition, proteins that repair DNA (such as ku70), stability of the protein (Hsp90), cytoskeleton proteins such as

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tubulin and other proteins that are not directly related to the regulation of gene expression can be directly acetylated [15]. The HDACi probably effect on performance of these proteins and reduce tumor growth and survival [20]. Given that role of histone methyltransferase (HMT) in tumor genesis, lead to the production of small molecule regulator against these enzymes. Chaetocin is first HMT inhibitors and seem to have selective effects against HMT particularly Suv39 class. This inhibitor is cause of cancer cells death under *in vitro* condition, while it has not any obvious effect normal cells [21]. Chaetocin has also strong antitumor effect under *in vivo* conditions [22]. In a study, it has been reported that BRD4770 lead to reduction of cancer proliferation in PANC-1 cell lines. Indeed this study confirmed that BRD4770 has anti-inhibitory effect on histone methyltransferase G9, an enzyme with high expression in cancer types [23]. A number of DNA methylation inhibitors are under study including azacitidine, decitabine and hydralazine. Decitabine approved by FDA for treatment of myelodysplastic syndrome, while azacitidine has antitumor activity against refractory anemia and chronic leukemia myelocytes [11,24,25]. Recently, it has been approved the effect of hydralazine as an antihypertensive drug through inhibitory effect on DNA methylation [26]. Pharmacological inhibition of DNA methylation causes the enzymes entrapment and destruction of targeted-DNMT and re-expression of genes due to aberrant hypermethylation that prevent proliferation of tumor and cell differentiation and induce cell death [24]. Mechanism of DNMT inhibition by DNMTi during abrogation of tumor cells still is not well understood. But these factors reduce cancer cell growth followed by entering into new DNA. Clinical studies have been shown that short-term and manageable side effects reduced by DNMTi at appropriate and effectiveness doses and. However, long-term effects of these inhibitors need to assess [24,27].

An Example of Ovarian Cancer, Genetics and Epigenetics

Zhang et al. [28] have shown that Mifepristone increases mRNA translation rate, triggers the unfolded protein response, increases autophagic flux, and kills ovarian cancer cells in combination with proteasome or lysosome inhibitors. Cancer cells act in contrast to non-cancerous cells by increasing the expression of ER stress-associated proteins and a common the unfolded protein response (UPR), a phenomenon that occurs as an exacerbation of endoplasmic reticulum (ER) [29] Or UPR addiction [30] this allows the cancer cells to heavily rely on the UPR for survival in the environment within which they usually proliferate: reduced nutrients, acidosis, energy deficiency, and low oxygen tension (hypoxia) [31,32].

Discussion and Conclusion

Today, epigenetic is defined as study of inheritance changes in gene expression or function without any histone modifications and changes in DNA sequencing. The DNA methylation is main epigenetic mechanism as changes in nucleosomes position. In several studies, it has been shown association between epigenetic changes with the development, progression and metastasis of various types of cancer. Unlike genetic mutations, most epigenetic changes may be reversible or preventable. Therefore, restoring aberrant epigenetic events in neoplastic cells can be considered as a promising therapy method to treat or prevent cancer. It is now clear that epigenetic mechanisms along with carcinogenic mutations can be affect in promotion of tumor. Thus, management of aberrant epigenetic events as a way to target the formation and progression of cancer is a logical and effective treatment. Understanding the relationship between epigenetic and cancer is also important in prognostic of cancer. It seems that still many aspects of epigenetic are unknown and various studies need to perform in order to explore the epigenetic mechanisms and their relationship

with each other as well as with development and progression of various diseases, especially cancer. Considering on important role of epigenetic defects in the development and progression of cancer has dramatically increased in recent years. It is now known that disruption of epigenetic mechanisms can influence tumor growth. The promising effect of treatment related to epigenetic in myelodysplastic syndromes and prevention of leukemic changes is indicated starting of epigenetic disorders prior onset of cancer. Thus, epigenetic therapy is a promising way to prevent and treat malignancy. Finally, we suggest that focusing on events related to epigenetic can be a prominent strategy to treat cancer and there is dire need to do further studies in this field.

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Conflict of interest statement

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

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Contribution of authors

This work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article was borne by the authors named in this article.

Ethical approval

This research does not contain any studies with human participants or animals and was performed by the authors alone.

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