THOUSAND WORDS ABOUT...

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Thousand words about cervical cancer and epigenetics

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ABSTRACT

Epigenetic modifications include DNA methylation, DNA demethylation along with the major role fulfilled by TET protein. Epigenetic modifications refer to the regulation of gene expression without the alteration of the DNA sequence. Some of the most common epigenetic modifications include DNA methylation and demethylation, as well as the functional role of TET proteins. Epigenetic alterations are heritable traits, therefore one of the key elements to understanding the mechanisms of cancer development is to further our knowledge on the role and function of epigenetic modifications.

This mini-review takes into consideration the overview of the literature on the impact of epigenetic changes in cancer development, especially in the development of CC. Researchers believe that certain compounds are capable of inhibiting the process of DNA methylation and may play an important role in future cancer therapy.

Keywords: cervical cancer, epigenetic, DNA methylation, TET.

Introduction

Cervical cancer (CC) is one of the most common malignancies among women worldwide. An important diagnostic method of CC is the Papanicolau test, also called 'pap test'. The test consists of collecting a sample of cells from the cervix and assessing them for cytopathological changes, to diagnose the stage of the disease [1]. Despite the low cost of research, low risk of complications, high availability and low invasiveness of this diagnostic method, morbidity and diagnosis of CC is still high. Each year, there is about 500,000 new cases of CC among women and 250,000 deaths [2, 3]. This assessment takes into account exposure to risk factors such as age, early onset of coitus, number of pregnancies and deliveries [1]. There are also many studies linking cigarette smoking and the use of oral contraceptives to the development of CC [1, 4].

Progressively more studies have been focusing on epigenetics and its regulatory mechanism in the development of cancer [5], as well as leukemia [6] and CC [7]. The understanding of epigenetic regulation in normal and cancer cells has been rapidly growing since the beginning of the new millennium. This progression of knowledge has been mainly due to new technological developments and has opened the door to new opportunities such as the development of epigenetic therapies [5].

DNA methylation and demethylation

Epigenetic modifications, which include DNA methylation and histone modifications are included in the regulation of gene expression. Gene expression disorders which may occur in any population, might contribute to the emergence and progression of cancer [8]. Although infection with human papillomavirus (HPV) is obligatory, it is not the only factor contributing to the full malignant transformation. Other factors such as epigenetic modifications, might be risk factors for the devel-

opment of CC [2, 8]. It is still unclear how many different factors are linked to the pathogenesis of CC [6].

The pattern of DNA methylation is determined in the early stages of embryonic development and maintained during the whole life of the DNA methyltransferases [9]. The normal genome is not subjected to CpG island methylation, however, researchers have observed excessive methylation of CpG islands and global hypomethylation in tumorigenic transformed cells [10]. During tumor formation, epigenotype cells are significantly altered due to changes in DNA methylation. The possible changes in DNA methylation include hypermethylation of CpG islands, hypomethylation of genes normally methylated, transposition in cancer cells and induction of chromosome instability [11].

Role of hypomethylation in cancer

Hypomethylation is the overexpression of oncogenes due to the demethylation of promoter regions, causing excessive stimulation of cellular proliferation [12]. Hypomethylation may lead to alterations in gene expression, which can cause genomic instability [5]. The genes altered by hypomethylation are usually regulating growth, which is an important factor for the development of the organism or encoding enzymes [13]. Hypomethylation is frequently observed in solid tumors such as colorectal cancer or gastric cancer [12, 13].

Role of hypermethylation in cancer

Research studies have shown that hypermethylation of CpG islands is associated with transcriptional silencing of tumor suppressor genes and DNA repair genes [10]. Inhibition of the expression of these genes causes the cell to be deprived of the normal cell cycle, which leads to cell proliferation and tumor growth [12]. Some of the genes in which methylation is observed include: BRCA1, p16, hMLH1, GSTP1 or APC [12, 13].

Role of TET proteins

The family of TET (ten-eleven translocation, TET1, TET2 and TET3) proteins play an important role in the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethylocytosine (5-hmC) [7]. This family of enzymes has significant biological functions in embryonic stem cells and plays an important role in development, aging and disease [14]. It has been observed that a reduction in the concentration of 5-hmC is strongly correlated with the development of cancer. In many studies, researchers have observed the loss of TET1 expression in colorectal cancer, gastric cancer and/or in CC [7, 8, 14–16].

Epigenetic "risk factors" and cervical cancer

In a study conducted by Yin *et. all* (2016), STK31 hypomethylation was observed in the HPV16/18-positive HeLa, SiHa and Caski cell lines. In contrast, HPV-negative cell lines exhibited hypermethylation and silenced expression [17]. Li *et. all* (2015) discovered that RASSF1A promoter hypermethylation increased the risk of CC. These studies provide proof for a possible correlation between HPV infection and RASSF1A promoter methylation in the development of CC [18]. Blanco-Luquin *et. all* (2015) observed significantly longer disease-free survival and overall survival periods in adenocarcinoma (of the uterine cervix) patients with RASSF1A hypermethylation. Researchers suggest that the involvement of DNA hypermethylation in CC varies depending on the histological type and prognosis factors [19], similarly to TET2 in colorectal cancer [15].

A study by Narayan *et. all* (2004) showed the involvement of BRCA1 gene by promoter hypermethylation or down-regulated expression in CC. Researchers also observed important inactivation of genes in the FA-BRCA pathway by epigenetic alterations. This suggests that epigenetic modifications play a major role in this pathway, and therefore in the development of CC [20]. Jha *et. all* (2012) demonstrated significant hypermethylation of p73 and p53 genes by CC patients. They also observed an important correlation between tested genes with some risk factors parameters of CC [21].

Bronowicka-Kłys *et. all* (2016) showed the important reduction of TET1 transcripts in tumoral tissues compared to histopathologically unchanged tissues of CC. Simultaneously, they observed the connection between TET1, TET2 and TET3 transcripts with various clinicopathological data [7]. Similar results were observed in other studies, where a reduction of TET family proteins was demonstrated in colorectal cancer or radically lower levels of TET1 transcripts and proteins were observed in gastric cancer [15, 16].

Conclusion

Advances in genetic and epigenetic research have provided us with appropriate knowledge regarding the development of cancer. Many studies have shown that the development of cancer such as CC, can be linked to genetic and epigenetic factors. It is believed that epigenetic modifications may have an effect on the course of a disease as well as the treatment. There is still a growing interest on this topic, and a number of stud-

ies suggest that understanding the role of epigenetic mechanisms may become a key element in developing cancer therapy and prognosis factors in the future.

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