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Epigenetic Dysregulation in Oral Cancer and Its Implications

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Abstract

Malignant diseases are no longer thought of as exclusively hereditary illnesses; instead, epigenetic changes have become one of the characteristics of cancer. Both normal development and tissue heterogeneity in terms of gene expression patterns are caused by the epigenetic landscape. Cancer is currently receiving more attention to benefit from these changes in terms of new treatment approaches or diagnostic/prognostic tools, as dysregulation in these systems has been linked to the stage of the illness. Epigenetic analysis has also been used in oral cancer, and several studies have shown that a changed epigenetic substrate, in addition to genetic changes and extended exposure to environmental risk factors, partially induces the development and progression of this malignancy. This article outlines the most significant epigenetic changes linked to oral cancer and their prospective use as novel treatment targets.

Keywords: oral squamous cell carcinoma; epigenetic; DNA methylation; oral cancer

Introduction

About 650,000 individuals are affected by head and neck cancers, which rank as the sixth most prevalent malignant tumors globally and result in almost 350,000 cancer-related deaths annually. [1,2] These cancers include tumors originating from the paranasal sinus, pharynx, larynx, nasal, and oral cavity epithelium.

Both environmental and endogenous variables influence the multi-step process of oral carcinogenesis. These latter include chronic infection with the Human Papillomavirus (HPV) and use of alcohol and tobacco. [3–8] Numerous genetic and epigenetic processes that support genomic instability and the emergence and spread of tumors may be brought on by these risk factors. The genetic changes that contribute to the onset and progression of OSCC and oral premalignancy are brought on by irreversible changes in the DNA sequence, such as gene deletions, amplifications, and mutations that either activate oncogenes or inactivate tumor suppressor genes. [9, 10]

Epigenetics

Another important factor in the multistep carcinogenesis of oral malignancies is epigenetics. DNA methylation, histone modifications, non-coding RNA-mediated control, chromatin remodeling, and genomic imprinting are examples of epigenetic changes. Any heritable changes in gene expression that do not involve changes to the DNA sequence are referred to as epigenetic changes. These changes are more common than gene mutations and can last for the duration of a cell's existence or even for several generations. [11] Depending on the impact of "epimutations," which obstruct the operation of activators and suppressors on certain promoters in the chromatin environment, the transcription of each gene may fluctuate from high-level expression to total silence. [12]

All differentiation processes, except T- and B-cells in the immune system, are initiated and sustained by epigenetic mechanisms. Histone alterations, RNA-mediated silencing, and DNA methylation are examples of epigenetic inheritance. Inappropriate gene expression causes cancer and other "epigenetic diseases" when any one of these three unique and mutually reinforcing epigenetic processes is disrupted. [13–16]

Numerous studies have examined and documented the methylation rate of CDKN2A in the literature. The cell cycle regulating protein p16, which is encoded by the CDKN2A gene and maps on chromosome 9p21, prevents the action of cyclin-dependent kinases 4 and 6 and causes cell-cycle arrest in the G1 phase. In OSCC, the reported prevalence of p16 hyper methylation varies from 23% to 76%. [17–23]

DNA Methylation in Oral Cancer

It has been shown that there are notable variations in the epigenetic signatures between normal and malignant samples of oral cancer, with the tumor samples displaying elevated It has been shown that there are significant changes in the epigenetic signatures of oral cancer tumor samples compared to normal samples. The tumor samples show greater promoter region hyper methylation and genome-wide hypo methylation. [24,25] Due to the release of repetitive sequences within the genome and the potential activation of suppressed proto-oncogenes by the removal of promoter hypermethylation, hypomethylation can lead to increased chromosomal instability.

The reverse process, hypermethylation, is also seen in oral cancer, where methylation of CpG sites within the promoter sequence of tumor suppressor genes prevents transcription factors from accessing these regions and, indirectly, inhibits the production of certain genes. both hypermethylation of promoter areas and hypomethylation across the genome. Because hypomethylation releases repetitive sequences into the genome, it might lead to increased chromosomal instability. It can also potentially activate suppressed proto-oncogenes by removing promoter hypermethylation. The reverse process,

hypermethylation, is also seen in oral cancer, where methylation of CpG sites within the promoter sequence of tumor suppressor genes prevents transcription factors from accessing these regions and, indirectly, inhibits the production of certain genes. [24,25]

Certain risk factors for oral cancer have been connected to dysregulations in the epigenetic pattern of the methylation status. These risk factors include alcohol and tobacco use, as well as chronic inflammation of the oral mucosa. Smokers, for instance, have been linked to higher levels of global hypomethylation. [26,27] Several risk factors for oral cancer have been connected to dysregulations in the epigenetic pattern with respect to the methylation status, including alcohol and tobacco use, as well as chronic inflammation of the oral mucosa. Clinical research conducted on patient samples and in murine models for oral cancers, for instance, have shown that alcohol drinkers are characterized by CpG hypermethylation, whereas smokers have been linked to an elevated global hypomethylation. [26,27]

By blocking apoptotic processes and controlling the cell cycle, survivin promotes the overcoming of checkpoints and plays a significant role in oral cancer as well as other forms of cancer. [28,29]

E-cadherin is synthesized from the CDH1 gene and is responsible for keeping the adhesion between cells intact. The loss of CDH1 expression is frequent in numerous types of cancers, an event that facilitates the epithelial to mesenchymal transition (EMT) and implicitly the colonization of secondary sites (metastasis) [30]

The "new guardian of the genome," PTEN (phosphatase and tensin homolog deleted on chromosome 10) is responsible for the suppression of cell survival and proliferation, as well as differentiation, apoptosis, and invasion. It ranks second in terms of the frequency of mutations in cancer, after TP53. [31]

Histone Modifications in Oral Cancer

Although DNA hypermethylation and hypomethylation are closely related processes, the process of abnormal histone modification in oral cancer has not received as much research attention.[32]

Changes in miRNA Epigenetics in Oral Cancer Since changed expression of these sequences is linked to malignant signalling pathways, alteration of the miRNA profile is a critical event for the induction, development, invasion, and metastasis of cancer. Sethi et al. have provided a thorough presentation of the key miRNAs implicated in head and neck malignancies [33] along with their potential translated clinical function; nevertheless, the information about epigenetic modification of miRNAs is far more limited for oral cancers.

Epigenetic Therapies in Oral Cancer

Preclinical research is now being conducted to investigate the reversible nature of epigenetic alterations for therapeutic reasons in a variety of malignancies, including mouth cancer. As an inhibitor of DNA methyltransferase, zebularine treatment of the HSC-3 cell line (OSCC model) led to both a reduction in the number of cells in the G2/M cell cycle phase and impeded cell proliferation. [34] However, zebularine's untargeted nature continues to be a persistent issue for the future use of this kind of medication in clinical settings. Zebularine and cisplatin increased cell death by an apoptotic mechanism, however, when the two substances were mixed with 5-fluorouracil, the chemotherapeutic agent's effect was lessened. [35]

By inhibiting the acetylation process and maintaining the loose structure of chromatin, histone deacetylase inhibitors are becoming more and more popular in the

treatment of oral cancer. Their goal is to increase the activation of tumor suppressor genes. [36]

Additionally, miRNAs have a greater potential for altering the pathogenic epigenetic profile in oral cancer treatments. The non-coding profile of oral cancer is also changed, as is the case with other cancer types, which helps to preserve the cancer's characteristics. [37–39]

Some of the downregulated sequences may also be restored to their baseline level via epigenetic modifiers, even if the "classical" strategy involves adding exogenous tumor suppressor sequences to strengthen their expression (as well as inhibitor sequences for oncogenic miRNAs). [40]

Conclusion

It is now evident that these kinds of changes are also a component of the diverse cancer signalling, which is why epigenetic processes have gained a role in the characteristics of cancer. The reversible aspect of epigenetics, which allows the aberrant signature to be altered by administering exogenous inhibitors of histone deacetylase or DNA methyltransferase, is one consistent benefit. Since genes linked to chemoresistance, for instance, have been discovered to be hypermethylated, the notion of combining the traditional therapy with novel epigenetic modulatory drugs might greatly enhance the clinical result. The effectiveness of the traditional therapy might be greatly increased in this way.

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