EDITORIAL

Assessing the Potential Applications of Epidrugs in Epigenetic-mediated Head and Neck Squamous Cell Carcinoma

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Dear Editor,

Head and neck squamous cell carcinoma (HNSCC) is the sixth most frequent cancer globally. It arises from the squamous epithelium and is localized in the head and neck area, involving the oral cavity, pharynx, and larynx.[1] The overall survival remains poor (39.7%), despite the intensive therapy that has improved from the past. The molecular pathogenesis of HNSCC is a complex process due to the epigenetic alterations causing changes in the expression of genes associated with apoptosis, DNA repair, cell cycle, growth signaling, proliferation, and differentiation. The DNA methylation, histone modifications, and the non-coding RNAs (e.g., microRNAs, and lncRNAs) are the common epigenetic alterations that play a role in carcinogenesis.[2,3] Currently, epigenetic changes have been identified as prospective therapeutic targets in various cancers, including head and neck cancer.[3] As a result, research into new epigenetic modifying medicines that improve both chemotherapy and immunotherapy responses in HNSCC is progressing. Both preclinical and clinical initiatives to investigate epigenetic medicines as monotherapy in combination with chemotherapy or immunotherapy have been evolving in this setting.[4]

Hypermethylation of promoter regions causes the silencing of genes primarily involved in tumor suppression, such as genes in cell cycle control, DNA repair, and apoptosis pathways.[5] Alternatively, the hypomethylation of a CpG dinucleotide in the global DNA causes the activation of several oncogenes. According to research, CDKN2A, MGMT, DAPK, APC, RASSF1, CDH1, HOXA9, MLH1, CDKN2B, TIMP3, ATM, MINT31, CALCA, NPY, HS3ST2, ZNF, FAM135B, and PROM1 are the commonly observed hypermethylated genes in HNSCC. Likewise, hypomethylation causes activation of oncogenes in HNSCC such as ADG3ST2, PI3, AIM2, and SPP1 which are associated with cell cycle signaling. Changes in the environment or the treatment can cause altered methylation patterns.[6,7] As a result, enzymes such as DNA methyltransferases are important targets for cancer therapy. Reversing DNA hypermethylation with pharmacological drugs such as 5-azacytidine and zebularine (a DNA methyltransferase inhibitor) is successful adjuvant therapy for a variety of malignancies, including HNSCC.

Additionally, the epigenetic state of cancer cells is altered by post-translational histone modifications such as acetylation and methylation. Histone acetylation is a key method for controlling gene expression by influencing chromatin structure. Histone acetylation and methylation are the mechanisms having the greatest potential for predicting the onset and progression of HNSCC. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) are the key enzymes that play a crucial role in regulating gene expression by modifying chromatin structure. Interestingly, the changes in the expressions of HDACs alter the genes controlling key processes such as cell signaling, proliferation, differentiation, invasion, apoptosis, and metastasis in various malignancies. Similarly, histone methylation in post-translational modification affects the expression of cancer genes. A few histone methylation modifiers such as H3K4me3, H3K36me3, and H3K79me3 are well reported, which are involved in the activation of genes, whereas H3K27me3, H3K9me2, and H3K9me3 transcriptionally involved in gene silencing mechanisms. For instance, a member of the histone methyltransferase (HMT) family responsible for transcription (MLL1) exhibits a loss of function and affects the expression of essential genes linked with cellular differentiation, which is frequently detected in many forms of cancer.[8] A novel class of anticancer medications called HDACi controls gene expression by modifying the epigenetic process. By hyperacetylating targets, HDACi therapy returns normal gene expression and function to the cell. It has

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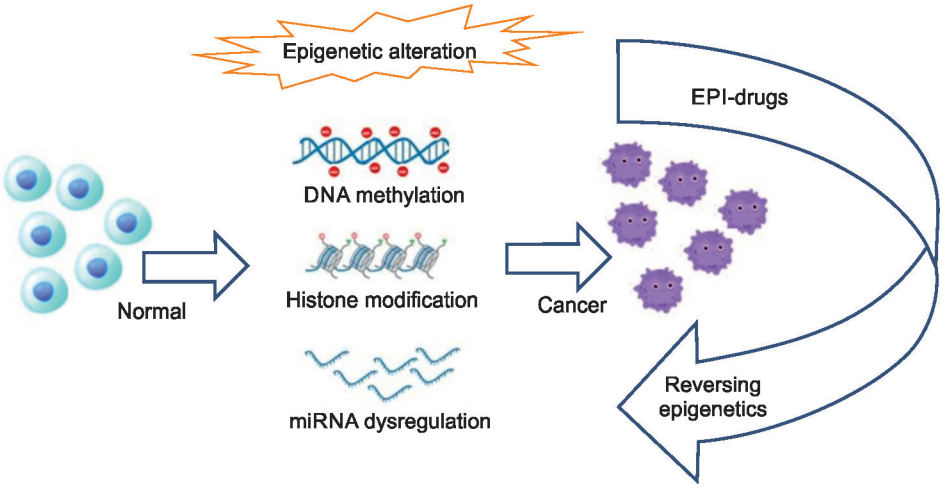

Fig. 1: Reversing epigenetic alteration in cancer by epidrugs benefits patients with cancer

shown benefits in treating hematopathological malignancies, but further research is needed to determine its effects on solid tumors. The best results are seen when HDACi is combined with chemotherapy and radiotherapy due to its synergistic effects. Furthermore, HDACi is most effective against HNSCC when taken in combination with other medications for treatment.[9]

On the other hand, non-coding RNAs (ncRNAs) have emerged as new players in the cancer paradigm in recent years, showing potential roles in both tumor-suppressive and oncogenic pathways. By controlling gene expression at both transcriptional and translational levels, the ncRNA regulates a variety of physiological processes that have been shown to play a significant role in the development of cancer and its metastasis. Inferring prognosis and carcinogenesis in HNSCC, ncRNA expression is a promising diagnostic for cancer detection. Among the variety of noncoding RNAs, microRNA up- and downregulation has been shown to have diagnostic importance.[10] For instance, apoptosis is influenced by the upregulation of miR34 and miR-17-92 and the downregulation of miR137. The gene instability is caused by the upregulation of miR210 and the downregulation of miR29. Immune evasion is affected by the upregulation of miR21 and the downregulation of miR210. Inflammation is characterized by the downregulation of miR26 and miR218. Cellular metabolism is characterized by the downregulation of miR26 and miR125b.[8,10] New computational methods can predict microRNAs' associated gene regulatory networks and their functional targets. Given the reversibility of such epigenetic alterations, it is obvious that changes identified throughout disease progression represent appealing targets for cancer treatment.

Overall, the epigenetic regulation by DNA methylation, histone modifications, and specific microRNAs is often associated with early events and advanced stages in oral cancer and thus indicates epidrug therapy for intervention (Fig. 1). The presence of epigenetic marks in oral lesions, cancers, and tumor-associated mucosa emphasizes indications as biomarkers and epidrugs with therapeutic potential for better patient management.[11] It is now important to analyze the importance of epigenetic alterations for diagnosis and therapeutics, especially for cancer associated with chemoresistance. To conclude, these epigenetic modifications may be utilized to diagnose, treat, and predict the prognosis of HNSCC patients. Therefore, considering its potential, a growing number of epigenetic medicines are being developed and novel drugs such as epidrugs targeting the identified epigenetic biomarkers can be used as adjuvant therapy to chemotherapy in HNSCC.

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