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EPIGENETIC ALTERATIONS DRIVING ONCOGENESIS IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

To the Editor,

Head and neck squamous cell carcinoma (HNSCC) accounts for about 600,000 new cases globally every year and stands the sixth most common cancer, arising from the squamous epithelium. It is localized in the head and neck area involving oral cavity, pharynx, and larynx. Despite the rigorous therapy, the 5-year overall survival remains poor in HNSCC and has not changed appreciably in the last 30 years. The majority of patients develop resistance to chemotherapeutic agents, and cancer progression occurs. Cetuximab, which targets the epidermal growth factor receptor, and pembrolizumab, an anti-programmed-death ligand 1 antibody, are among few FDA-approved medications. Current therapies are poor and cause severe long-term toxicity, which has a long-term impact on the quality of life [1].

The molecular pathogenesis of HNSCC is a complicated process because of the heterogeneity of genes and epigenetic alterations in apoptosis, DNA repair, cell cycle, growth signaling, proliferation, and differentiation. The term epigenetics was initially described in 1942 by Conrad Waddington as stable heritable phenotypic changes in the cell without any gene alterations. Today, it is referred to as persistent and heritable alterations in genetic expression that do not involve DNA sequence changes. In cancer, the basic central dogma of life is deregulated by epigenetic changes and hence can serve for early detection of malignant transformation, treatment monitoring, and prognosis of patients. DNA methylation, histone modifications, and non-coding RNAs (microRNAs, long non-coding RNAs) are common epigenetic alterations that play a role in carcinogenesis. The evidence suggests that epigenetic al-

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terations have a high potential for targeting oncogenes in cancer [2]. As a result, research into new medicines that improve both chemotherapy and immunotherapy responses in HNSCC is continuing. Preclinical and clinical initiatives to investigate epigenetic therapeutics along with the existing treatment modalities have gained interest [3].

DNA methylation

DNA methylation is a covalent alteration that was the first and most studied chromatin modification involving the addition of methyl groups to the carbon of 5-nitrogenous bases (5-methylcytosine) located 5' position of guanine (G), therefore, in CpG dinucleotides. DNA methyltransferases are responsible for the transcriptional suppression when CpG islands become methylated [4]. Cancer cells generally exert global DNA hypomethylation, which is accompanied by the local hypermethylation of CpG islands, affecting DNA repair, cell cycle control, and apoptosis. Based on the literature, few common hypermethylated genes in HNSCC are *CDKN2A*, *MGMT*, *DAPK*, *APC*, *RASSF1*, *CDH1*, *HOXA9*, *MLH1*, *CDKN2B*, *TIMP3*, *ATM*, *MINT31*, *CALCA*, *NPY*, *HS3ST2*, *ZNF*, *FAM135B*, and *PROM1*. Hypomethylated genes in HNSCC are *ADG3ST2*, *PI3*, *AIM2*, and *SPP1* (Fig. 1). More translation research for diagnostic and therapeutic purposes is warranted [5].

In HNSCC, DNA hypermethylation is a typical occurrence that results in suppressing the transcription of genes regulating the cell cycle. Therefore, enzymes like 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 a successful adjuvant therapy and chemotherapy for a variety of malignancies, including HNSCC. On the other hand, demethylation agents can be used as chemosensitizers to reduce the effects of chemical carcinogens [6].

Histone modification

Post-translational histone modifications include methylation, acetylation, ubiquitination, phosphorylation, and sumoylation, which result in the epigenetic changes in cancer cells. Histone acetylation and methylation are the most well-studied processes with predictive potential for HNSCC development and progression [7].

Histone acetylation is a key method for controlling gene expression and influencing chromatin structure. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) are the enzymes that attach and remove acetyl groups. The changes in the expression of the numerous HDACs have been linked to several genes regulating the cell cycle, apoptosis, signaling, proliferation, differentiation, invasion, and metastasis in various malignancies [8].

Histone methylation undergoes gene regulation by posttranslational modification in lysine or arginine. Several regulators activate or repress gene transcription, which leads to histone methylation. *H3K36me3*, *H3K79me3* and *H3K4me3* are associated with active transcription, while *H3K9me2*, *H3K9me3* and *H3K27me3* are associated with silenced genes (Fig. 1). *MLL1* affects target gene expression by a loss of function and affects cellular differentiation, which is frequently detected in many forms of cancer. An anomaly in the demethylases that govern *H3K9me3* and *H4K20me3* levels might contribute to the carcinogenic potential [9].

HDACi is a new anticancer drug family that re-establishes cellular acetylation equilibrium by histone acetylation, restoring normal gene expression and function. HDACi has been shown to be useful in hematological malignancies, whereas its effect on solid tumors needs to be studied. The synergistic effects show the most promising outcomes when HDACi is coupled with radiotherapy and chemotherapy. Indeed, when combined with other drugs, HDACi is the most effective against HNSCC [6].

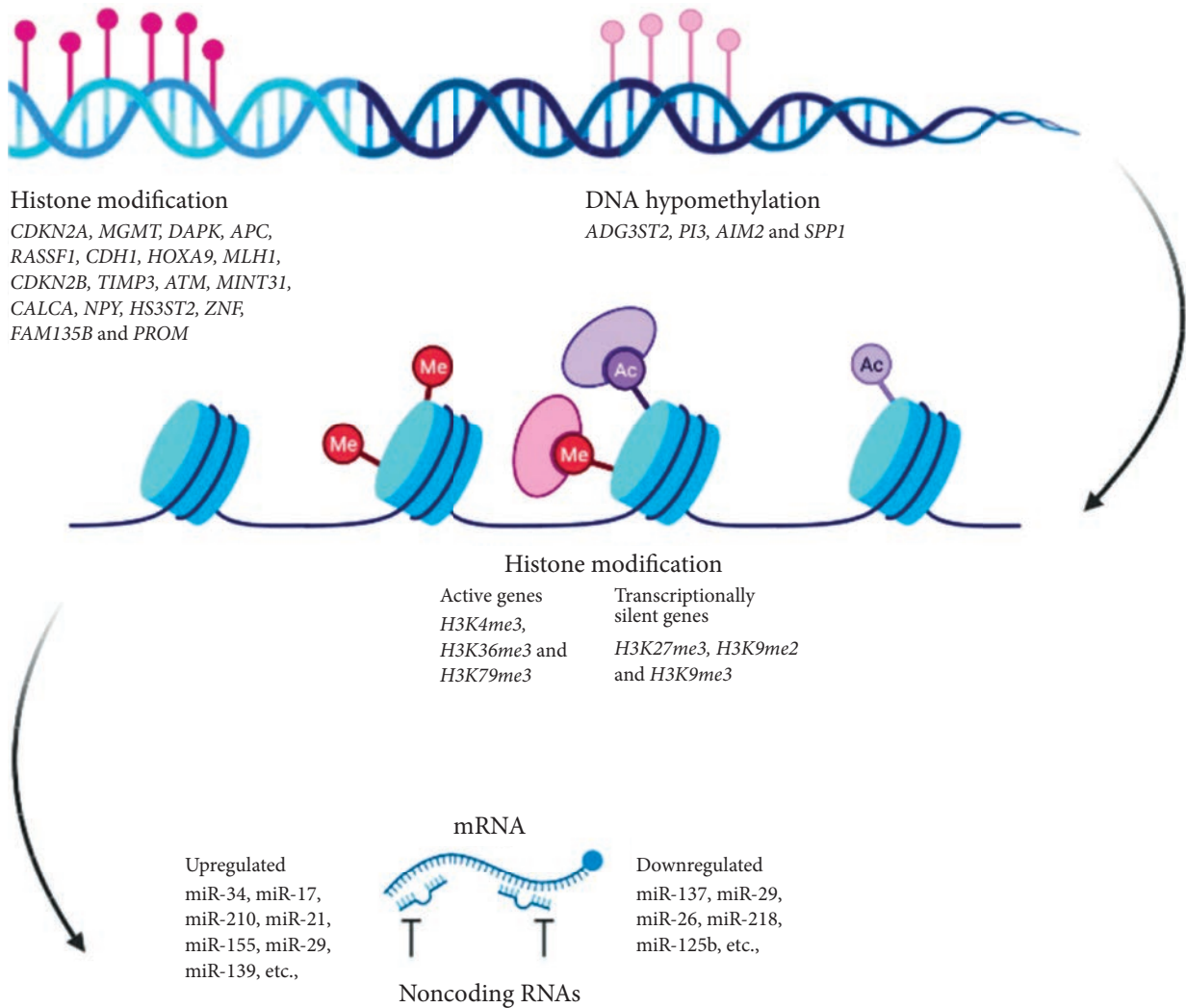


Fig. 1. Important epigenetic modifications in HNSCC via DNA methylation, histone modification, and non-coding RNAs

Non-coding RNAs

In recent years, non-coding ribonucleic acid (ncRNAs) has been of increasing interest in research beyond transfer RNA (tRNA) and ribosomal RNA (rRNA). MicroRNAs (miRNAs) are the most common type of non-coding RNA (ncRNA), which govern various physiological activities. miRNA expression dysregulation alters normal cellular processes and has been linked to the development of human diseases including cancer. miRNAs (18–24 nucleotides) alter the

gene expression via post-transcriptional regulation by binding to untranslated complementary regions. Most human malignancies exhibit miRNA expression deregulation in the course of the disease. The upregulated and downregulated microRNAs have diagnostic significance; downregulation of miR137, upregulation of miR34, and miR-17-92 are influenced by apoptosis; upregulation of miR210, and downregulation of miR29 are associated with gene instability; upregulation of miR21 and downregulation of miR210 impact the immune evasion; downregu-

lation of miR26, miR218 is demonstrated in inflammation; downregulation of miR26, miR125b effects cellular metabolism, and upregulation of miR21, miR155 and miR29, miR139 are associated with proliferation (Figure) [9, 10].

MicroRNAs play a role in carcinogenesis and tumor metastasis by regulating gene expression at both the transcriptional and translational levels. As a result, ncRNA expression is a promising biomarker for cancer diagnosis and can predict prognosis in HNSCC. In addition to microRNA profiling, new computational approaches are capable of predicting tumor sup-

pressor microRNAs and their functional targets from gene expression [11].

Given the reversibility of epigenetic alterations, it is obvious that changes identified throughout disease progression represent the appealing targets for cancer treatment. A growing number of epigenetic medicines are being developed. The epigenetic modifications may be utilized to diagnose, treat, and predict the prognosis of HNSCC patients. The novel Epi-drugs targeting the identified epigenetic biomarkers can be used as adjuvant chemotherapy in HNSCC.

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