Review Article

Narrative review of research progress of RNA m^{5}C methylation in head and neck malignancies

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Background and Objective: Head and neck malignancies encompass a spectrum of malignant tumors occurring in the head and neck region, characterized by rapid progression, high recurrence rates, and dismal prognoses. Despite significant advancements in comprehensive surgery-based therapies, the 5-year survival rate for patients has not shown substantial improvement. There is an urgent need to investigate novel targeted therapies. With the advancements in epigenetics, RNA 5-methylcytosine (m^{5}C) methylation, a prevalent form of RNA modification, has been identified by numerous studies as playing a pivotal role in the pathological processes of tumorigenesis and development. However, a comprehensive review within the realm of head and neck malignancies is currently lacking. This study aims to comprehensively review the biological implications of RNA m^{5}C methylation regulators in the pathogenesis and progression of various systemic malignant tumors, with a specific focus on exploring the potential impact of RNA m^{5}C methylation on head and neck malignancies.

Methods: A literature search on RNA m^{5}C methylation and head and neck malignancies was conducted using PubMed, resulting in the inclusion of 46 relevant articles. The Cancer Genome Atlas (TCGA) database was utilized to analyze the correlation between m^{5}C regulatory factors and clinicopathological features in patients with head and neck squamous cell carcinoma (HNSCC).

Key Content and Findings: Aberrant expression of RNA m^{5}C methylation regulators is observed in head and neck malignancies, displaying a correlation with the clinicopathological grading of tumors.

Conclusions: RNA m^{5}C methylation may contribute to the progression of head and neck malignancies and could be associated with an unfavorable prognosis for patients. These findings offer valuable insights for the development of targeted treatments for head and neck malignancies.

Keywords: RNA 5-methylcytosine methylation (RNA m^{5}C methylation); epigenetics; head and neck malignancies

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Introduction

Head and neck malignancies refer to primary tumors located in the head, maxillofacial region, and neck, including oral squamous cell carcinoma (OSCC), nasopharyngeal carcinoma (NPC), sinus cancer, and thyroid cancer, etc. In China, head and neck malignancies account for approximately 10% of all malignant tumors. Due to abundant vascularity and dense lymphoid tissue in head and neck region, the risk of lymphatic metastasis and distant metastasis is relatively high, leading to poor patient prognosis. Therefore, it is crucial to identify reliable epigenetic targeted therapy to improve patient outcomes. RNA methylation modification has been confirmed in various types of tumor cells and tissues, and it has been found to be closely related to the occurrence and development of various malignant tumors, including esophageal cancer, lung cancer and liver cancer, etc. Understanding the expression patterns of RNA 5-methylcytosine (m^5C) methylation in malignant tumors can help improve the prognosis of malignant tumors through targeted therapy. This review summarizes the epigenetic characteristics of RNA m^5C methylation and provide preliminary prospects for its application in the diagnosis, treatment, and prognosis assessment of head and neck malignancies.

In recent years, a large number of studies have proved that the tumor immune microenvironment (TIM) played a vital role in cancer progression and therapeutic efficacy (1). These studies further elucidate the potential mechanisms by which the m^5C methylation process influences tumor development.

Despite the above-mentioned studies and literature, there is no literature to describe the role of m^5C methylation in tumorigenesis and development, and there is no literature to discuss the potential impact of m^5C methylation on head and neck malignancies. In this paper, the relevant literature will be summarized in a narrative review to discuss the above issues. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-103/rc).

Methods

This review aims to comprehensively explore the epigenetic characteristics of RNA m^5C methylation and offer initial insights into its potential applications in diagnosing, treating, and assessing the prognosis of head and neck malignancies. A thorough literature search on RNA m^5C methylation and head and neck malignancies was conducted using PubMed, focusing on articles published between 1999 and 2023. The search terms included "m^5C", "cancer", "carcinoma", "head and neck", and "oral". A total of 58 relevant articles were selected for inclusion.

Our retrieval strategy summary is shown in *Table 1* and the results of PubMed search are shown in *Table 2*.

Subsequently, we employed The Cancer Genome Atlas (TCGA) database to conduct an in-depth analysis of the correlation between m^5C regulatory factors and clinicopathological features in patients with head and neck squamous cell carcinoma (HNSCC). The objective of this review is to provide a comprehensive overview of the role played by the RNA m^5C methylation process and its regulatory factors in the initiation and progression of systemic malignant tumors, with a particular emphasis on head and neck malignancies.

Epigenetic characteristics of RNA m^5C methylation

RNA methylation involves the modification of RNA molecules at different positions through the catalysis of methyltransferase. This phenomenon is involved in various biological processes, including cell differentiation, sex determination, and stress response. It is catalyzed by RNA methyltransferase, demethylated by demethylase (such as FTO and ALKBH5), and read by methylated binding proteins (such as YTHDF1 and IGF2BP1). Increasing evidence shows that this process is closely related to tumor cell proliferation, cellular stress, metastasis and immune response. RNA methylation-related proteins have become a promising target for tumor therapy.

RNA m^5C methylation, in which an active methyl group [usually S-adenosine methionine (SAM)] from the donor is added to the Carbon-5 site of the cytosine base in RNA to form. In recent years, m^5C has been detected in a variety of RNA molecules, including transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), messenger RNAs (mRNAs), viral RNAs and non-coding RNAs (ncRNAs) (1-6). It was found that tRNA m^5C modification can maintain homeostasis, optimize codon-anticodon pairing, regulate stress response, and regulate translation efficiency and accuracy. m^5C modifications of eukaryotic mRNAs, such as hamster cell mRNAs and certain viral RNAs, were first identified in the 1970s. Later, sulfite sequencing of full transcripts of HeLa cells revealed widespread m^5C modifications in mRNA and ncRNA. mRNA m^5C modification is related to various

Table 1 Retrieval strategy summary

Items	Specification
Date of search	2023.2–2023.9
Databases and other sources searched	PubMed, TCGA database
Search terms used	"m^{5}C", "cancer", "carcinoma", "head and neck", "oral"
Timeframe	1999–2023
Inclusion criteria	Related to "m^{5}C", "cancer", "carcinoma", "head and neck", "oral"
Selection process	L.C. and C.W. retrieved the literatures respectively, and the literatures with different opinions were decided by S.W. whether to include them

TCGA, The Cancer Genome Atlas.

Table 2 Results of PubMed search

Search item (mentioned in the title and abstract)	The number of documents retrieved	Number of references included
"m^{5}C", "head and neck"	13	9
"m^{5}C", "oral"	30	4
"m^{5}C", "cancer"	384	27
"m^{5}C", "carcinoma"	101	17

biological processes, such as mRNA stabilization, splicing, nucleoplasmic shuttle, DNA damage repair, diffusion and migration, stem cell development, differentiation and reprogramming. Abnormal modification of mRNA m^{5}C is commonly associated with various diseases, including arteriosclerosis, autoimmune diseases, and cancer.

m^{5}C is an essential post-transcriptional modification of RNA (7). It is a dynamic and reversible process with three primary regulatory factors: RNA m^{5}C methyltransferase (Writer), demethylase (Eraser) and RNA m^{5}C methylation-binding protein (Reader). In general, the methyltransferase "Writer" enhances RNA methylation at the Carbon-5 site, mainly consisting of the NOL1/NOP2/sun (NSUN) protein family (NSUN1-7) and the DNA methyltransferase analogue DNMT2 (DNA methyltransferase 2). Different "Reader" binding proteins recognize and bind methylated mRNAs, while "Eraser" demethylase reverses RNA m^{5}C methylation modification by degrading Written methylation of RNA molecules. Three regulatory factors work together to dynamically regulate the expression of RNA m^{5}C methylation 1 (*Figure 1*). To date, RNA m^{5}C modification and changes in its regulatory factors have been shown to affect RNA stability, gene expression and protein synthesis, thereby significantly impacting various cellular and physical processes (8-16).

Overview of RNA m^{5}C modification

RNA cytosine-5-methyltransferases (RCMTs)

RCMTs utilize adenosine methionine as a methyl donor to transfer methyl groups to cytosine, forming m^{5}C. The catalysis of RNA m^{5}C methylation is carried out by RNA m^{5}C methyltransferase, also known as "Writer" enzyme (15). RNA m^{5}C methyltransferase utilize S-adenosine-L-methionine (SAM) as a methyl donor to methylate cytosine, resulting in the formation of m^{5}C. Currently, more than 10 known RNA m^{5}C methyltransferases have been identified, including the NSUN family, DNA methyltransferase analogizes DNMT family, and tRNA specific methyltransferase TRDMT (tRNA aspartic acid methyltransferase) family (16-18). The NSUN family consists of NSUN1-NSUN7, with NSUN2 being one of the extensively studied methyltransferases in this family. NSUN2 can catalyze m^{5}C methylation of various RNAs, such as rRNA, tRNA, mRNA and viral RNA. NSUN2-mediated RNA m^{5}C is distributed widely throughout all coding regions. NSUN2 serves various biological functions, such as regulating epithelial cell differentiation, human immunodeficiency virus-1 (HIV-1) transcription, Epstein-Barr virus degradation, etc. Additionally, NSUN2 is highly expressed in several tumors and contributes to tumor

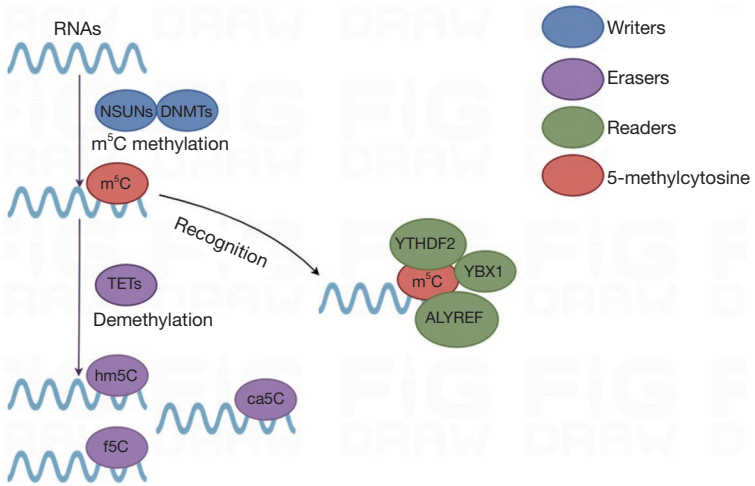

Figure 1 Mechanism diagram of RNA m^5C methyltransferase (Writers), RNA m^5C demethylase (Erasers) and binding protein (Readers), three regulatory factors of RNA m^5C methylation. RNA m^5C Methyltransferase transfers methyl groups to RNAs for RNA m^5C methylation, binding proteins can recognize and bind to RNAs after RNA m^5C methylation, and demethylase can remove methyl groups from RNAs. The three cooperate with each other to achieve RNA m^5C methylation dynamic modification. TET, ten-eleven translocation; m^5C, 5-methylcytosine.

development. The DNMT family comprises DNMT1, DNMT2, DNMT3A, and DNMT3B, with DNMT2 being a particularly active area of research. DNMT2 possesses sequence and structural characteristics similar to DNA methylases, enabling it to catalyze cytosine DNA methylation. Furthermore, DNMT2 can also catalyze the methylation of tRNA at C38, which plays a crucial role in tRNA processing, maintaining translation accuracy, stability, and differentiation, and safeguarding it against ribonuclease cleavage. Two other methyltransferases, TRM4A and TRM4B, exhibit specific activity in tRNA m^5C methylation. In conclusion, RNA m^5C methyltransferase serves as a vital regulatory factor in RNA m^5C methylation modification, and different methyltransferases can catalyze methylation of one or more RNA species.

RNA m^5C demethylase

The "Erasers" of demethylase proteins encompass the ten-eleven translocation (TET) family, consisting of TET1, TET2, and TET3 members (19,20). All three members, TET1, TET2, and TET3 have significant associations with the overall survival rate of gastric cancer patients, although only TET3 shows abnormal expression in gastric cancer tissues, as indicated by previous studies (21). Moreover, TET2 has also been found to exhibit abnormal expression in colorectal cancer (20). In summary, the three demethylation enzymes of the TET family can influence tumor occurrence and development through demethylation mediated by the demethylase proteins, along with the synergistic effects of methylation mediated by the methyltransferases.

RNA m^5C methylated binding protein

In addition to the regulation by methyltransferase and demethylase, the entire process of RNA m^5C methylation is also controlled by a cluster of specialized RNA-binding proteins known as "Reader". These proteins include ALYREF (RNA methyltransferase Aly/REF output factor) and YBX1 (Y box binding protein 1) (18,21). RNA m^5C methylation binding proteins mediate the occurrence of methylation and demethylation by recognizing and binding RNA m^5C methylation sites (22).

Research progress of RNA m^5C modification in tumors

Currently, it has been established that RNA m^5C methylation is significantly associated with hepatocellular carcinoma (HCC). Comparative analysis of HCC and paracancerous tissues revealed a significantly higher mRNA m^5C peak in HCC tissues, accompanied by a

more widespread distribution (23). Furthermore, the methylation frequency of circRNA and lncRNA m^{5}C, as well as the number of methylated genes, were significantly higher in HCC tissues compared to paracancerous tissues (23,24). The modification of RNA m^{5}C played a role in promoting HCC progression, and increased levels of RNA m^{5}C methylation regulators, such as NSUN4 and ALYREF, were negatively associated with poor prognosis in HCC patients (25). Recent studies have demonstrated that the deletion of NSUN2 inhibits cell proliferation and migration in hepatoma cells HepG2 (26). Notably, the loss of NSUN2 led to a significant decrease in the methylation and gene expression of lncRNA H19 m^{5}C, as revealed by transcriptional sequencing and bisulfite sequencing (Bis-Seq). Mechanistic investigations have shown that lncRNA H19 is a specific target of NSUN2, and RNA m^{5}C modification influences the half-life and stability of H19. The RNA m^{5}C modified H19 can promote the occurrence and development of liver cancer through specific binding to G3BP1 tumor protein (27).

In bladder cancer, Chen *et al.* (22) discovered a high frequency of RNA m^{5}C methylation in bladder cancer tissues compared to adjacent tissues using RNA Bis-Seq. The majority of RNA m^{5}C methylation sites were found in mRNA, and highly methylated mRNA was significantly enriched in carcinogenic pathways. Further studies revealed abnormal elevation of NSUN2 and YBX1 expressions in bladder cancer tissues, and the proto-oncogene heparin binding growth factor (HDGF) mRNA was methylated by NSUN2. By binding to the m^{5}C methylation site of HDGF mRNA and recruiting ELAV-like RNA binding protein, a member of the lethal abnormal RNA protein family of human embryos, YBX1 maintained the stability of HDGF mRNA and promoted tumorigenicity.

Chen *et al.* (28) classified two RNA m^{5}C methylation modification patterns in lung adenocarcinoma based on 11 RNA m^{5}C regulatory factors, which displayed distinct characteristics of tumor microenvironment (TME) immune cell infiltration. A scoring system of RNA m^{5}C methylation modification was established, revealing that patients in the high score group exhibited better prognosis, whereas those in the low-score group had a worse prognosis. Pan *et al.* (29) constructed a prognostic model for lung adenocarcinoma patients based on 14 RNA m^{5}C-related lncRNAs. The results demonstrated that the high-risk group had a poorer prognosis than the low-risk group, with higher sensitivity and specificity.

TME is an important part of tumor, which is composed of tumor cells, immune cells and stromal cells. The changes of expression, invasion and activation of immune cells are closely related to the malignant degree of tumor and the prognosis of patients. A growing body of research has found that RNA m^{5}C modification can significantly affect the TME by targeting different populations of immune cells, including B cells, T cells, macrophages, granulocytes, natural killer (NK) cells, dendritic cells (DC), and mast cells. Studies have shown that CD4$^+$ T cells are associated with NSUN1 and NSUN2, while CD8$^+$ T cells are associated with NSUN3 and NSUN6 (1,15,30-32). Genes related to m^{5}C RNA modification in B cells include NSUN2 and NSUN6, among which NSUN6 plays a crucial role in the process of antibody secretion in plasma cells (15,30,33). Risk scores based on m^{5}C related genes in patients with four tumors (liver cancer, HNSCC, glioma, and pancreatic cancer) were positively associated with infiltration of resting macrophages (M0), M1, or M2 macrophages (34-38). Analysis of TME in prostate cancer patients showed that NSUN6 was differentially expressed in M1 and M2 macrophages (15). In patients with HNSCC, NSUN3 promotes M2 macrophage penetration but inhibits M1 macrophage penetration (39). Regarding m^{5}C RNA modification in NK cells, both resting and activated NK cells were associated with m^{5}C activation in patients with HNSCC (35), glioma (37), and lung adenocarcinoma (38), with NSUN2 being the most closely associated *m^{5}C* gene (30). In patients with lung adenocarcinoma, the infiltration of DC was more in the low-risk group, suggesting that m^{5}C had a protective effect on DC (40). In patients with colorectal cancer, the m^{5}C writer DNMT3A was found to be involved in regulating DC (41).

Furthermore, numerous studies have demonstrated the overexpression of RNA m^{5}C methyltransferase NSUN2 in various types of cancer, including lung squamous cell carcinoma (29), breast cancer (42), esophageal cancer (43), gallbladder cancer (14), gynecological cancer (44). The heightened expression of NSUN2 has been linked to the promotion of tumor cell proliferation, invasion and other malignant characteristics, significantly correlating with poor prognosis of patients.

The above studies provide strong evidence for the correlation between m^{5}C methylation and the occurrence and development of tumors.

Research progress of RNA m^{5}C modification in head and neck malignancies

Head and neck malignancies encompass a range of

malignant tumors originating in the head and neck region, such as OSCC and NPC (45). Given the global prevalence and high mortality rate of head and neck malignancies, it is crucial to unravel the mechanisms underlying their occurrence and progression to enhance early detection and reduce mortality.

Among head and neck malignancies, NPC exhibits the highest incidence and poorest prognosis, with China bearing the largest burden of NPC patients worldwide. Targeted therapy has emerged as a promising approach for the treatment of NPC (34). The study by Tong *et al.* (46) confirmed the high expression of the RNA m^5C methyltransferase NSUN2 in NPC and established a close relationship between its expression level, tumor staging, and distant metastasis. NSUN2 enhances the pathogenicity of NPC cells by promoting their invasion and migration. In addition, the study revealed that NPC tissues with low NSUN2 expression displayed heightened sensitivity to chemotherapy drugs AZD6482 and P.02341066. Consequently, the high expression of NSUN2 in NPC was directly correlated to the poor prognosis and survival outcome for patients. Chen *et al.* (47) discovered a significant overexpression of NSUN2 in hypopharyngeal squamous cell carcinoma (HPSCC) and its pivotal role in the disease. Based on the level of NSUN2 expression, 73 HPSCC patients were categorized into a high-expression group (47 patients) and a low-expression group (26 patients). Survival analysis revealed a considerably lower survival time for patients with high NSUN2 expression compared to those with low NSUN2 expression. The basic experiment of this study further demonstrated that NSUN2 knockdown significantly reduced the proliferation and migration abilities of HPSCC cells. These results strongly suggest that a close association between RNA m^5C methyltransferase, NSUN2, and the development and prognosis of nasopharyngeal malignant tumors.

In a study focusing on head and neck melanoma, Luo *et al.* (48) used ELISA and blot-blot analysis to observe a significant increase in overall RNA m^5C level in both uveal melanoma (UM) cell and tissue samples. Furthermore, they discovered upregulation of NSUN2 was in these two types of samples. Notably, NSUN2 knockdown significantly reduced the RNA m^5C level. Additionally, Luo *et al.* utilized bioinformatics analysis, m^5C-Rip-qPCR, and luciferin assay to determine that β-catenin (CTNNBl) served as the direct target of NSUN2-mediated m^5C modification in UM cells. They also found that overexpression of miR-124a in UM cells led to a decrease in NSUN2 expression, suggesting miR-124a as an upstream regulator of this response. Luo *et al.*'s study provided evidence highlighting the close association between NSUN2-mediated m^5C RNA methylation and the occurrence and progression of UM. These findings offer valuable insights for targeted therapy in UM.

Furthermore, Li *et al.* (49) developed an RNA m^5C score system to investigate the impact of RNA m^5C methylation on papillary thyroid carcinoma (PTC). The results demonstrated that patients with low RNA m^5C score had higher survival rates and prognoses, while those with high RNA m^5C score exhibited reduced effective immunofiltration, indicating a worse prognosis. Subsequently, Li *et al.* employed the RNA m^5C score system to screen out 10 potential drugs for PTC, providing valuable perspectives for enhancing the therapeutic efficacy and prognosis of patients.

OSCC is a malignant tumor that arises in the squamous cells of the mouth, including the gingiva, palate, tongue, buccal mucosa, lip and floor of the mouth. Histologically, OSCC is the most aggressive and carries the worst prognosis among head and neck malignancies, accounting for approximately 50% of HNSCC cases. It also represents the highest incidence of oral cancer in Asia, with around 64.2% of diagnoses occurring in this region (47). Smoking, alcohol consumption, and areca nut chewing are all associated with the onset, growth, and progression of OSCC (50,51). Although surgical and radiotherapeutic advancements have improved the prognosis of OSCC patients, the overall survival rate remains low compared to other head and neck malignancies. Therefore, there is an urgent need to identify novel therapeutic targets for epigenetic and mechanistic treatment of OSCC (52,53). Currently, there are limited researches on RNA m^5C methylation modification in OSCC. Gao *et al.* (54,55) conducted a comprehensive evaluation of m^5C RNA modification patterns by integrating genomic and clinical data from 558 OSCC samples. Through this analysis, two distinct RNA m^5C-modified clusters with different TIM characteristics and prognoses were identified in OSCC using 16 RNA m^5C methylation regulators. Weighted gene co-expression network analysis (WGCNA) was subsequently employed by Gao *et al.* to identify RNA m^5C-modified cluster-related modules. The selected genes from these modules were used to construct the RNA m^5C score system for OSCC. The study revealed that the high RNA m^5C methylation rating group had significantly lower overall survival rates, progression-free survival rates, and tumor recurrence rates compared to the normal group.

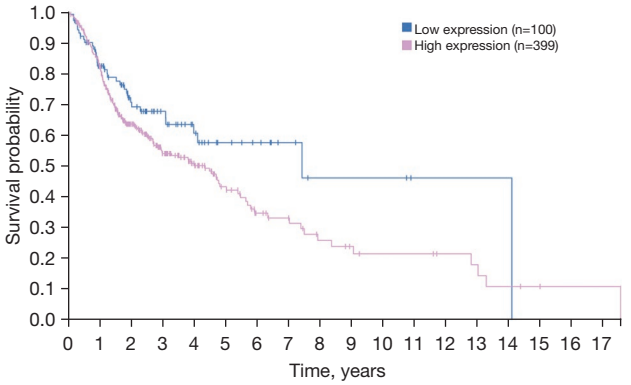

Figure 2 We searched The Human Protein Atlas website for associations between m^{5}C methyltransferase NSUN2 and the clinicopathological features of 499 patients with head and neck squamous cell carcinoma in the TCGA database. Survival analysis showed that patients with low expression of NSUN2 had a better survival prognosis than those with high expression of NSUN2. m^{5}C, 5-methylcytosine; TCGA, The Cancer Genome Atlas.

Additionally, OSCC patients with high RNA m^{5}C scores in oral leucoplakia showed a higher risk of worsening OSCC. Delaunay *et al.* (56) discovered that mitochondrial tRNA m^{5}C modification, mediated by methyltransferase NSUN3, enhanced energy supply by promoting protein synthesis in the mitochondrial respiratory chain. This mechanism facilitated increased capacity supply in OSCC cells and promoted their invasion, growth, and migration. High expression of the NSUN3 and increased modification of RNA m^{5}C modification predicted lymph node metastasis and more severe disease progression in OSCC patients. These finding suggest the potential of RNA methylation-related modifications as biomarkers for metastatic cancer and predictors of lymph node metastasis. Han *et al.* demonstrated that the dynamic modification of RNA m^{5}C methylation is involved in the regulating of the progression of HNSCC. The expression patterns of NSUN5, DNMT1, and DNMT3A were found to be useful in predicting the prognosis of HNSCC (56,57). In our previous study on RNA m^{6}A, we discovered that RNA m^{6}A methyltransferase METTL3 and METTL14 were overexpressed in OSCC, promoting the proliferation and invasion of OSCC cells and leading to a lower overall survival rate in OSCC patients. However, Li *et al.* (58) found that in in the 3'UTR of p21, Mettl3/MettL14-regulated RNA m^{6}A methylation and NSUN2-regulated RNA m^{5}C methylation mutually enhanced each other, thereby promoting the expression of p21 and contributing to the occurrence and development of tumors.

At the same time, taking NSUN2, the most common m^{5}C methyltransferase, as the representative, we selected the HNSCC dataset of TCGA database and analyzed the correlation between NSUN2 and HNSCC through The Human Protein Atlas website. The results showed that NSUN2 was correlated with survival and prognosis of 499 patients with HNSCC. The survival curve showed that the survival rate of patients with high NSUN2 expression was lower than that of patients with low NSUN2 expression under the same survival time (as shown in *Figure 2*).

Conclusions

The head and neck region is characterized by abundant blood supply, lymphatic tissue, and space. These anatomical features contribute to the higher incidence of blood circulation metastasis, cervical lymph node metastasis, and faster development in malignant tumors of the head and neck, including OSCC, NPC, adenoid cystic carcinoma, and mucoepidermoid carcinoma. Treating head and neck malignant tumors and controlling their metastasis and progression pose significant challenges. Moreover, surgical interventions for head and neck malignancies often result in substantial trauma, making it difficult to restore the morphology of the head and neck post-surgery. Furthermore, the improvement in prognosis for head and neck malignancies, particularly OSCC, remains limited. Consequently, the search for new therapeutic targets has become a key focus of research in targeted therapy for head and neck malignancies.

Studies investigating RNA m^{5}C methylation in various tumor types have suggested that RNA m^{5}C methylation serves as an independent prognostic factor for diverse tumors. High expression of RNA m^{5}C methylation is closely associated with tumor occurrence and development, providing a novel avenue for targeted therapy in various head and neck malignant tumors. It is anticipated that inhibitory drugs targeting regulatory proteins or pathway factors involved in RNA m^{5}C methylation could be developed to suppress or block the RNA m^{5}C methylation process in tumors, thereby enhancing treatment efficacy and patient prognosis. Therefore, to further study and explore the potential targeted therapeutic applications of m^{5}C Methylation is crucial in head and neck malignant tumors, which will provide a new target for the treatment of patients with head and neck malignant tumors, effectively improve

the prognosis of patients, increase the survival cycle and reduce the recurrence rate of tumors.

Although RNA m^5C methylation modification is still in its early stages regarding head and neck malignancies, the application of RNA m^5C methylation research in targeted therapy for malignant tumors in other body regions inspires the potential application of RNA m^5C methylation in head and neck malignancies. NSUN2, a representative RNA m^5C methyltransferase, is frequently overexpressed in malignant tumor cells and tissue samples. By inhibiting or knocking down RNA m^5C methyltransferases such as NSUN2 or employing inhibitors targeting related pathways, the level of RNA m^5C can be reduced, leading to inhibition of tumor growth and development, as well as improved survival prognosis for patients. In the case of rapidly progressing, highly metastatic, poor-prognosis, and surgically challenging head and neck malignant tumors, RNA m^5C methyltransferases or downstream factors of related pathways can be targeted directly to delay and inhibit tumor progression through targeted therapy. Combined with surgical treatment, this approach can minimize the extent of resection, reduce surgical trauma and complications, shorten operation time, improve the likelihood of achieving radical surgical treatment, implement the concept of induction chemotherapy, and significantly enhance the survival rate and quality of life for patients with head and neck malignant tumors.

However, we are also clearly aware that due to the limitation of search strategy and search scope, the summary of this review is not comprehensive, and the discussion on the influence of m^5C methylation on the occurrence and development of systemic tumors is not completely reasonable. In the future, we will verify the expression and role of m^5C regulatory factors in OSCC and other head and neck malignancies through basic experiments.

In summary, the study of RNA m^5C methylation holds significant clinical value and importance in the treatment and prognosis of head and neck cancer. It has emerged as one of the current research hotspots in the field of biological treatment for head and neck cancer.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-103/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-103/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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