Molecular Characterization of Sinonasal Undifferentiated Carcinoma—Past, Present, and Future

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Abstract

Sinonasal undifferentiated carcinoma is a rare and aggressive tumor. Despite aggressive management of patients, their prognosis is still poor. To better understand the biological features of sinonasal undifferentiated carcinoma and develop reliable therapeutic strategies for this disease, molecular characterization of sinonasal undifferentiated carcinoma is crucial. However, even nearly a decade ago, sinonasal undifferentiated carcinoma was still a poorly understood malignancy on both the clinical and molecular levels. The advent of next-generation sequencing technologies has resulted in a significant increase in the identification of molecular markers, including diagnostic and predictive markers, as well as gene alterations, leading to emerging distinct entities and new therapeutic approaches for sinonasal undifferentiated carcinoma. As new technologies continue to develop, new molecular markers for sinonasal undifferentiated carcinoma are expected to be discovered. Nevertheless, regardless of the methodology employed, sample size remains a crucial factor for the success of such investigations. Therefore, it is essential to establish a centralized banking system through multi-institutional collaboration. Additionally, investigation of the tumor microenvironment, including spatial immunophenotyping, is necessary to develop successful immunotherapy approaches.

Keywords: Sinonasal undifferentiated carcinoma, next-generation sequencing, molecular profiling, gene expression, DNA mutations, DNA methylation

INTRODUCTION

Sinonasal undifferentiated carcinoma (SNUC) is a rare, highly aggressive cancer arising in the nasal cavity or paranasal sinuses with an estimated incidence of 0.02 per 100 000.[1] Initially described by Frierson et al[2,3] in 1986, the latest definition of SNUC by the World Health Organization is "a malignant epithelial tumor without any identifiable line of differentiation (including squamous, glandular, and neuroendocrine) and is a diagnosis of exclusion." In general, SNUCs present as large tumors that involve multiple sinonasal structures and often extend into the orbit or cranial cavity. Around 10%-30% of SNUC patients exhibit signs of cervical lymph node metastases upon their initial presentation, while the presence of distant metastases is rare at the time of diagnosis.[4] Currently, it is generally accepted that the management of SNUC should involve aggressive, multimodal therapy incorporating surgery, radiation therapy, and chemotherapy.[4] However, despite aggressive management of patients, their prognosis remains poor, with a median survival time of 22.1 months.[3] To better understand the biological behavior of SNUC and help develop reliable therapeutic strategies for this disease, molecular characterization of SNUC is essential. Up until approximately 10 years ago, however, little was known about the molecular features of SNUC because of the rarity of cancer.

The etiology of SNUC has not been identified yet. The majority of SNUC samples are positive for epithelial markers like pancytokeratin (AE1/AE3),[3] and simple keratins like CK7, CK8, and CK18 by immunohistochemistry,[3,5] but negative for CK5/6 and p40.[6] Epithelial membrane antigen, neuron-specific enolase, and p53 tend to be focally positive in the tumors. There may also be focal positivity for synaptophysin and chromogranin.[5] Epstein-Barr virus is generally not detected in SNUC.[5] The expression of p16 and human papillomavirus (HPV) in SNUC remains debatable. While Wadsworth et al[7] found that p16 expression in the absence of high-risk HPV, Gray et al[8] demonstrated p16-positive staining with the expression of HPV DNA in approximately 47% of SNUC patients.

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Some consider SNUC to be a member of neuroendocrine sinonasal malignancies, yet this is still a matter of debate since most SNUC cases show no evidence of neuroendocrine differentiation or display only weak and focal immunochemistry signals.[5] Furthermore, due to its histological similarity to other poorly or undifferentiated tumors, neuroendocrine carcinoma, and high-grade olfactory neuroblastoma (ONB), misdiagnosis of SNUC is frequent. Since the prognosis and treatments for these malignancies vary greatly,[4] accurate diagnosis of SNUC is vital. Therefore, it is necessary to identify molecular markers that are specific to SNUC, which is another reason why molecular profiling of SNUC is so important.

What Hinders Molecular Studies in Sinonasal Undifferentiated Carcinoma?

The study of molecular profiling of SNUC is hindered by the limited availability of surgical specimens due to their rarity. Furthermore, most of the existing biological materials are in the form of formalin-fixed paraffin-embedded (FFPE) specimens, which are not suitable for gene expression/molecular marker studies. This has been a barrier until the arrival of the next-generation sequencing (NGS) era.

Cytogenetic Alterations in Sinonasal Undifferentiated Carcinoma by Karyotyping

According to our knowledge, Gollin and Janecka made the first attempt to understand molecular changes in SNUC in 1994. Through their cytogenic analysis, they found that their SNUC sample had a partial trisomy 17.[9] Subsequent research by Gil et al looked at the cytogenetic alteration of 14 sinonasal carcinomas and, of the 5 SNUC cases, 2 had an abnormal karyotype. One had a complex karyotype, with 2 chromosomal translocations involving chromosomes 1, 6, 12, and 17, and the other had a triploid composite with 60-69 chromosomes.[10] While these initial investigations provided insight into molecular changes in SNUC, these cytogenetic data may be too limited to be used for diagnosis and prognosis assessment.

Detection of Transmembrane Tyrosine Kinase Receptors Expression

Transmembrane tyrosine kinase receptors are considered to be essential for tumorigenic pathways associated with cell growth, adhesion, and migration.[11] Thus, Chernock et al applied an immunohistochemical approach to detect the expression of epidermal growth factor receptor (EGFR), c-KIT, and human epidermal growth factor receptor 2 (HER2) in SNUC specimens. They observed that c-KIT was frequently expressed in SNUC (9 of 11 cases; 81.8%). However, Sanger sequencing and in situ hybridization indicated that the overexpression of c-KIT was not caused by acting mutations or gene amplification.[12] This result implies that using c-KIT inhibitors may not be a promising treatment option for SNUC.

Main Points

- *Sinonasal undifferentiated carcinoma is a rare and aggressive tumor that requires molecular characterization to better understand its biological features and develop therapeutic strategies.*
- *Next-generation sequencing technologies have improved the discovery of molecular markers and gene abnormalities in sinonasal undifferentiated carcinoma, resulting in the reclassification of the disease.*
- *To effectively develop immunotherapy approaches for sinonasal undifferentiated carcinoma, it is critical not only to perform molecular profiling but also to investigate the tumor immune microenvironment.*

Entering the New Era—First Attempt to Identify Key Hot Spot Mutations

Even nearly 10 years ago, SNUC was still a poorly understood malignancy on both the clinical and molecular levels. In contrast, research on more common cancers, such as lung, breast, and melanoma, had identified key mutations within oncogenes or tumor suppressor genes that increase susceptibility to molecular targeted therapies.[13] Our team employed a mass spectroscopy-base methodology developed by Sequenome, which evaluated 95 single nucleotide variations (SNVs) within 12 oncogene or tumor suppressor genes (*AKT*, *BRAF*, *CDK4*, *CTNNB1*, *EGFR*, *FBXW7*, *JAK2*, *KIT*, *KRAS*, *PDGFRA*, *PI3KCA*, and vascular endothelial growth factor [*VEGF*]) in 13 SNUC samples.[14] Unfortunately, none of the 13 samples had known activating mutations of any of the 95 SNVs. However, we found polymorphism in the *VEGF* gene at 1154 locations (the GG genotype 62%, GA genotype 8%, and AA genotype 30%), which is located in the *VEGF* promoter. It is noteworthy that the 1154 GG genotype is associated with higher VEGF production,[15] while the 1154 AA genotype has been reported to decrease the risk of prostate cancer and less advanced melanoma.[16-18] Consequently, further research might be necessary to assess these genotypes as potential biomarkers for treatment response or survival.

Establishment of Human Sinonasal Undifferentiated Carcinoma Cell Lines

To better understand the biological features of SNUC and help develop new therapeutic strategies for this disease, establishing a reliable model for laboratory-based analysis is essential. In 2012, our research team succeeded in creating the first-ever stable human cell lines, MDA8788-6 and MDA8788-7, from a SNUC patient. These cell lines are highly tumorigenic and maintain the same histologic and molecular characteristics as the original tumor.[19] Stiirnweiss et al[20] also developed a cell line from a patient with "SNUC"; however, it was later discovered that the patient had a NUT carcinoma. Consequently, our cell lines remain the only available SNUC cell lines, which have been distributed both domestically and internationally.

Then we conducted a whole genome single-nucleotide polymorphism analysis on the MDA8788-6 cell line to determine if any genes encoding targetable tyrosine kinase receptors that could be used for the treatment of SNUC were amplified.[21] We discovered that the *ERBB2* gene was highly amplified, leading to an overexpression and high phosphorylation of HER2 protein. Inhibition of the HER2 signaling pathway in the MDA8788-6 cell line caused growth suppression both in vitro and in vivo, suggesting that targeting HER2 could be a viable option for the development of therapies for patients with SNUC. This study was published as the first molecular targeted therapy for SNUC.[21]

Identification of Novel Molecular Diagnostic Markers for Sinonasal Undifferentiated Carcinoma

It is unclear whether SNUC is a distinct pathologic entity with poorly differentiated neuroendocrine features or it represents an undifferentiated tumor of squamous lineage.[5] Furthermore, there are currently no reliable histopathologic markers that can differentiate SNUC from poorly differentiated sinonasal squamous cell carcinoma (SNSCC). This is clinically important, as the prognosis and treatment strategies for the 2 entities differ. To identify gene expression signatures and specific diagnostic markers, our group conducted a comprehensive gene expression analysis of treatment-naïve SNUC and SNSCC specimens using the HTG EdgeSeq system, which is an NGS-based platform and enabled us to analyze small FFPE samples.[22] Our study identified 132 differentially expressed genes (DEGs) between SNUC and SNSCC samples. Moreover, we found that gene

expression levels of 7 markers (*CLCA2*, *ARID2*, *HELLS*, *KRT16*, *MAP1LC3A*, *MAPKAPK5-AS1*, and *SMAD4*) completely distinguished SNUC from SNSCC. Additionally, gene ontology analysis revealed that SNUC samples had an enrichment of genes related to DNA repair, synthesis/replication, and cell division.

Identification of Molecular Markers Predictive for Response to Induction Chemotherapy

Due to the locally advanced nature of SNUC at presentation and its high propensity for distant metastasis, our institution frequently employs cisplatin-based induction chemotherapy before definitive therapy in patients. Our previous study found that about 30% of the patients did not respond to this treatment, and the lack of response was associated with a poor survival rate.[23] To identify biomarkers for predicting the response to induction chemotherapy, we performed the HTG EdgeSeq system-based comprehensive gene expression analysis of SNUC samples obtained from treatment naïve patients.[24] We identified 34 DEGs between responders and non-responders. Pathway analysis of these 34 DEGs revealed significant differences between the 2 groups in pathways related to the immune system, cell–extracellular matrix interaction, PI-3K signaling, the cell cycle, and apoptosis. Further analysis revealed 24 of the 34 DEGs could individually differentiate the responders from the non-responders. Despite our success in identifying predictive markers for induction chemotherapy response in SNUC patients, the use of single transcripts as biomarkers has limitations since the measurement of absolute transcript expression is methodology-dependent and relies on normalization through housekeeping genes. To overcome these shortcomings and to enhance the potential clinical relevance of our findings, we applied the top-scoring pairs algorithm. This algorithm selects pairs of genes whose relative expression levels between 2 genes are consistent with 2 prognostic groups regardless of the gene expression assay platform.[25] We found that 16 gene pairs were significantly associated with the response to induction chemotherapy.[24] While further validation is necessary, we believe these 16 gene pairs could play an important role in selecting the optimal therapeutic approach for SNUC patients. To the best of our knowledge, this study was the first report of the identification of predictive markers for induction chemotherapy response in SNUC patients.[24]

Discovery of *IDH2* Mutations in Sinonasal Undifferentiated Carcinoma

During our gene expression-base studies, 2 research groups, Jo et al [26] and Dogan et al.[27] utilized DNA-based NGS platforms, including targeted tumor-sequencing test panels. They reported that the isocitrate dehydrogenase 2 (*IDH2*) R172 mutations were detected in 55%-82.4% of SNUC cases, but not in ONB, which is a histologic mimic of SNUC, and SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1)-deficient carcinoma.[27] The detection of *IDH2* hot spot mutations through immunohistochemistry was evaluated by 2 groups, using 11CB1 by Dogan et al and MsMab-1 by Mito et al as a surrogate marker. However, it should be noted that not all mutations can be detected by these antibodies.[28-30] The activating hot spot *IDH2* and its analog *IDH1* mutations have been reported in various cancers.[31] The wild-type IDH1 and IDH2 catalyze the conversion of isocitrate to α-ketoglutarate (α-KG), but these mutants change the activity of the IDH1 and IDH2 enzyme function and increase levels of the oncometabolite 2-hydroxyglutarate (2-HG). 2-Hydroxyglutarate acts as an α-KG antagonist, resulting in genome-wide changes in histone and DNA methylation.[31] In 2017, the US Food and Drug Administration approved a small-molecule inhibitor of mutant-IDH2 enzymes, Enasidenib (AG-221), for relapsed or refractory acute myeloid leukemia (AML). The first in-human phase I/II study (NCT01915498) showed that Enasidenib treatment was generally well-tolerated and induced hematologic response in patients for whom prior AML therapy had failed.[32] Therefore, it is essential to identify *IDH2* mutations and investigate the efficacy of IDH2 inhibitors in SNUC patients. Other gene alterations found in *IDH2* R172 mutants were *TP53* mutations, *KIT* mutations, *CDKN2A/2B* loss-of-function alterations, *MYC*-amplification, *SETD2* mutations, and PI3K pathway mutations.[26, 27, 29] Although *IDH1* mutations have also been reported in SNUC, their frequency is much lower than that of *IDH2* mutations.[29]

The Switch/Sucrose Non-Fermentable Chromatin Remodeling Complex in Sinonasal Undifferentiated Carcinoma–SMARCB1-Deficient Carcinoma

The SMARCB1-deficient sinonasal carcinoma was first identified by Agaimy et al[33] and Bishop et al [34] in 2014, with characteristic rhabdoid features and lack of SMARCB1 (INI1) protein expression. Initially, it was recognized as a subset of SNUC in the fourth edition of the WHO Classification of Head and Neck Tumors.[35] SMARCB1 is a ubiquitously expressed nuclear protein, and it is a core subunit of the switch/sucrose non-fermentable (SWI/SNF) protein complex, which is involved in chromatin remodeling and gene transcription.[36] More than 20% of human cancers carry mutations in the *SWI/SNF* genes, and the loss of *SMARCB1* gene is the genetic driver in malignant rhabdoid tumor and epithelial sarcoma.[36]

The nature of SMARCB1-deficient sinonasal carcinoma is aggressive, and its prognosis is poor. A recent study involving 39 cases of SMARCB1-deficient sinonasal carcinoma showed that 56% of patients died of the disease at their last follow-up, which occurred 0-102 months after diagnosis.[37] Another cohort compared the survival outcome of 6 SMARCB1-deficient SNUC cases with 8 SMARCB1-retained SNUC cases. The results showed that SMARCB1-deficient SNUC had poorer overall survival and disease-free survival with higher recurrence and mortality rates.[38]

Currently, clinical trials are ongoing to investigate the potential of EZH2 inhibitors, histone deacetylase inhibitors, and CDK4 inhibitors as treatment options for nonsinonasal SMARCB1-deficient malignancies.[38,39] Notably, a team in Hong Kong is initiating a phase II trial with the EZH2 inhibitor tazemetostat for locally advanced SMARCB1-deficient sinonasal carcinoma (NCT05151588).[40]

Loss of other SWI/SNF gene/proteins, such as SMARCA2, SMARCA4, and ARID1A, has also been found in SNUCs and SMARCB1-deficient carcinomas.[26,29,37,41-43] Interestingly, these SWI/SNF losses and *IDH2* mutations are mutually exclusive, indicating their ability as oncogenic drivers in *IDH2* wild-type sinonasal carcinomas.

Finally, in the fifth edition of the WHO classification of Head and Neck Tumors, SMARCB1-deficient carcinoma and SMARCA4-deficient carcinoma were reclassified as SWI/SNF complex-deficient sinonasal carcinoma.[3]

DNA Methylation-Based Classification of Sinonasal Undifferentiated Carcinoma

DNA methylation is an important epigenetic modification that regulates gene expression and genome stability. DNA methylation patterns are highly tissue specific[44] and disruption of DNA methylation mechanisms can lead to various diseases, including cancer.[45] A technical advantage of using DNA methylation for cancer is its high stability, which allows for retrospective analysis using FFPE samples.[42] Recent DNA methylation studies

on sinonasal tumors suggested the possibility that SNUC could be reclassified into multiple distinct entities.

Dogan et el[43] investigated DNA methylation in 42 cases of sinonasal tumors, including SNUC, large-cell neuroendocrine carcinoma (LCNEC), small-cell neuroendocrine carcinoma (SCNEC), SMARCB1-deficient carcinoma, and ONB. Their semi-supervised hierarchical clustering analysis revealed that *IDH2* R172-mutated SNUCs and LCNECs formed a distinct cluster that segregated from other sinonasal tumors, despite being currently defined as separate entities by WHO classification.[3,46] *IDH2*-mutated sinonasal carcinomas displayed a global hypermethylation pattern and an increase in repressive H3K27 trimethylation. In addition, pathway analysis showed no significant difference in pathway activation between *IDH2* R172-mutated SNUCs and LCNECs.[43]

In a subsequent study, their group collected a cohort of 395 sinonasal tumors covering 18 tumor entities and normal sinonasal tissue to identify DNA methylation-based tumor classes.[42] While 14 classes matched their established entities as defined in the WHO classification at that time, the remaining 4 methylation classes contained all SNUC samples. These 4 SNUC DNA methylation classes were named NEC-like IDH2, SMARCB1, adenoid cystic carcinoma, and NEC-like SMARCA4/ARID1A based on further molecular characterization**.** Comparison among the 4 classes showed that NEC-like IDH2 and NEC-like SMARCA4/ARID1A groups had favorable 5-year disease-specific survival rates of 59% and 46%, respectively.

Future Direction

1. The utilization of NGS has significantly expedited the molecular characterization of SNUC. As new technologies will be developed in the future, additional molecular markers might be discovered. However, regardless of the methodology employed, sample size remains a crucial factor for the success of such investigations. To achieve the desired objective, it is essential to establish a centralized banking system through multi-institutional collaboration.
2. The use of immune checkpoint inhibitors has led to improved outcomes in patients with various types of solid cancers. In the case of SNUC, Bell et al[47] have demonstrated altered immune infiltration, with the downregulation of major histocompatibility complex molecules, dysregulated humoral immune response, and a tumor microenvironment driven toward immune evasion. Another study reported that $CD8^+$ tumor-infiltrating lymphocytes and PD-L1 were present in 32% and 16% of SNUC cases, respectively.[48] These findings suggest that patients with SNUC may benefit from immunotherapy. To gain a better understanding of the tumor immune microenvironment in SNUC and to develop successful immunotherapy approaches, it is necessary to undertake a detailed investigation of SNUC samples, including spatial immunophenotyping.

CONCLUSION

Sinonasal undifferentiated carcinoma is a rare and aggressive tumor. Molecular characterization of SNUC is essential to better understanding its biological features and developing therapeutic strategies. Next-generation sequencing technologies have led to an increased identification of molecular markers and gene alterations in SNUC. With the continued advancement of new technologies, additional molecular markers are expected to be discovered. Sample size remains crucial for success, and a centralized banking system through multi-institutional collaboration is necessary. Additionally, investigation of the tumor immune microenvironment is needed to develop successful immunotherapy approaches.

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