Editorial Commentary

Small cell lung carcinoma with YAP1 expression and SMARCA4-deficient undifferentiated tumors

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Over the last four decades, minimal progress has been made in treating and improving the survival outcomes of patients with small cell lung cancer (SCLC). However, a notable 2021 transcriptomic analysis revealed that SCLC can be classified into molecular subtypes based on gene expression profiles (1). Three of the four identified subtypes are characterized by the predominant expression of specific transcription factors [i.e., ASCL1 (SCLC-A), NEUROD1 (SCLC-N), and POU2F3 (SCLC-P)], while the fourth is an inflamed subtype (SCLC-I), also known as the "triple-negative" subtype. The SCLC-I subtype exhibits elevated expression of inflammation-related genes and increased T-cell infiltration compared to other subtypes, suggesting that patients with SCLC-I may respond to immune checkpoint blockade therapy. Indeed, the Impower133 trial (NCT02763579) demonstrated improved survival in patients with SCLC-I following chemoimmunotherapy using atezolizumab, carboplatin, and etoposide compared with the survival outcomes of patients with other subtypes (1). YAP1 was initially proposed to define a distinct SCLC subtype, termed SCLC-Y. However, most tumors used to establish this classification were derived from cell lines alone (2). Immunohistochemical analysis in a well-characterized patient cohort confirmed the expression of ASCL1, NEUROD1, and POU2F3 in SCLC subtypes, whereas YAP1 was expressed at low levels. Notably, YAP1 was primarily detected in combined SCLC and was consistently expressed in the non-SCLC component (3). These findings highlight the ongoing controversy surrounding the existence and clinical relevance of the SCLC-Y subtype.

Recently, Ng *et al.* investigated SCLC-Y cell lines to better understand the biology of this subtype. Genomic analyses revealed pathogenic *SMARCA4* mutations in six of eight YAP1-expressing SCLC-Y cell lines, which were associated with reduced SMARCA4 RNA and protein expression (4). In two SCLC-Y cell lines without *SMARCA4* mutations, further pathological examination revealed that one displayed sarcomatoid features, with differential diagnoses including sarcomatoid carcinoma, sarcoma, mesothelioma, and melanoma (4). The other was found to represent metastatic small cell neuroendocrine carcinoma (NEC) of the cervix, based on the following evidence: (I) the cell line was derived from a cervical tumor biopsy in a 26-year-old woman with no signs of extrapelvic

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spread; (II) no mutations in *TP53* or *RB1* were detected; (III) human papillomavirus (HPV) was present, which is a characteristic feature of small cell NEC of the cervix; and (IV) the tumor exhibited *SMARCB1* deletion, which has been previously reported in small cell NEC of the cervix. Detailed pathological and immunohistochemical evaluation of SCLC xenograft models derived from SCLC cell lines demonstrated that the histology of SCLC-Y is consistent with that of SMARCA4-deficient undifferentiated tumors (SMARCA4-UT) rather than SCLC. RNA sequencing analysis showed that SCLC-Y cell lines with *SMARCA4* mutations exhibited a transcriptomic profile similar to that of SMARCA4-UT. Furthermore, SMARCA4-UT expresses YAP1 at both the mRNA and protein levels. These findings suggest that most cell lines previously classified as SCLC-Y are actually SMARCA4-UT.

The 5th edition of the World Health Organization (WHO) Classification of Thoracic Tumors includes thoracic SMARCA4-UT in the "other epithelial tumors of the lung" category (5). Our current understanding is that these tumors represent dedifferentiated/undifferentiated carcinomas, characterized by primitive round cells interspersed with rhabdoid cells (5). SCLC and SMARCA4-UT share clinicopathologic features, such as an association with heavy smoking, aggressive behavior, poorly differentiated histology with crush artifacts in biopsy specimens, and neuroendocrine marker expression (6). These overlapping characteristics may contribute to the misclassification of SMARCA4-UT as SCLC. A genomic analysis of 3,600 patients with SCLC revealed that 1.5% had inactivating SMARCA4 mutations, and these tumors should have been diagnosed as SMARCA4-UT (7). Before the recognition of SMARCA4-UT as a distinct entity, these tumors were often categorized as NECs in patient samples (8,9).

SMARCA4-UT is a highly aggressive tumor, urging the development of effective therapeutic strategies. SMARCA4 plays a central role in the function of the switch/sucrose-non-fermentable (SWI/SNF) chromatin remodeling complex (10). Enhancer of zeste homolog 2 (EZH2), the catalytic subunit of the polycomb repressive complex 2 (PRC2), is responsible for H3K27 methylation (11). Abnormal levels of PRC2 have been observed in cancers with *SMARCB1* or *SMARCA4* mutations (12,13), highlighting the natural antagonistic relationship between PRC2 and the SWI/SNF complex, and suggesting that inactivation of EZH2 can induce therapeutic effects (14). Ataxia-telangiectasia and Rad3-related (ATR) is a critical regulator of multiple DNA repair pathways, responding to both single- and double-stranded DNA damage (15). Interestingly, the loss of SMARCA4 in lung cancer cells activates replication stress responses, resulting in ATR dependency. Additionally, SMARCA4 loss reduces cyclin D1 expression via a dual mechanism: restricting *CCND1* chromatin accessibility and suppressing c-Jun, a transcriptional activator of *CCND1*. SMARCA4 loss exhibits synthetic lethality with CDK4/6 inhibition in both *in vitro* and *in vivo* models (16). Finally, Aurora kinase A (AURKA) expression is frequently elevated across various cancer types, and preclinical data suggest that dysfunction of the SWI/SNF complex increases sensitivity to AURKA inhibitors (17). These findings underscore the therapeutic potential of targeting pathways such as EZH2, ATR, CDK4/6, and AURKA in SMARCA4-UT, emphasizing the need for further investigation (18).

A recent comprehensive analysis of transcriptional programs in approximately 1,000 NECs from 30 different anatomical sites identified a novel NEC subtype, defined by *HNF4A* expression, which is characterized by a gastroenteropancreatic lineage signature, wild-type *RB1*, and resistance to chemotherapy (19). In lung cancer, approximately 3% of SCLC cases belong to the *HNF4A* subtype, while a higher frequency (13%) was observed in large cell NEC (LCNEC) (19). Given the well-recognized challenges in distinguishing between LCNEC and SCLC due to interobserver variation and morphological heterogeneity (20), further investigation is warranted to determine whether a distinct *HNF4A*-expressing subgroup can be identified in a well-characterized cohort of patients with SCLC. The study by Ng *et al.* (4) highlights the importance of comprehensive histopathological and molecular characterization of SCLC tumors in clinical cohorts, particularly with the aim of excluding potential SCLC mimics.

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Footnote

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