Review Article

SMARCA4 deficiency: implications for non-small cell lung cancer and management strategies, with relevance to and distinctions from thoracic undifferentiated tumor

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Abstract: In 2021, the fifth edition of the World Health Organization (WHO) classification of thoracic tumors introduced a new category, "Thoracic *SMARCA4*-deficient undifferentiated tumor", highlighting *SMARCA4* deficiency as a key molecular marker for classifying as "other pulmonary epithelial tumors". *SMARCA4* is a gene encoding a protein involved in chromatin remodeling, and approximately 8% of non-small cell lung cancer (NSCLC) patients exhibit *SMARCA4* deletions. These patients are more prone to drug resistance, early recurrence, and unfavorable clinical outcomes. Moreover, NSCLC patients with concomitant *SMARCA4* mutations may not benefit from currently available treatments, underscoring the distinctiveness of this subgroup. Thoracic *SMARCA4*-deficient undifferentiated tumors (*SMARCA4*-UT) represent distinct entities from *SMARCA4*-deficient non-small cell lung cancer (*SMARCA4*-dNSCLC). This distinction is supported by their divergent pathological characteristics, demographic profiles, and survival outcomes. NSCLC cases deficient in *SMARCA4* exhibit high malignancy, yet the precise biological mechanisms underlying this phenomenon remain under intensive investigation. Pathological examination and immunohistochemistry can effectively differentiate *SMARCA4*-UT from *SMARCA4*-dNSCLC. *SMARCA4*-UT typically manifests as adenocarcinoma or, more rarely, as squamous cell carcinoma with undifferentiated rhabdomyoblastic morphology. Therefore, elucidating the mechanisms underlying *SMARCA4* alterations in NSCLC and their regulatory roles in tumorigenesis and the microenvironment is crucial. This article aims to discuss the structure, biological functions, significance in NSCLC development, and emerging potential therapeutic strategies related to *SMARCA4* while providing clinical practice guidance for NSCLC patients with *SMARCA4* deletions.

Keywords: *SMARCA4*; non-small cell lung cancer (NSCLC); clinical features; pathology; therapeutic uses

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Introduction

According (1) to estimates published by the National Cancer Center in 2022, the number of new cancer cases in China is about 4.82 million. Ganti *et al.* (2) conducted a cross-sectional epidemiological survey and found that the incidence of non-small cell lung cancer (NSCLC) in the United States increased from 175.3 per 100,000 to 198.3 per 100,000, and the 5-year survival rate was about 26.4%. Huang *et al.* (3) analyzed multiple cancer registries around

the world [e.g., Global Cancer Observatory (GLOBOCAN), World Health Organization (WHO), Surveillance, Epidemiology, and End Results (SEER), etc.] and estimated that the global standardized incidence and mortality rates of lung cancer were 22.4 per 100,000 and 18.0 per 100,000, respectively. In 2019, the global mortality rate attributed to lung cancer (including tracheal and bronchial lung cancer) was approximately 2.04 million, ranking first among 29 types of tumors (excluding non-melanoma skin cancer) (4). Therefore, as one of the malignant tumors with high incidence, the prevention and control of lung cancer are of great significance.

SMARCA4 (SWItch/Sucrose Nonfermentable, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4) was first reported in 2015 by Le Loarer *et al.* (5). Through RNA sequencing of unclassified thoracic sarcomas, the team identified 19 cases of *SMARCA4*-inactivated thoracic sarcomas that shared distinct clinical features. These tumors were characterized by compressive mediastinal masses, a predilection for adults aged 30–35 years, and a notably short median survival time of only 7 months. To classify these tumors accurately, the team conducted transcriptomic profiling and gene enrichment analysis, revealing that *SMARCA4*-deficient thoracic sarcomas are not associated with lung cancer, regardless of the *SMARCA4* mutation status.

With the release of the fifth edition of the WHO classification of thoracic tumours in 2021, molecular diagnostic techniques were officially incorporated into tumor classification. This edition introduced a new category: "Thoracic SMARCA4-deficient undifferentiated tumor (SMARCA4-UT)" (6). *SMARCA4*-UT is a high-grade malignant tumor characterized by an undifferentiated or rhabdoid phenotype and loss of *SMARCA4*. Such tumours are always referred to as the "*SMARCA4*-deficient thoracic sarcoma, *SMARCA4*-DTS" (7-9), and therefore, such tumors are renamed and classified as "other epithelial tumors of the lung".

SMARCA4 is a gene encoding a chromatin remodeling protein, encoding a protein BRG1 that is part of the SWI/SNF complex (10), and BRG1 functions to mediate chromatin remodeling (11). SWI/SNF mutations are widespread in different human cancers with an excess of deleterious mutations, with an average mutation frequency of 19% (12). The SWI/SNF (13) family of chromatin remodeling complexes, also known as the BRG1/BRM-associated factor (BAF) complex (BOX1), is a key regulator of nucleosome positioning, partially purified human homologue of the yeast hSWI/SNF complex mediates the adenosine triphosphate (ATP)-dependent disruption of a nucleosome, the hSWI/SNF complex acts directly to reorganize chromatin structure so as to facilitate binding of transcription factors (13). According to the available tumor samples in The Cancer Genome Atlas (TCGA) database (up to July 22, 2024), *SMARCA4* mutation rate was 5% (602/10,967) in all tumors and 8.6% (228/2,653) in lung adenocarcinoma (14), the frequency of *SMARCA4* mutation in metastatic NSCLC was 5.3% (67/2,621) (15). About 8% of NSCLC patients are associated with *SMARCA4* deletion (16). It has been shown (17,18) that NSCLC patients with *SMARCA4* mutations, especially homozygous deletions and truncating mutations, are more likely to develop drug resistance, early recurrence, and poor clinical outcomes compared to patients with wild-type *SMARCA4*. These studies indicate that NSCLC patients with *SMARCA4* mutations may not respond to current standard therapies, highlighting the unique nature of this patient group. *SMARCA4*-deficient thoracic sarcomas and NSCLC share distinct yet related clinical features, pathological traits, imaging findings, and prognoses (6,9,19). This review compares the impact of *SMARCA4* deficiency in both conditions, its role in tumorigenesis and the tumor microenvironment, and provides an overview of *SMARCA4*'s structure, functions, significance in NSCLC development, and emerging therapies, aiming to guide clinical management of *SMARCA4*-deficient NSCLC.

Structure, function, and oncogenic mechanism of *SMARCA4*

SMARCA4 structure

SMARC family full name: "The SWI/SNF-related, matrix-associated, actin-dependent regulators of chromatin (*SMARC*)", also known as BRG1-related factors, they are components of the human SWI/SNF-like chromatin remodeling protein complex. *SMARC* family members include *SMARCA4* (BRG1), *SMARCA2* (BRM), *SMARCB1*, *SMARCC1*, *SMARCC2*, *SMARCD1*, *SMARCD2*, *SMARCD3*, and *SMARCE1* (20).

SMARCA4 is located on chromosome 19p13 (21) and encodes the transcriptional activator BRG1. As one of the most important mutually exclusive catalytic ATPase subunits of SWI/SNF complex, *SMARCA4* activates or inhibits transcription through the function of ATPase and provides energy for chromatin remodeling process, *SMARCA4*

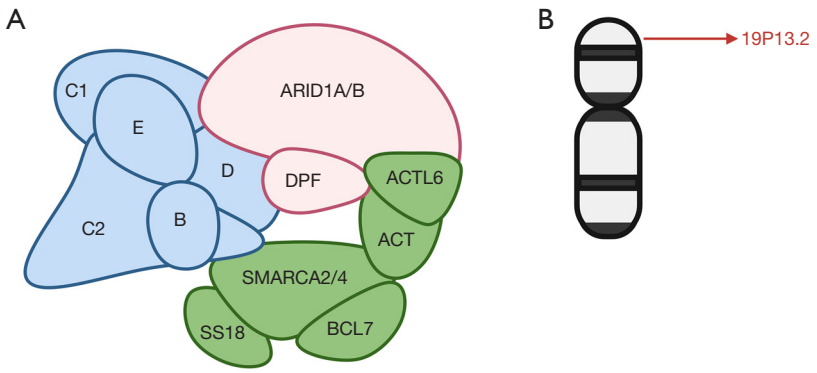

Figure 1 The structure and chromosomal localization of *SMARCA4*. (A) Schematic representation of the structure of the mSWI/SNF complex. *SMARCA4*, as one of the most important mutually exclusive catalytic atpase subunits of the SWI/SNF complex, provides energy for chromatin remodeling by activating or inhibiting transcription through ATpase function. The mSWI/SNF complex is further classified into three subtype—-cBAF, PBAF, and ncBAF—based on distinct differences in their subunit compositions (22). The cBAF encompasses *ARID1A*, *ARID1B*, *BRM/BRG1*, *et al.* The PBAF incorporates *ARID2*, *PBRM1*, *BRD7*, *et al.* The ncBAF comprises *BRD9*, *BRM/BRG1*, *et al.* (23). (B) Localization of *SMARCA4* in chromosomes. This image is created by BioRender. cBAF, canonical BAF; mSWI/SNF, mammalian SWItch/Sucrose Nonfermentable family; ncBAF, non-canonical BAF; PBAF, polybromo-associated BAF.

has a bromine domain, which is a domain capable of recognizing acetylated lysine residues, such as those in the n-terminal tail of histones, that play a regulatory role in gene transcription (20). The structure and chromosomal localization of *SMARCA4* are illustrated in *Figure 1* (22,23).

SMARCA4 biological functions

SMARCA4 has a variety of biological functions. *SMARCA4* encodes the BRG1 protein, which is essential for maintaining the expression of several smooth muscle-specific genes in primary cultures of aortic smooth muscle cells (24). The *SMARCA2* and *SMARCA4* play different roles in early mammalian embryogenesis. Ectopic expression of *SMARCA2* and *SMARCA4* can lead to developmental arrest of a single female porcine embryo (25). BRG1 protein also plays an important role in sperm development, the loss of BRG1 will hinder the process of meiotic spermatogenesis, resulting in increased apoptosis, and its loss of function will lead to infertility (26). In Sonic hedgehog (SHH) signaling, the chromatin regulators *SMARCA4*/BRG1 are required for Gli-mediated transcriptional activation. BRG1 controls a transcriptional program that specifically regulates the growth of SHH medulloblastoma. The absence of BRG1 markedly suppresses tumor formation and progression (27). A comprehensive overview of the biological functions of *SMARCA4* is provided in *Figure 2* (28).

SMARCA4 is aberrated in a variety of malignant tumors, including *SMARCA4*-deficient thoracic sarcoma, lung cancer, colon adenocarcinoma, bladder urothelial carcinoma and breast cancer, as well as some rare tumors such as ovarian hypercalca4-deficient small cell carcinoma (small cell carcinoma of the ovary of hypercalcemic type; SCCOHT) and *SMARCA4*-deficient uterine sarcomas (5,29-34).

Mechanisms of SMARCA4 in NSCLC

Study (35) has indicated that the loss of *SMARCA4* increases the sensitivity of lung secretory protein-positive cells to malignant transformation and tumor progression, resulting in an elevated incidence of tumor metastasis. Loss of *SMARCA4* would compromise the functionality of the SWI/SNF complex, leading to diminished chromatin accessibility of pulmonary lineage motifs and ultimately facilitating tumor progression. Therefore, during lung cancer development, *SMARCA4* deficiency triggers the formation of invasive malignant tumors by directly impacting the function of the SWI/SNF complex and chromatin regulation. *SMARCA4*-deficient NSCLC is highly aggressive, with vascular invasion and pleural metastasis (36).

Research (37) indicates that the deficiency of BRG1 results in the loss of sensitivity of tumor cell lines to retinoic acid (RA) and glucocorticoids (GC). Moreover, there exists an antagonistic functional relationship between BRG1 and MYC. The presence of BRG1 significantly inhibits the

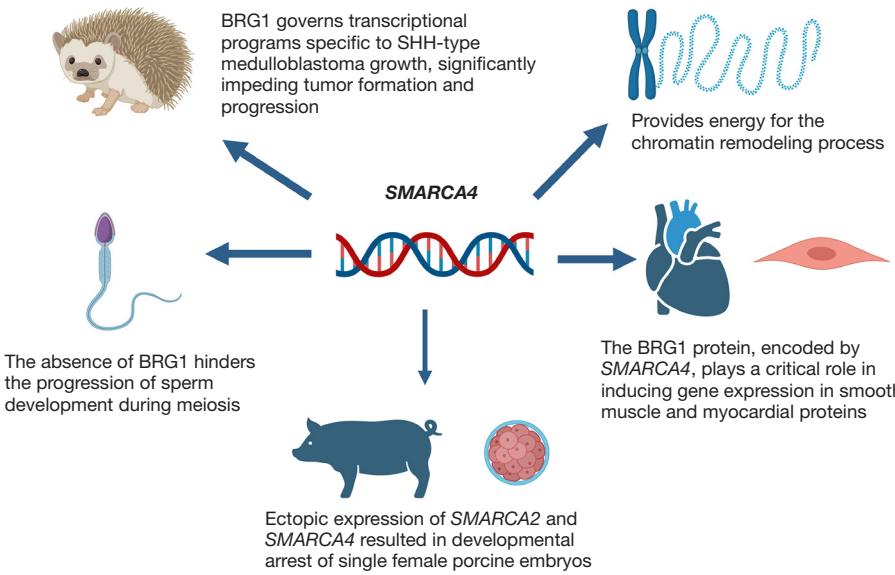

Figure 2 Multiple biological functions of *SMARCA4*. This image is created by BioRender (28). SHH, Sonic hedgehog signaling.

invasion and progression of lung cancer cells in nude mice and reduces MYC.

Research (38) has documented the impact of BRG1 silencing on human NSCLC cells. The absence of BRG1 resulted in altered cell morphology, increased tumorigenic potential, and gene expression analysis indicated a reduction in the expression of genes associated with human NSCLC progression. These findings demonstrate that the lack of BRG1 in NSCLC cells is correlated with changes in chromatin structure, including variances in nucleosome positioning and occupancy around transcription start sites of disease-related genes. These results imply that BRG1 depletion contributes to the invasiveness of NSCLC by influencing nucleosome positioning across a broad spectrum of genes, including crucial cancer-related genes.

Currently, there is a wealth of research investigating the impact of *SMARCA4* on the onset and progression of NSCLC. However, a definitive conclusion remains elusive. Nevertheless, clinical observations suggest that NSCLC with concurrent *SMARCA4* deficiency demonstrates heightened malignancy in its biological behavior.

SMARCA4 deficiency and NSCLC

SMARCA4 mutation rate

Schoenfeld *et al.* (16) analyzed genomic data from 4,813 NSCLC patients and found that the *SMARCA4* mutation rate was approximately 8% (407/4,813). The identified *SMARCA4* mutations can be primarily categorized into two types (16): Type I mutations encompass truncation mutations, fusions, and homozygous deletions, while Type II mutations comprise missense mutations.

Pathological features

The thoracic *SMARCA4*-deficient undifferentiated tumor is considered a distinct entity from *SMARCA4*-deficient NSCLC due to its unique phenotypic characteristics (6). Pathologically, *SMARCA4*-UT is characterized by irregularly shaped, variably sized, interconnected epithelioid cells with prominent nucleoli and vacuolated chromatin. The nuclear morphology is relatively uniform, with occasional mild pleomorphism observed in some cells. The stroma is sparse, and there is typically no discernible epithelial histological structure (such as glandular or squamous differentiation), except in rare cases where coexistence with NSCLC has been reported (6). When the pathological examination reveals the absence of epithelial structures and strongly positive diffuse cytokeratin expression, it is usually possible to exclude *SMARCA4*-deficient non-small cell lung cancer (*SMARCA4*-dNSCLC) (7).

In the pathological diagnosis of *SMARCA4*-UT and *SMARCA4*-dNSCLC, they are typically differentiated based on morphological features, with the latter manifesting as typical adenocarcinoma or less common squamous cell carcinoma (19).

Herpel *et al.* (39) conducted an immunohistochemical analysis of 316 NSCLC specimens, revealing that in SWI/SNF-deficiency lung cancer, the differentiation of glandular or squamous histology was more prevalent compared with SWI/SNF-deficient cancers from other organs. Retrospective data (40) also indicate that among 105 patients with *SMARCA4*-dNSCLC, a minority of them (23%) exhibited negative expression of *SALL4*. Consequently, it is proposed that for lung adenocarcinoma with negative TTF1 expression, the assessment of *SMARCA4* and *SMARCA2* should be augmented, as 80% of TTF-1-negative lung adenocarcinoma cases present *SMARCA4/SMARCA2* gene deletion (39). *SMARCA4*-UT is characterized by an undifferentiated rhabdomyoid morphology and loss of *SMARCA4* expression (5).

However, *SMARCA4*-UT also contains some NSCLC components (5). Research indicates that the association between *SMARCA4*-UT and SD-NSCLC is more akin to sarcoma than NSCLC. In a study by Rekhtman *et al.* (9), the pathological characteristics of *SMARCA4*-UT were compared with those of *SMARCA4*-dNSCLC, revealing that *SMARCA4*-UT is overrepresented in male patients and linked to a more extensive history of smoking as well as a higher prevalence among young individuals, consistent with findings reported by Le Loarer *et al.* (5). However, the most notable disparity lies in the primary tumor size, with *SMARCA4*-UT exhibiting significantly larger dimensions than *SMARCA4*-dNSCLC. Moreover, immunohistochemistry also demonstrated that unlike *SMARCA4*-UT, all *SMARCA4*-dNSCLC displayed widespread membrane marker claudin-4 expression, while the presence of stem cell markers such as *SALL4* and *CD34* was frequently absent or rare. Additionally, the research team identified *TP5* as the two most common mutations in both entities, followed by STK11 and KEAP1. *SMARCA4*-UT is also characterized by the overexpression of *SMARCB1* (9). Thus, *SMARCA4*-UT and *SMARCA4*-dNSCLC represent two closely related yet distinct tumor entities.

To distinguish *SMARCA4*-UT from *SMARCA4*-mutated lung cancers and *SMARCA4*-sparing thoracic undifferentiated sarcomas, Le Loarer's group (5) compared gene enrichment analysis for these three tumors. *SOX2* gene was the most enriched gene in *SMARCA4*-deficient thoracic sarcoma.

Imaging features of SMARCA4-deficient NSCLC

The study (41) found no significant difference in lesion distribution between the two lungs; however, there was a higher incidence in the upper lobes. The median tumor size was 42.83 mm. Lymph node metastasis was observed in a substantial proportion of patients (20/23), with mediastinal lymph node involvement being predominant (18/23). Common metastatic sites included bone (10/23). Lesion diameters were comparable to those of typical ground-glass opacities (GGOs), and most lesions exhibited spiculation (21/23).

In addition to aiding in the diagnosis of *SMARCA4*-dNSCLC through methods such as computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) (42), ultrasound can also be utilized for diagnostic assistance (43), ultrasound examination can aid in evaluating the lymph node status.

There is limited literature available regarding the radiological characterization of *SMARCA4*-UT and *SMARCA4*-DTS. Previous research has suggested that *SMARCA4*-UT commonly presents as a mediastinal compressive mass. In terms of imaging features, Kim *et al.* (42) conducted CT and PET-CT examinations on nine *SMARCA4*-dNSCLC patients. They found that most tumors exhibited lobulated features, were located in the outer lung zones, and frequently invaded the pleura or chest wall. Fludeoxyglucose (FDG) PET-CT imaging showed strong FDG accumulation within the tumors, with a median standard uptake value (SUV) max of 13.5 and a consistently diffuse uptake pattern.

The imaging features of *SMARCA4*-deficient thoracic sarcoma (*SMARCA4*-DTS) were retrospectively analyzed by Crombé *et al.* (44) conducted a retrospective analysis of 21 *SMARCA4*-DTS patients. Primary tumors were mainly in the mediastinum and pleura, with indistinct margins. Contrast-enhanced scans showed heterogeneous enhancement in 20 cases. PET-CT imaging revealed high ^{18}F-FDG uptake in 8 patients, and 19 cases had lymph node necrosis. The main metastatic sites were the adrenal glands, lungs, and bones.

Clinical characteristics and prognosis of *SMARCA4*-deficient NSCLC

Retrospective analysis (41) showed that *SMARCA4*-dNSCLC was predominantly male (22/23), with an average age of 62.7 years (range, 48–82 years) and a median survival of 12 months. Most patients exhibited clinical features similar to those of typical lung cancer patients. In contrast, *SMARCA4*-UT is characterized by compressive mediastinal

masses, occurring more frequently in adults aged 30–35 years, with a median survival of only 7 months. This highlights significant differences in patient demographics and survival times between *SMARCA4*-UT and *SMARCA4*-dNSCLC, suggesting that *SMARCA4*-UT has a higher malignancy and is more common in younger populations.

As well as retrospective data analysis (40) showed that *SMARCA4*-dNSCLC patients with older age, male, smoking history, invasive tumor larger, high proliferation index (Ki-67), more adrenal metastasis and lymph node metastasis was significantly associated with the factors such as more and less epidermal growth factor receptor (EGFR) mutations.

In comparing the survival prognosis between *SMARCA4*-dNSCLC and *SMARCA4*-UT, it has been reported in the literature (9) that the overall survival (OS) of *SMARCA4*-UT patients is significantly lower than that of *SMARCA4*-dNSCLC patients [median overall survival (mOS) 5.2 *vs.* 20.7 months, P=0.004]. Previous reports (45) show that 63% (58/92) of *SMARCA4*-UT patients were diagnosed at stage IV, and 17% developed recurrent or metastatic disease. The mOS from metastatic diagnosis was 7.3 months, indicating the aggressive nature and poor prognosis of *SMARCA4*-UT.

Study (40) has indicated that *SMARCA4* status, smoking history, and invasive tumor size are independent factors influencing the prognosis of NSCLC. Furthermore, compared to patients with *SMARCA4*-iNSCLC, those with *SMARCA4*-dNSCLC exhibit poorer overall prognoses. Amongst patients with *SMARCA4*-dNSCLC, the median survival time was found to be 12.2 months, with a one-year survival rate of 51% and a 2-year survival rate of 20%. However, a retrospective study (46) has suggested that there is no significant difference in median survival time between *SMARCA4*-UT and *SMARCA4*-dNSCLC, nor in progression-free survival.

At present, it is firmly established that *SMARCA4* mutations represent an independent risk factor linked to unfavorable prognosis in NSCLC patients (30,47). As previously noted by Schoenfeld *et al.* (16), they stratified the N=4,813 *SMARCA4* mutations into two categories and assessed the survival outcomes for each mutation type. The findings demonstrated a significant association between type 1 mutations (n=212) and the shortest survival time (P<0.001), suggesting that type 1 mutations, encompassing truncated mutations, fusions, and homozygous deletions, were associated with the poorest survival outcomes.

Fernando *et al.* (17) conducted a large-scale retrospective analysis comparing 2,194 patients with wild type-*SMARCA4* and those with *SMARCA4* mutations in NSCLC. The results demonstrated that NSCLC patients harboring homozygous *SMARCA4* alterations had a significantly worse prognosis. Specifically, compared to the wild type-*SMARCA4* cohort, patients with homozygous truncating *SMARCA4* mutations exhibited a markedly reduced OS. Moreover, these patients showed a significantly poorer OS when treated with chemo-immunotherapy (CIT). Therefore, advanced NSCLC patients with homozygous truncating *SMARCA4* mutations represent a distinct population with unmet clinical needs. Long *et al.* (48) found that patients with *SMARCA4* mutations had significantly poorer survival compared to those with wild-type *SMARCA4*. In the *SMARCA4*-Mut group, Napsin-A expression was associated with longer survival.

In general, *SMARCA4*-UT and *SMARCA4*-dNSCLC have different clinical characteristics and survival prognosis. *SMARCA4*-UT is more aggressive than *SMARCA4*-dNSCLC and occurs in younger age group. In the NSCLC population, *SMARCA4*-mutated patients have a poor OS and may not benefit from currently available treatments.

Treatment of *SMARCA4*-deficient NSCLC

Application of chemotherapy in SMARCA4-deficient NSCLC

Platinum-based chemotherapy is the preferred treatment for *SMARCA4*-deficient NSCLC, but its efficacy remains controversial. Shi *et al.* (49) found that *SMARCA4*-deficient undifferentiated tumor were generally resistant to chemotherapy but sensitive to chemotherapy combined with immunotherapy. Moreover, patients with *SMARCA4*-deficient thoracic tumors who received paclitaxel-based chemotherapy had longer median progression-free survival (mPFS) than those who received pemetrexed-based chemotherapy.

Furthermore, recent basic research (50) has demonstrated that the loss of *SMARCA4/2* in ovarian and lung cancer is correlated with resistance to chemotherapy. The absence of *SMARCA4/2* in tumor cells results in reduced expression of the estrogen receptor-Ca^{2+} (ER-Ca^{2+}) channel IP3R3, leading to decreased transfer of Ca^{2+} to mitochondria and inhibition of cell apoptosis, ultimately contributing to increased chemotherapy resistance.

Both clinical studies and basic experiments have revealed limitations in the efficacy of chemotherapy for treating *SMARCA4*-dNSCLC. However, research (51) show that

low *SMARCA4*/BRG1 expression in NSCLC is significantly associated with better prognosis and predicts sensitivity to platinum-based adjuvant therapy. Patients with low *SMARCA4* expression have longer 5-year disease-specific survival (DSS) after cisplatin-based treatment compared to those with high expression. Multivariate analysis indicates improved OS in these patients post-treatment. This may be due to the distinct roles of DNA damage repair defects and chromatin remodeling in cisplatin response (52).

Given the limited response of *SMARCA4*-dNSCLC patients to traditional chemotherapy (53), it is crucial to understand the molecular mechanisms and real-world clinical data behind this suboptimal outcome. Identifying these mechanisms can help detect predictive and prognostic biomarkers for this NSCLC subgroup. This chapter reviews current knowledge on chemotherapy, immunotherapy, and targeted therapy to provide robust evidence-based guidance for clinical practice.

Advances in the regulation of immune system mediated by SMARCA4

Study has indicated (54) that the effectiveness of immune checkpoint inhibitors (ICIs) in the treatment of *SMARCA4*-dNSCLC may be constrained, primarily attributed to the distinct immune microenvironment characteristics of *SMARCA4*-dNSCLC compared to non-*SMARCA4*-dNSCLC. In *SMARCA4*-dNSCLC, there is an elevated density of $FOXP3^+$ cells and neutrophils, while the density of $CD8^+$ T cells remains unaltered. Additionally, patients with early-stage and metastatic *SMARCA4*-dNSCLC receiving anti-programmed death-1 (PD1) treatment demonstrate a notably reduced OS.

The efficacy of immunotherapy may be critically influenced by the impact of *SMARCA4* deficiency on the tumor immune microenvironment. Study (55) has demonstrated that in a murine model of *SMARCA4*-deficient ovarian cancer, *SMARCA4* loss leads to enhanced intrinsic immunogenicity of cancer cells, characterized by upregulation of long terminal repeat (LTR) sequences, increased expression of interferon-stimulated genes (ISGs), and heightened antigen presentation machinery. The mammalian canonical BRG1/Brm-associated factor (cBAF) is essential for the differentiation of activated CD8 T cells into T effector (T + eff) cells, and manipulation of cBAF at the early stage of T cell differentiation can improve cancer immunotherapy (56). In the context of SMARCA4 deficiency, the expression of BRG1 protein is abrogated, leading to impaired cBAF-mediated activation of CD8 T cells. Consequently, this may affect the efficacy of immunotherapy in SMARCA4-deficient tumors. However, a study (57) has found that the loss of SWI/SNF complex function is not significantly associated with the clinical prognosis of tumors treated with ICIs, and SWI/SNF variants should not be considered as biomarkers of response to ICIs.

Based on the effect of *SMARCA4* on tumor immune microenvironment, there are many clinical studies on immunotherapy of *SMARCA4*-dNSCLC. Naito *et al.* (36) analyzed immunohistochemical results of 1013 NSCLC pathological samples using tissue microarray (TMA) to detect the expression of SWI/SNF complex (BAF) subunits, *SMARCA4*, *SMARCA2*, *ARID1A*, and *ARID1B*. The results found that lack of BAF was observed in 5.4% of cases. Simultaneous loss of expression of two or more SWI/SNF complex subunits was detected in 0.7% of cases. The proportion of patients with programmed cell death ligand 1 (PD-L1)-positive tumors was higher in BAF-disrupted NSCLC patients than in BAF-intact patients. In stage I NSCLC, SWI/SNF deletion (n=23) was associated with shorter survival and recurrence-free survival compared with the BAF-intact group (n=563). The degree of tumor mutation burden (TMB) in the BAF deletion group (n=3) was significantly higher than that in the BAF intact group (n=7). It is concluded that the loss of SWI/SNF expression in NSCLC is associated with aggressive clinicopathological features, PD-L1 positive status and high TMB.

In a retrospective analysis (58), it was determined that NSCLC samples with SWI/SNF mutations demonstrate elevated TMB, but no statistically significant difference in PD-L1 expression levels. Moreover, patients with advanced NSCLC and SWI/SNF mutations exhibited a poorer prognosis (mOS: 25.37 *vs.* 35.45 months, P<0.001). Schoenfeld *et al.* also noted (16) that *SMARCA4* mutant tumors have higher TMB but lower or negative PD-L1 expression. Additionally, recent research (59) has suggested that patients receiving ICI therapy with high TMB (TMB ≥10 mut/Mb) demonstrated improved PFS and OS compared to those with low TMB (TMB <10 mut/Mb), indicating superior clinical outcomes for high-TMB patients undergoing immunotherapy.

However, there is controversy about (58) the relationship between TMB level and ICIs treatment effect. In the above-mentioned study, despite the higher TMB level in SWI/SNF mutant patients, the objective response rate (ORR) of immunotherapy in SWI/SNF mutant patients

was significantly lower than that in SWI/SNF wild-type patients. In addition, SWI/SNF mutations were not significantly associated with PFS in first-line ICI treatment or ICIs combined with chemotherapy.

The utilization of immunotherapy in combination with chemotherapy for SMARCA4-deficient NSCLC

A retrospective analysis (60) indicated that for IV-stage *SMARCA4*-UT patients, the combination of ICIs and chemotherapy significantly prolonged mPFS compared to traditional first-line chemotherapy (26.8 *vs.* 2.73 months, P=0.0437), while the ORR was similar between the two treatments (71.4% *vs.* 66.7%). Under comparable treatment conditions, there was no significant difference in disease-free survival (DFS) between *SMARCA4*-UT and *SMARCA4*-dNSCLC patients. Additionally, the mOS of *SMARCA4*-UT or *SMARCA4*-dNSCLC patients receiving first-line ICI treatment was significantly longer than that of those receiving later-line ICI treatment or no ICI treatment. These findings suggest that a first-line regimen combining immunotherapy and chemotherapy may confer benefits to both *SMARCA4*-UT and *SMARCA4*-dNSCLC patients.

Research (61) indicates that there is no significant difference in the ORR (76.5% *vs.* 69.0%, P=0.836) or disease control rate (DCR) (100.0% *vs.* 89.7%, P=0.286) between the PD-1 monoclonal antibody plus chemotherapy group and the chemotherapy-alone group. However, the combination therapy significantly extends mPFS.

A large-scale sequencing study from China (58) analyzed 2,027 lung tumor samples and found that 14.7% (297/2,027) of patients had SWI/SNF mutations, with *SMARCA4* being the most common (32%). NSCLC patients with these mutations who received first-line immunotherapy plus chemotherapy (n=20) showed significantly better survival outcomes (mPFS: 8.7 *vs.* 6.93 months, P=0.028) compared to those treated with chemotherapy alone (n=63). These results suggest potential benefits of immunotherapy for SWI/SNF-mutated patients.

Schoenfeld *et al.* (16) evaluated the prognosis of patients with NSCLC treated with ICI (n=445) and found that, compared with *SMARCA4* class 2 mutations or *SMARCA4* wild-type NSCLC, patients with class 1 mutations or *SMARCA4* wild-type NSCLC had a higher ORR after ICIs treatment (P=0.027), and there were no significant differences in PFS (P=0.74) or OS (P=0.35) between patients with class 1 and class 2 mutations after ICIs treatment. These results suggest that *SMARCA4* class 1 mutant NSCLC has a better response to immunotherapy.

Fernando *et al.* (17) compared wild-type *SMARCA4* patients with NSCLC patients harboring a homozygous truncating mutation in *SMARCA4*, and observed that within the context of CIT, NSCLC patients with a homozygous truncating mutation in *SMARCA4* exhibited significantly shorter OS (HR =1.62; P=0.01). Consequently, individuals with NSCLC carrying a homozygous truncating mutation in *SMARCA4* represent an underserved population who may not derive benefit from currently available targeted molecular therapies and CIT.

Therapeutic strategy for concurrent mutations in other genetic loci

As *SMARCA4* mutations and co-occurring oncogenic mutations in NSCLC continue to be identified, there is increasing interest in determining the impact of these co-mutations on clinical treatment outcomes. *SMARCA4* mutations display mutual exclusivity with the most prevalent targeted oncogenic mutations in NSCLC, such as *EGFR*, *ALK*, *MET*, *ROS1*, and *RET*, with *EGFR* mutations exhibiting the strongest mutual exclusivity (17).

The predominant co-occurring genetic mutations associated with *SMARCA4* loss include *TP53*, *KRAS*, *KEAP1*, and *STK11*. A retrospective analysis (16) of a substantial sample size (n=407) revealed that in lung cancer, the most prevalent mutations concurrent with *SMARCA4* alterations were *TP53* (56%), *KEAP1* (41%), *STK11* (39%), and *KRAS* (36%). Another retrospective study (61) presented genetic testing findings for 46 patients with *SMARCA4*-dNSCLC, demonstrating primary mutations such as *TP53* (10/11), *KRAS* (5/33), and *STK11* (2/9). The aforementioned research (40) also indicated that among 19 cases of *SMARCA4*-dNSCLC patients, *SMARCA4* mutations most commonly coexisted with alterations in *TP53* (80%), *LRP1B* (40%), *STK11* (27%), *KEAP1* (27%), and *KRAS* (20%).The results of gene sequencing in the retrospective data (58) showed that the most common co-mutations of SWI/SNF were *TP53* (71%), *EGFR* (31%), *LRP1B* (22%), *CDKN2A* (20%), *KRAS* (18%), *PIK3CA* (12%), *KEAP1* (12%), and *STK11* (10%).

Patients with *SMARCA4* deficiency and *KRAS* mutation may have worse clinical outcomes. *SMARCA4* deficiency and *KRAS* mutation patients had lower ORR and shorter mPFS after immunotherapy (30). The mPFS and mOS of patients with *KRAS* mutation alone were significantly shorter.

By analyzing the clinical outcomes of lung adenocarcinoma patients with *KRAS* mutations, Liu *et al.* (62) found that concurrent *SMARCA4* mutation was one of the adverse factors for clinical outcomes.

Patients with SWI/SNF mutations and *TP53* mutations have a better outcome after ICIs combined with chemotherapy, but *STK11/KEAP1* mutation status also has a negative impact on ICIs treatment outcome. SWI/SNF merger *TP53* mutations of first-line chemotherapy in patients with immunotherapy ORR *TP53* is significantly higher than patients with wild type (53.49% *vs.* 20.00%, P=0.026). However, there was no statistically significant difference in mPFS between patients with SWI/SNF and *TP53* mutations (10.9 *vs.* 5.3 months, P=0.096). Patients with *STK11/KEAP1* mutations had a lower survival advantage than those with SWI/SNF mutations (PFS: 5.9 *vs.* 12.1 months, P=0.008).

In conclusion, patients with *SMARCA4* deficient combined with *KRAS* mutation and *STK11/KEAP1* mutation exhibit poorer clinical outcomes. Conversely, patients with SWI/SNF mutation combined with *TP53* mutation may experience improved responses to combination therapy of ICIs and chemotherapy.

The potential for targeted therapy in SMARCA4-deficient lung cancer

Cyclin-dependent kinase 4/6 inhibitors

Studies have demonstrated (63) that *SMARCA4*-deficient small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) cells exhibit high sensitivity to cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (64). Currently, palbociclib (PD-0332991), ribociclib (LEE001), and abemaciclib (LY2835219) are FDA-approved CDK4/6 inhibitors for the treatment of estrogen receptor-positive (ER^+) and human epidermal growth factor receptor 2-negative ($HER2^-$) advanced breast cancer.

Given the positive therapeutic outcomes of CDK4/6 inhibitors in *SMARCA4*-deficient SCCOHT and breast cancer, it is proposed that this category of medications may offer potential for treating NSCLC.

Oxidative phosphorylation inhibitors

Study has shown (65) that tumors with *SMARCA4* mutations display increased oxidative phosphorylation (OXPHOS), resulting in elevated oxygen consumption in cells with *SMARCA4* mutations. Moreover, lung cancer cell lines and xenograft tumors with *SMARCA4* mutations exhibit heightened sensitivity to the novel small molecule OXPHOS inhibitor drug IACS-010759. Additionally, other study has demonstrated (66) that deficiency of *SMARCA4/2* suppresses the expression of glucose transporter GLUT1, leading to reduced glucose uptake and glycolysis while increasing reliance on OXPHOS. To adapt to this scenario, *SMARCA4/2*-deficient cells depend on elevated SLC38A2 (an amino acid transporter) for increased glutamine intake to support energy production through OXPHOS. Consequently, cells and tumors deficient in *SMARCA4/2* are highly susceptible to inhibitors targeting OXPHOS or glutamine metabolism. Experiments have shown (67) that SMARCA4-deficient lung cancer cells are more sensitive to the glutathione inhibitor eprenetapopt, which lowers GSH levels and induces apoptosis. Therefore, targeting OXPHOS may represent a promising strategy for treating NSCLC lacking functional *SMARCA4*.

Topoisomerase II and EZH2 inhibitors

Study has shown that SWI/SNF deletion leads to increased PRC2 activity and H3K27me3 level (68) and PCR2 is a potential therapeutic target of topoisomerase inhibitors II such as etoposide, which can bring benefits (68) NSCLC patients. *SMARCA4*-deficient tumor cells showed sensitivity (69). Previous study has shown (70) that EZH2 inhibitors can effectively suppress *SMARCA4* mutant tumors while silencing the transcriptional para-helicase *SMARCA2*. *SMARCA4* mutated in SWI/SNF atpase is sensitive to EZH2 inhibition. In *SMARCA4* mutant tumor model, low expression of *SMARCA4* was associated with the sensitivity of cells to EZH2 inhibition. Therefore, the combination of EZH2 inhibitor and TopoII inhibitor may be a potential therapeutic approach (71). A report on EZH2 inhibitors: Results of a phase II multicenter study (NCT02601950) of tazemetat in adults (ovarian hypercalcemia small cell carcinoma SCCOHT and *SMARCA4*-DUT-deficient sarcoma of the breast) showed (72) that a total of 2 patients (2/31) achieved PR. FHD-26 (73), an orally available dual ATPase subunit inhibitor, has shown anti-SWI/SNF-dependent tumor activity in animal models and is currently in clinical trials for treating SMARCA4-mutant tumors.

Ataxia telangiectasia and Rad3-related inhibitors

The integrity of the genome is constantly challenged by both intrinsic and extrinsic stressors, disrupting the progression of replication forks. Intrinsic challenges encompass inadequate or imbalanced dNTP supply, conflicts arising from R-loop transcriptional replication,

among others. Extrinsic challenges include chemical inducers, ultraviolet radiation, ionizing radiation, and other stimuli (74). The ataxia-telangiectasia mutated and Rad3-related kinase (ATR) serves as a primary regulatory factor in the replication stress response to prevent cell apoptosis. As a major activator of the replication stress response, ATR inhibitors have been shown to significantly suppress the occurrence of replication stress response in *SMARCA4*-deficient NSCLC cells by inducing cellular toxicity (75). Furthermore, study has demonstrated (76) that lung adenocarcinoma (LADC) cells lacking *SMARCA4* exhibit increased DNA replication stress both *in vitro* and *in vivo* and show good sensitivity to ATR inhibitors. Enhanced heterochromatin-associated replication stress due to the absence of *SMARCA4* increases susceptibility to ATR inhibitor-induced cellular toxicity and destabilizes reverse fork stability through Mre11 activity. These dual mechanisms collectively heighten sensitivity of *SMARCA4*-deficient LADC cells to ATR inhibitors. Collectively, these findings suggest that targeting ATR inhibitors may represent a potential therapeutic strategy for patients with *SMARCA4*-deficient NSCLC.

Aurora kinase inhibitors

The primary role of Aurora is to facilitate the formation of bipolar spindles, which are essential for mitosis and often overexpressed in tumors (77). Study has demonstrated (78) that the function of AURKA is critical in NSCLC cells lacking *SMARCA4*/BRG1. In these cells, RNA inhibitors or AURKA inhibitors induce apoptosis and cell death both *in vitro* and in xenograft mouse models. The protein HURP/DLGAP5 relies on AURKA and is vital for survival and proliferation in *SMARCA4*/BRG1 mutant cells, but it is not required for microtubule-dependent spindle assembly. Currently, clinical Aurora kinase inhibitors mainly include Alisertib, VIC-1911, LY3295668, etc., indicating potential prospects for treating NSCLC with *SMARCA4*/BRG1 loss-of-function mutations.

Bromodomain and extra terminal motif protein inhibitors (BETi)

BETi is a type of reversible inhibitor that binds to the bromodomain of BET protein BRD2-4, thereby disrupting the protein-protein interactions between BET proteins and acetylated histones or transcription factors. Study has demonstrated (79) that low doses of BETi exhibit significant anti-proliferative effects *in vitro* and *in vivo* against aggressive ovarian and lung cancer models with *SMARCA4* and *SMARCA2* mutations. Moreover, the presence of *SMARCA4* or *SMARCA2* has been found to confer resistance to BETi. Additionally, BETi effectively downregulates the gene network involved in receptor tyrosine kinase (RTK) signal transduction in cells lacking *SMARCA4/2*, including the oncogenic RTK HER3. Hence, BETi represents a rational therapeutic approach for tumors deficient in *SMARCA4/2*.

Discussion

Lung cancer is the leading cause of cancer morbidity and mortality in China, which brings a huge national economic and health burden every year. *SMARCA4*-dNSCLC has gradually come into people's attention with the classification of *SMARCA4*-UT in the fifth edition of WHO classification. Study has shown (16) that about 8% of NSCLC patients have *SMARCA4* deletion, and these patients have the characteristics of high invasiveness, poor response to immunotherapy, poor prognosis, and no good therapeutic drugs have been found. *SMARCA4* is a gene encoding a protein involved in chromatin remodeling. The encoded protein BRG1 is part of the SWI/SNF complex. The gene has multiple biological functions such as DNA replication, cell proliferation and differentiation, and DNA repair (80), resulting in a variety of changes in biological functions. Studies have also found (17,18) that *SMARCA4*-deficient patients are prone to chemoresistance, early relapse, and other adverse outcomes. *SMARCA4* deficiency also affects tumor development through SWI/SNF complex, which is mainly involved in chromosome remodel (13).

In terms of clinical pathological features, distinctions exist between *SMARCA4*-dNSCLC and *SMARCA4*-UT. Le Loarer *et al.* (5) delineated the clinical characteristics of *SMARCA4*-UT as "*mediastinal mass compression*, *predominantly occurring in adults aged 30–35*, *with a median survival time of 7 months*", while the clinical profile of *SMARCA4*-dNSCLC primarily encompasses advanced age, male gender, and a history of smoking (9,40,41). Furthermore, the survival time and prognosis for *SMARCA4*-dNSCLC are superior to those for *SMARCA4*-UT (9,40). Pathologically speaking, apart from both being associated with *SMARCA4* deficiency, some NSCLC components are present in *SMARCA4*-UT. The genetic relationship between *SMARCA4*-UT and sarcoma is closer than that with *SMARCA4*-dNSCLC. Immunohistochemically speaking, compared to *SMARCA4*-UT, claudin-4 exhibits diffuse cell membrane marker expression in cases of *SMARCA*

4-dNSCLC,whereas stem cell markers are mostly absent or weakly expressed (9). Regarding imaging findings (41,42), mediastinal compressive masses are more common in cases of *SMARCA4*-UT, while *SMARCA4*-dNSCLC patients often present with solitary nodules or masses. Most tumors are located peripherally within the lungs; they exhibit relatively strong FDG accumulation and have a higher incidence rate in the upper lobe. With regard to metastasis patterns: it tends to spread to mediastinal lymph nodes as well as sites such as bone, brain, adrenal glands etc.

The choice of treatment strategy for *SMARCA4*-dNSCLC is slightly different from the traditional NSCLC treatment. The reason is that *SMARCA4* deficiency leads to the change of tumor immune microenvironment, and then immune combined with chemotherapy or other methods are used to treat *SMARCA4*-dNSCLC. Emerging evidence from clinical studies (58,60,61) suggest that *SMARCA4*-dNSCLC exhibits elevated TMB, a biomarker potentially associated with enhanced immunotherapeutic efficacy. However, this correlation remains clinically contentious, with ongoing debates regarding its predictive value in treatment outcomes. Patients with *SMARCA4* deletion and *KRAS* mutation, SWI/SNF mutation and *STK11/KEAP1* mutation may have worse clinical outcomes, but patients with SWI/SNF mutation and *TP53* mutation have better outcomes after ICIs combined with chemotherapy, which may be due to the interaction between genes that cause different responses of tumors to chemotherapy.

At present, there are also a series of targeted drugs such as CDK4/6 inhibitors, oxidative phosphorylation inhibitors, topoisomerase II and EZH2 inhibitors, ATR inhibitors, AURKA inhibitors, bromodomain/BET inhibitors, but most of them are in the clinical trial stage. Moreover, the clinical efficacy lacks high-level clinical evidence such as large sample, multi-center cohort studies or randomized controlled trials. It is believed that in the future, with the deepening of molecular biology research, more and more studies on the mechanism of *SMARCA4*-induced tumor development will be gradually clarified, in the hope of the emergence of specific drugs with clear targets, exact efficacy and high safety.

Conclusions

"*SMARCA4*" is a gene encoding a protein crucial for chromatin remodeling. Approximately 8% of patients with NSCLC present with deletions in the *SMARCA4* gene, which are strongly associated with an augmented propensity for developing drug resistance, early recurrence, and adverse clinical outcomes. Patients harboring mutations in *SMARCA4* may not reap benefits from currently available therapeutic regimens, highlighting the distinctiveness of this specific patient cohort. NSCLC cases deficient in *SMARCA4* are highly malignant, yet the precise biological mechanisms remain under intense investigation. Pathological examination and immunohistochemistry can proficiently differentiate between *SMARCA4*-UT and *SMARCA4*-dNSCLC. The former typically manifests as adenocarcinoma or, rarely, as squamous cell carcinoma featuring undifferentiated rhabdomyoblastic morphology.

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Footnote

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