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Chromatin remodeling and cancer: the critical influence of the SWI/SNF complex

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Abstract
The SWI/SNF complex was first identified in yeast and named after studies of mutants critical for the mating-type switch (SWI) and sucrose non-fermenting (SNF) pathways.The SWI/SNF complex plays a pivotal role in regulating gene expression by altering chromatin structure to promote or suppress the expression of specific genes, maintain stem cell pluripotency, and participate in various biological processes. Mutations in the SWI/SNF complex are highly prevalent in various human cancers, significantly impacting tumor suppressive or oncogenic functions and influencing tumor initiation and progression. This review focuses on the mechanisms by which ARID1A/ARID1B, PBRM1, SMARCB1, and SMARCA2/SMARCA4 contribute to cancer, the immunoregulatory roles of the SWI/SNF complex, its involvement in DNA repair pathways, synthetic lethality, and applications in precision oncology.

Background

The SWI/SNF complex was initially discovered in yeast, where it plays a critical role in chromatin remodeling, and homologous complexes exist in mammals [1–4]. Chromatin is a highly ordered structure composed of DNA and proteins that wraps around the DNA, obstructing the access of transcription factors and other regulatory elements [1–4]. The SWI/SNF complex utilizes the energy generated by ATP hydrolysis to mobilize nucleosomes, exposing specific genomic regions from the chromatin structure, thereby promoting or repressing gene expression [5]. It also participates in DNA repair, replication, maintenance of stem cell pluripotency, and various other biological processe [1–4].

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Research significance

Mutations in the SWI/SNF complex occur at high frequencies in various human cancers, including breast, ovarian, colorectal, gastric, and pancreatic cancers. These mutations significantly impact tumor suppressive or oncogenic functions, influencing tumor initiation and progression [6–16].

ARID1A mutations are highly prevalent in breast cancer. Loss of ARID1A alters chromatin accessibility, affecting gene expression, which in turn promotes tumor cell proliferation and endocrine therapy resistance [1, 8]. In the MCF7 breast cancer cell line, BRD9 regulates cell proliferation through the TGF-β pathway. Inhibition of BRD9 significantly reduces the proliferative and migratory capacities of these cells [17].

Studies indicate that ARID1A, a critical subunit of the SWI/SNF complex, is mutated in over 50% of ovarian clear cell carcinomas (OCCC) [11, 18–20], thereby disrupting chromatin remodeling and promoting tumor initiation and progression. Furthermore, ARID1A mutations are associated with resistance to conventional therapies, such as platinum-based chemotherapy, in OCCC [11, 18–20].

High levels of BRD9 expression have been observed in tumor tissue samples from colorectal cancer patients. Knockdown of BRD9 may inhibit colorectal cancer progression through the Wnt/β-catenin signaling pathway [21]。Spisak utilized patient-derived organoid (PDO) models and in vitro organoid xenograft models to evaluate the in vivo function of SMARCB1. The results demonstrated that SMARCB1 loss promotes colorectal cancer cell differentiation and inhibits tumor growth in various colorectal cancer cell models [22].

In gastric cancer, mutations in the ARID1A gene are often accompanied by impaired chromatin remodeling, leading to abnormal gene expression that affects tumor behavior and prognosis. Loss of ARID1A function has been associated with poor prognosis in gastric cancer patients and may serve as a potential biomarker for immune checkpoint inhibitor therapies [23, 24].

Historical research progress of SWI/SNF complex

Advances in SWI/SNF complex research encompass detailed studies of its composition, structure, and functional mechanisms, as well as investigations into its mutations and therapeutic potential in cancer [4](Fig. 1).

2001–2002 Studies on SMARCB1 in tumor suppression

A significant proportion of rhabdoid tumors exhibit allelic loss on chromosome 22 [25], where the SMARCB1(SNF5/INI1/Baf47) gene frequently undergoes mutations in these tumors [26]. Studies confirmed that the loss of Snf5/Ini1/Baf47/SmarcB1 (a core subunit of the SWI/SNF complex) results in high susceptibility to aggressive cancers [27]. The study by Professor Charles W. M. Roberts and his team confirmed that heterozygous deletion of the SNF5 gene in mice led to the development of tumors resembling human malignant rhabdoid tumors (MRT). The loss of Snf5 protein in tumor cells provided strong evidence supporting Snf5 as a tumor suppressor gene; however, the incidence rate was low [28].

Two years later, Professor Charles W. M. Roberts' team generated Snf5-floxed and Snf5-inv mice using an inducible gene recombination system [27].The results from Snf5^floxed mice showed that Snf5 deletion led to extensive apoptosis and irreversible bone marrow failure [27]. As a result, 90% of the mice died within three weeks, with almost no tumor formation.In Snf5^inv mice, 100% developed tumors, and all eventually succumbed to cancer [27]0.90% of the mice developed mature CD8⁺T-cell lymphoma, while 10% developed malignant rhabdoid tumors (MRT), with a median onset of only 11 weeks [27].Immunohistochemistry confirmed the loss of SNF5 protein [27].

2009–2010 Studies on SMARCA2/SMARCA4 in tumor suppression

The regulation of stem cells partly relies on genetic pathways frequently dysregulated in tumorigenesis. The protein component of telomerase, TERT (telomerase reverse transcriptase), interacts with BRG1 (also known as SMARCA4) to activate Wnt pathway genes [29]. Telomerase directly regulates the Wnt/β-catenin signaling pathway by acting as a cofactor of the β-catenin transcriptional complex [29]. Pham LV demonstrated that the transcription factor NFATc1 regulates gene expression in diffuse large B-cell lymphoma (DLBCL) cells through chromatin remodeling mechanisms. The NFATc1/BRG1 complex induces DNase I hypersensitive sites at promoters and recruits other transcription factors to active chromatin sites to regulate gene transcription [30].

In pancreatic cancer, SMARCA2 often exhibits single-copy deletions, with homozygous deletions and localized single-copy losses observed in certain cell lines, such as Hup-T4 and YAPC [31]. SMARCA2 may act as a tumor suppressor in pancreatic cancer, and its deletion likely

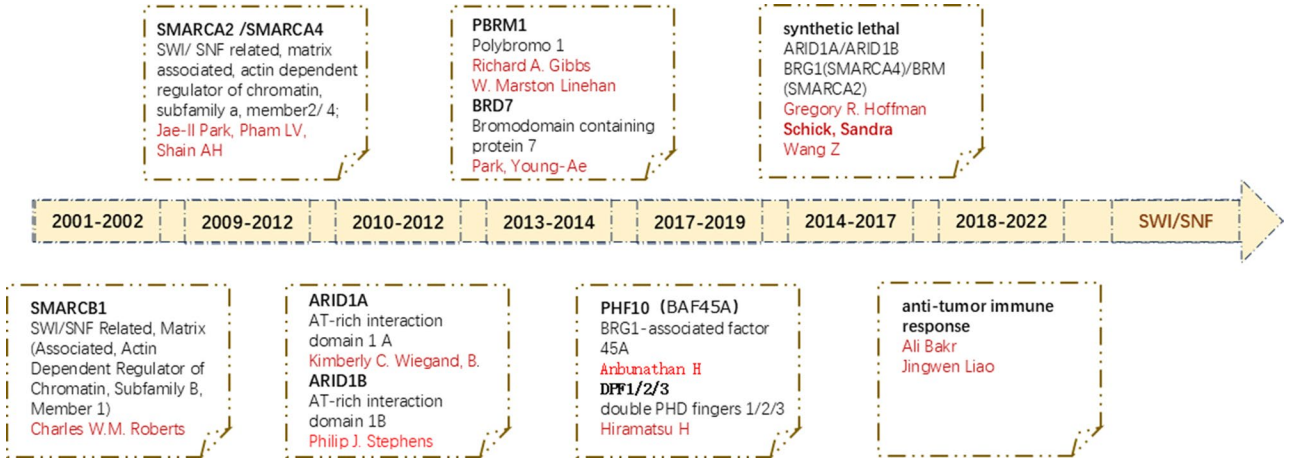

Fig. 1 Time line of SWI/SNF research. A brief history of molecular and therapy of SWI/SNF

impairs chromatin remodeling functions, disrupting the regulation of gene expression [31].

2010–2012 Studies on ARID1A/ARID1B in tumor suppression

ARID1A is a tumor suppressor gene, with mutations identified in 57% of ovarian clear cell carcinomas (OCCC) [32, 33] and 30% of endometrioid carcinomas [33]. In gastric cancer, ARID1A frequently exhibits inactivating mutations or protein loss [34]. ARID1B frequently undergoes inactivating mutations, such as truncating and missense mutations, in ER + breast cancer. Its inactivation may lead to aberrant chromatin closure, preventing the expression of tumor suppressor genes (CDKN1A and CDKN2A), thereby promoting breast cancer cell proliferation and evasion of apoptotic mechanisms [35].

2013–2014 Studies on PBRM1 in tumor suppression

PBRM1 mutations occur at a high frequency in clear cell renal cell carcinoma (ccRCC) [36], Tumors smaller than 4 cm with PBRM1 mutations are more likely to exhibit stage 3 pathological features. Most mutations result in loss of function, which is associated with advanced stage, higher tumor grade, and potentially worse cancer-specific survival [36–38].

2017–2019 Studies on PHF10 and DPF proteins in tumor suppression

Downregulation of PHF10 in uveal melanoma alters numerous biological pathways, including those related to development and adhesion. These findings support PHF10 as a novel tumor suppressor located on chromosome 6q27 [39]. The core SWI/SNF complex associates with a unique co-repressor complex through DPF family proteins, DPF1 or DPF3a. Serum-induced glioblastoma differentiation downregulates endogenous DPF1 and DPF3a expression, and shRNA-mediated knockdown of these genes reduces sphere-forming ability and tumorigenicity in murine xenograft models [40].

2014–2017 Synthetic lethal effect of SWI/SNF complex

ARID1A and ARID1B form a synthetic lethal pair, where ARID1A loss renders cancer cells dependent on ARID1B for survival. Targeting ARID1B in ARID1A-mutant cancers induces cell death and inhibits tumor growth [41, 42]. Depletion of BRM/SMARCA2 in BRG1/SMARCA4-deficient cancer cells results in cell cycle arrest [43].

2018–2022 Tumor microenvironment of SWI/SNF complex

Expression of PBRM1 and ARID2 is negatively correlated with the expression of T-cell cytotoxicity genes. Pbrm1-deficient murine melanomas are more intensely infiltrated by cytotoxic T cells [44]. Loss of ARID1A induces the chemotaxis of polymorphonuclear myeloid-derived suppressor cells, thereby promoting prostate cancer progression [45].

2023–2024 Compensatory role of EP400/TIP60 in the SWI/SNF complex

Most SWI/SNF-targeted enhancers fail to restore chromatin openness after complex loss. However, certain target regions maintain an open state via the EP400/TIP60 complex. This compensatory mechanism primarily functions at specific enhancers and promoters, allowing partial gene expression to continue in the absence of SWI/SNF [46].

Structure and function of SWI/SNF complex

The SWI/SNF complex comprises three distinct variants: BAF (canonical BAF, cBAF; BRG1/BRM-associated factors), PBAF (polybromo-associated BAF complex), and the newly identified ncBAF (non-canonical BAF)) [47] 。 Each SWI/SNF complex contains only one of the two ATPases, BRM (Brahma) or BRG1 (Brahma-related gene 1) [47].

BAF Complex: BRG1/SMARCA4 serves as the primary ATPase subunit, participating in various transcriptional regulatory processes in most cell types [2].

PBAF Complex: This variant also primarily includes BRG1/SMARCA4 but associates with distinct auxiliary subunits to perform specific biological functions, such as roles in inflammatory responses [2].

ncBAF Complex: BRG1/SMARCA4 and BRM/SMARCA2 may exhibit distinct subunit configurations in certain variants, regulating specific gene expression patterns [2, 48].

Composition of SWI/SNF complex

The SWI/SNF complex exists in three forms: cBAF, PBAF, and ncBAF. cBAF includes ARID1A or ARID1B and DPF1, DPF2, or DPF3, which are critical for establishing enhancers and super-enhancers [49–51]。 PBAF is localized to active promoters and is defined by the expression of three components: PHF10, PBRM1, ARID2, and BRD7 [51–53]. ncBAF does not include SMARCB1 or ARID proteins; instead, BRD9 serves as its specific factor (Fig. 2) [51].

The SWI/SNF complex consists of ATPases, core subunits, and auxiliary subunits. SMARCA4 (BRG1) and SMARCA2 (BRM) are the two primary ATPases on which the SWI/SNF complex depends [54]。 The SWI/SNF complex includes multiple core and auxiliary subunits, primarily SMARCB1 (BAF47), SMARCD1/2/3, and ARID1A/B [49, 54] (Fig. 2).

BRG1/SMARCA4 and BRM/SMARCA2

The core components of the SWI/SNF complex are ATPase subunits, which include two distinct genes:

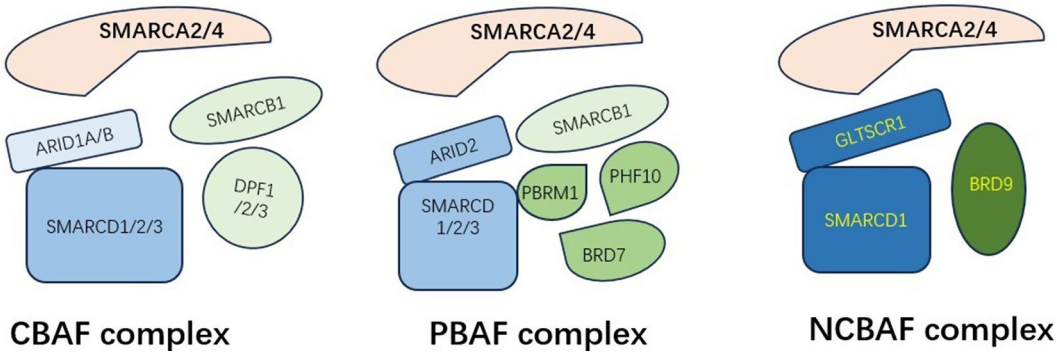

Fig. 2 Structure of the SWI/SNF complexes

BRG1 (SMARCA4) and BRM (SMARCA2) [2, 48, 55]. These subunits play a central role in chromatin remodeling and are typically found in mutually exclusive variants of the SWI/SNF complex [48, 50, 55]. The ATPase domains of BRG1 and BRM mediate nucleosome binding and facilitate nucleosome sliding or eviction through ATP hydrolysis. BRG1 connects to other modules within the complex via its HSA (helicase-SANT) and ATPase domains, enabling direct interaction with nucleosomes to maintain an open chromatin state, which permits transcription factor binding and gene expression activation [48]. BRM exhibits specificity in the ncBAF complex, particularly in the absence of BRG1, where it serves as the primary ATPase source [46]. Structurally, BRG1 and BRM are highly similar, but they may exhibit tissue-specific functions [50].

SMARCA4 is crucial for early development [51], and is commonly found in most SWI/SNF complex variants, particularly in the BAF and PBAF complexes [56]. SMARCA2 is predominantly expressed in a tissue-specific manner, such as in the brain and liver, where it appears in complexes distinct from those containing BRG1 [56].

*ARID1A*和*ARID1B*

ARID1A and ARID1B are distinct subunit genes from the same family, and they are typically not co-present in a single SWI/SNF complex [46, 48]. Both are core subunits of the BAF (BRG1/BRM-associated factor) and PBAF (Polybromo-associated factor) variants within the SWI/SNF complex. Their role involves promoting transcription factor binding by regulating chromatin accessibility at enhancers and promoter regions, thereby controlling gene expression [3, 55].

ARID2

ARID2 is a specific subunit of the PBAF variant of the SWI/SNF chromatin remodeling complex. ARID2 mutations are highly prevalent in non-small cell lung cancer (NSCLC), with a mutation frequency of approximately 7.3%, and are significantly associated with tumor progression and poor prognosis [57, 58]. Studies indicate that ARID2 loss significantly accelerates malignant progression in lung adenocarcinoma (LUAD) models and is linked to increased proliferation and survival of tumor cells [58].

SMARCD1/2/3

SMARCD1 (BAF60A), SMARCD2 (BAF60B), and SMARCD3 (BAF60C) are critical auxiliary subunits of the SWI/SNF chromatin remodeling complex. These subunits are widely present across various SWI/SNF complexes, including cBAF, PBAF, and ncBAF, and regulate gene expression by binding transcription factors through their specific domains [59].

GLTSCR1

GLTSCR1, a core subunit of the non-classical BAF (ncBAF) complex, is a potential tumor suppressor located on chromosome 19q13.3. It regulates chromatin structure and gene expression, playing a critical role particularly in DNA damage repair. In the ncBAF complex, GLTSCR1 cooperates with BRD9 to promote homologous recombination repair (HRR) by regulating the expression of RAD51 and RAD54 [60]. This mechanism helps maintain genomic stability, preventing malignant transformation of tumor cells due to the accumulation of DNA damage. GLTSCR1 polymorphisms are significantly associated with the risk of adult gliomas [61]. Mutations or deletions in the GLTSCR1 gene may result in impaired DNA repair functions, particularly in the nucleotide excision repair (NER) pathway, increasing the risk of glioma development [62].

BRD7

BRD7, a subunit of the PBAF complex, acts as a tumor suppressor and exhibits a high mutation and deletion rate in breast cancer. In breast cancer cells, BRD7 directly interacts with p53, enhancing p53-mediated transcriptional activation of its target genes (p21 and MDM2),

thereby inhibiting tumor cell proliferation and inducing cellular senescence [63, 64]. Following phosphorylation by ATM kinase, BRD7 is recruited to DNA double-strand break (DSB) sites, where it interacts with the PRC2 and NuRD complexes to promote H2AK119 monoubiquitination. This process suppresses local transcription and maintains chromatin stability [63].

BRD9

BRD9, a core subunit of the non-classical variant (ncBAF) of the SWI/SNF chromatin remodeling complex, is widely regarded as being involved in chromatin remodeling and transcriptional regulation [65, 66]. BRD9 is overexpressed or harbors gain-of-function mutations in various cancers, including pancreatic cancer, sarcomas, gastric cancer, and leukemia. These mutations are often associated with enhanced tumor cell proliferation, invasiveness, and therapeutic resistance [65–69].

Studies have shown that targeted degradation of BRD9 in acute myeloid leukemia (AML) suppresses the proliferation of AML cell lines while exhibiting minimal toxicity to normal hematopoietic cells [67]. Moreover, c-MYC and c-MYB protein levels are reduced in MV4-11 cells [67].

Three-Dimensional structure and function of the SWI/SNF complex

Using cryo-electron microscopy (cryo-EM), the team led by Shuang He revealed the unique 'sandwich-like' structure of the BAF complex, which encases the nucleosome and consists of the ATPase module, Base module, and Actin-Related Protein (ARP) module [70].

ATPase module Comprising SMARCA4 (BRG1), this module binds to nucleosomal DNA and mediates ATP hydrolysis-driven chromatin remodeling [70].The ATPase domain is positioned at superhelical location (SHL) 2.5 of the nucleosome [70]. Upon DNA binding, ATP hydrolysis facilitates DNA translocation, leading to nucleosome sliding or ejection [70].

Base module Comprising multiple substructures (Head, Thumb, Palm, Bridge, and Fingers), it adopts a compactly folded conformation [70].Thumb domain: Consists of the SANT domain, HSA region, and C-terminal helix. Fingers domain: Features a characteristic Y-shaped five-helix bundle [70].

Actin-Related protein (ARP) module Connecting the ATPase and Base modules, it ensures functional coordination of the complex [70]. It is composed of ACTL6A (BAF53A) and the long α-helix of the SMARCA4 HSA domain [70].

The functional mechanism of the SWI/SNF complex

The SWI/SNF complex is a major epigenetic regulator that promotes nucleosome incorporation and displacement by sliding or evicting histone octamers, thereby altering the accessibility of chromatin to transcription factors [54]. This complex can either displace nucleosomes from the DNA strand or slide them to specific positions, thereby creating space for transcriptional activation [48]. The ATPase domain of BRG1/SMARCA4 binds to nucleosomes and applies mechanical force, facilitating their repositioning on chromatin, which in turn adjusts the binding sites of transcription factors [3]. For instance, the loss of BRG1 results in a decreased binding capacity of crucial transcription factors such as REST, thereby affecting cellular differentiation and the expression of specific genes [55]. SMARCB1 deletion significantly alters the conformation of the SWI/SNF complex, reducing H3K27ac modification at typical enhancers and preventing the growth-promoting SWI/SNF complex from transitioning into the differentiation-inducing complex [71, 72].Studies have found that in MRT cells with SMARCB1 deletion, the binding of typical enhancers to SWI/SNF is significantly reduced, leading to a decrease in H3K27ac levels at these enhancers and subsequent silencing of differentiation-related genes [72]. The binding of super-enhancers (SEs) to SWI/SNF remains largely unchanged, which helps maintain the expression of key genes essential for cancer cell survival (e.g., SPRY1, SALL4) [72].

Gene mutations of the SWI/SNF complex and their impact on cancer

Mutations of the ARID1A subunit and their impact on cancer

ARID1A is the largest subunit of the BAF complex [70] and one of the most frequently mutated SWI/SNF subunits in cancer, with frequent mutations observed in lung, liver, ovarian, lymphoma, breast, colon cancers, and neurooncological tumors [6–15]. Mutations or inactivation of ARID1A impair chromatin remodeling, thereby promoting tumor cell proliferation and invasion [6, 7, 13]. ARID1A mutations can lead to uncontrolled cell proliferation by affecting the expression of cell cycle regulatory genes [7, 10]. Moreover, the loss of ARID1A is often associated with epithelial-to-mesenchymal transition (EMT), which further promotes tumor cell invasion and metastasis [6, 13]. Jiménez C confirmed that in neuroblastoma, ARID1A inactivation impairs cell proliferation and promotes cell cycle arrest. It reduces adhesion to the extracellular matrix and invasion, inhibiting neuroblastoma metastasis [6]. In breast cancer, ARID1A mutations regulate the estrogen receptor (ER) signaling pathway, affecting the proliferation and differentiation of breast cancer cells [8, 9, 70, 73]. Defects in the complex weaken

gene expression regulation, promoting tumor growth and influencing patient responses to hormone therapy [73, 74]. The loss of ARID1A triggers an increase in the proliferative transcriptome network but simultaneously suppresses eukaryotic elongation factor 2 (eEF2), leading to tumor suppression [12]. Wang Z et al. confirmed that mutations or deletions of ARID1A are associated with enhanced proliferation and invasion in colorectal cancer [15]. Cells with ARID1A loss exhibit synthetic lethality to the p53 activator RITA (Reactivating p53 and inducing tumor apoptosis), meaning that these cells are more sensitive to RITA treatment [15].(Table 1).

The synergistic interaction of ARID1A with transcription factors

ARID1A mutations not only affect chromatin remodeling but also impair the function of transcription factors [13]. Studies have shown that ARID1A interacts with YAP/TAZ, important oncogenic transcriptional co-activators, inhibiting their activity and preventing excessive cell proliferation and tumor formation [13]. ARID1A interacts with DNA-binding transcription factors such as TEAD to regulate gene expression, thereby participating in cellular fate determination and differentiation processes [13]. Moreover, ARID1A has been shown to affect the expression of estrogen receptors (ERα) and their downstream signaling pathways in ERα-positive breast cancer [13]. It exerts its effects by binding to ERα and collaborating with key factors such as FOXA1, GATA3, HDAC1, and BRD4, promoting cancer cell proliferation and survival [9, 73]. ARID1A interacts with p53 in colorectal cancer, influencing the expression of p53 target genes, such as p21, PUMA, and NOXA [15]. In ARID1A-deficient cells, p53 activity is increased, leading to a decrease in p21 expression, while the expression of pro-apoptotic genes PUMA and NOXA is upregulated, further enhanced by RITA treatment, ultimately inducing apoptosis [15].

Signaling pathway and target genes involved in ARID1A

The pathways involving ARID1A include the p53 pathway, DNA damage repair pathway, and Hippo signaling pathway [15]. ARID1A regulates the expression of multiple target genes through the SWI/SNF complex. Upstream regulatory factors include cell cycle control genes and EMT-related genes [6, 7]. Loss of ARID1A leads to dysregulation of these target genes, affecting tumor cell proliferation and invasion [13, 14]. ARID1A collaborates with histone deacetylases (HDAC1) and bromodomain-containing proteins (BRD4) to regulate histone acetylation (H3K27ac), influencing multi-layered gene expression regulation in breast cancer [73]. This combination not only affects chromatin state but also alters key pathways involved in cell differentiation and proliferation [74]. Downstream target genes of ARID1A include p21, PUMA, NOXA, and others [15]. Furthermore, ARID1A plays a critical role in cancer development

Table 1 Signaling pathway and target genes of SWI/SNF subunits

Subunit	Other name	Subfamily	Representative Cancer Types	Target Genes/Pathways	References
SMARCA2(BRM)	BAF190B	CBAF, PBAF, NCBAF	Thyroid cancer	PAX8 和 FOXE1	[106]
SMARCA4 (BRG1)	BAF190A	CBAF, PBAF, NCBAF	Lung cancer, endometrial cancer, glioma, breast cancer, ovarian cancer	HIF2A, GLUT1, TGFB2 和 SOX2	[12, 99, 100, 107, 108]
SMARCB1	BAF47, SNF	CBAF, PBAF	Rhabdomyoid tumors, colorectal cancer and pancreatic cancer	Wnt/β-catenin signaling Pathways	[22, 77, 93]
PBRM1	BAF180	PBAF	Colorectal cancer (CRC), prostate cancer, kidney cancer	WNT and PI3K/AKT signaling pathways ATM, ARID1A and TP53 Chromosome stability related genes APC and KRAS. PD-L1 and cGAS/STING pathway related genes	[86, 88, 109]
GLTSCR1	BICRA	NcBAF	Colorectal cancer (CRC),	Regulation of alternative splicing of ZO1	[110]
ARID1A	BAF250A	CBAF	Ovarian clear cell cancer, endometrial cancer, breast cancer, neuroblastoma, non-small cell lung cancer, colorectal cancer, prostate cancer,	CXCR2 signaling pathway, p21, CDK13, HERVH, FOXA1, BRD4,	[8, 9, 45, 79, 84, 111–113]
ARID1B	BAF250B	CBAF	Neuroblastoma, liver cancer, lung cancer, endometrial cancer	Wnt/β-catenin signaling Pathways NEAT1	[6, 41, 78, 114–117]
ARID2		PBAF	Hepatocellular carcinoma, non-small cell lung cancer	HSPA1A	
BRD7		PBAF	Breast cancer, prostate cancer, non-small cell lung cancer	YB1 (Y-box-binding protein-1) inhibition, AR signaling Pathways, PRC2 and NuRD complex, p53	[63, 64, 118–121]
BRD9		NcBAF	Pancreatic cancer, acute myeloid leukemia, multiple myeloma, gastric cancer	TGFβ/Activin-SMAD2/3 signaling pathway TUFT1/AKT/GSK-3β signal axis, MYC, RRS1, PES1, and BOP1 SOX4, PROM1 (CD133), SNAI2, SMAD1	[65, 67–69, 122]

by influencing various cell cycle and proliferation-related genes, such as CCND1 and MYC [7, 10]. The interaction between ARID1A and YAP/TAZ suppresses the oncogenic activity of these co-activators, preventing tumorigenesis caused by their overactivation [13].

ARID1A promotes chromatin loop formation at DSB sites upon DNA damage [75].The ability of DSBs to interact with adjacent genomic loci, i.e., the formation of chromatin loops within the damaged topologically associating domains (TADs), requires ARID1A and the ATPase activity of the SWI/SNF complex subunit BRG1 [75].ARID1A regulates the recruitment of RAD21 and CTCF to maintain TADs [75].

Association of ARID1A with other factors

In the absence of ARID1A, ARID1B can partially compensate for its function [6]. ARID1A acts in concert with subunits such as SMARCA4 and SMARCB1 to regulate SMARCC2 expression. Mutations in SMARCC2 and other SWI/SNF-associated subunits typically result in the disruption of cell cycle regulation, accelerating breast cancer development [73].

Studies on the broad mechanisms of ARID1A mutations in cancer have revealed their impact on chromatin remodeling, cell cycle regulation, signaling pathway integration, and treatment sensitivity, highlighting the potential of ARID1A as a therapeutic target.

Mutations of the ARID1B subunit and their impact on cancer

ARID1B is an exclusive subunit of the SWI/SNF (BAF) complex, functioning alongside its parallel counterpar. Loss of ARID1B has been detected in ovarian, lung, and pancreatic cancers [76–78]. ARID1B frequently mutates in breast, ovarian, and lung cancers, contributing to cancer onset and progression, affecting tumor cell proliferation, invasiveness, and response to immunotherapy [79–82]. In breast cancer, ARID1B mutations are associated with alterations in DNA repair pathways, potentially leading to a more aggressive cancer phenotype [81]. Loss of ARID1B alone typically leads to chromatin remodeling dysregulation, impairing normal gene expression control and promoting carcinogenesis. High-grade serous ovarian cancer (HGSOC) frequently exhibits ARID1B mutations, similar to ARID1A, which promote tumor invasiveness by altering transcriptional programs involved in cell cycle regulation and DNA repair [41, 81]. In lung cancer, ARID1B mutations are often associated with mutations in other chromatin remodeling complex genes, leading to increased tumorigenesis [83]. In colorectal cancer (CRC), ARID1B mutations may alter the transcriptional regulation of key oncogenes [84].

ARID1B mutations primarily promote cancer progression by disrupting chromatin remodeling, impairing DNA repair, and deregulating cell cycle control. A detailed analysis of the complementary functions of ARID1A and ARID1B provides new therapeutic strategies for cancer treatment.

Mutations of the PBRM1 subunit and their impact on cancer

PBRM1 is a key subunit of the SWI/SNF complex, playing a critical role in tumor biology by regulating chromatin remodeling. Mutations in PBRM1 are associated with the proliferation, invasion, and immune evasion of tumor cells in renal cell carcinoma (RCC), prostate cancer, colorectal cancer, and pancreatic cancer [54, 85–90].

In gliomas with H3K27M mutations, PBRM1 expression is higher in mutant cells compared to wild-type cells. Targeting the PBRM1 subunit with degraders, such as AU-153, suggests that PBRM1 plays a role in regulating tumor proliferation genes [54]. In renal cell carcinoma (RCC), PBRM1 is the second most frequently mutated gene, with a mutation rate of approximately 40%, and its inactivation typically promotes tumor proliferation and invasion [85, 89]. PBRM1 mutations are commonly considered to activate the NF-κB pathway, enhancing inflammation, cell survival, and tumorigenesis. Cells lacking PBRM1 exhibit abnormal activation of this pathway, promoting tumor growth and survival [91]. PBRM1 mutations lead to cell cycle dysregulation, promoting cancer cell proliferation. Especially in proximal tubular cells, PBRM1 mutations cause a phenotype resembling renal tubular cells but lacking terminal differentiation markers [85, 89]. In prostate cancer, PBRM1 mutations are associated with tumor cell resistance to certain therapies. Studies indicate that PBRM1, in conjunction with the degradation regulation of the mSWI/SNF ATPase complex, plays a critical role in prostate cancer cell proliferation and therapeutic resistance [88]. In pancreatic ductal adenocarcinoma, PBRM1 mutations and deletions impact anti-tumor immunity, facilitating the effectiveness of immunotherapy against tumors [77]. (Table 1)

The synergistic interaction of PBRM1 with transcription factors

PBRM1 is a key subunit of the PBAF complex and contains a bromodomain that binds to acetylated lysines on histones (H3K27ac), which are associated with active transcription regions [85]. Through this interaction, PBRM1 promotes the repositioning of nucleosomes, thereby facilitating the transcription of genes associated with differentiation, cell cycle regulation, and tumor suppression. Studies have shown that in renal cancer cells, PBRM1 collaborates with the transcription factor PAX8 to regulate the expression of proximal tubular genes [85]. PAX8 is a key transcription factor in renal cell fate, and PBRM1, by collaborating with PAX8, regulates the

expression of genes involved in proximal tubular differentiation, inhibiting cancer cell proliferation and invasion [85]. In addition, PBRM1 mutations are closely associated with intracellular cotranscription factors, such as KMT2A and KMT2B, which further influence chromatin structure and gene expression [85]. In gliomas, FOXO1 expression is downregulated following PBRM1 targeting, leading to reduced chromatin accessibility and decreased gene expression, particularly in enhancer regions crucial for cell survival [54]. PRC2 (Polycomb Repressive Complex 2) typically promotes a repressive chromatin state through H3K27 methylation. In cancers where PRC2 is inhibited (gliomas with H3K27M mutations), PBRM1 becomes more critical in promoting chromatin remodeling and transcriptional activation [54, 91].

Signaling pathway and target genes involved in PBRM1

PBRM1 is involved in several important signaling pathways, including p21, HIF1A, and c-MYC, where changes in the expression of these genes lead to abnormal proliferation and drug resistance in tumor cells [90]. Studies suggest that PBRM1 mutations affect p21 expression, thereby influencing the sensitivity of renal cancer cells to CDK4/6 inhibitors [92]. Additionally, PBRM1 mutations can regulate the Wnt and mTOR pathways, affecting cell growth and metabolism [92]. PBRM1 mutations activate the NF-κB pathway in renal cancer, promoting tumorigenesis through enhanced inflammatory and survival signals [91].

PBRM1 interacts with various transcription factors, including PAX8, which is a key regulator of proximal tubular epithelial fate in RCC. PBRM1 collaborates with PAX8 to regulate differentiation and gene expression in renal epithelial cells. Loss of PBRM1 results in the suppression of key epithelial differentiation markers, thereby promoting tumorigenesis [85]. In RCC, PBRM1 loss leads to the dysregulation of PAX8 target genes and the inhibition of differentiation programs [85]. (Table 1)

Associations of PBRM1 with other factors

In renal cancer, functional collaboration between PBRM1 and SMARCA4 is disrupted, exacerbating tumor invasiveness [85]. PBRM1 inactivation is often accompanied by mutations in ARID1A and ARID1B, which further disrupt chromatin remodeling complex functions, driving tumorigenesis and progression [85, 89]. Pancreatic cancer with mutations in ARID1A and PBRM1 shows enhanced responsiveness to immunotherapy [77]. When combined with ARID1A mutations, PBRM1 loss further exacerbates chromatin remodeling defects [85, 88]. PBRM1, in conjunction with SMARCA2/4, regulates cellular plasticity. Inhibition of these bromodomains promotes mesenchymal-to-epithelial transition (MET), upregulating the expression of adhesion molecules such as E-cadherin, while downregulating extracellular matrix (ECM) genes, particularly COL11A1, which plays a barrier role during reprogramming [77].

PBRM1 influences cancer cell proliferation, invasion, immune evasion, and therapeutic response by regulating chromatin remodeling, transcription factor binding, and key signaling pathways. Further functional studies are needed to explore the relationship between PBRM1 mutations and therapeutic strategies to advance precision medicine.

Mutations of the SMARCB1 subunit and their impact on cancer

SMARCB1 is a core subunit of the SWI/SNF (BAF) chromatin remodeling complex, and mutations or deletions of SMARCB1 are associated with rhabdoid tumors, colorectal cancer, and pancreatic cancer [22, 77, 93]. Deletion of SMARCB1 disrupts chromatin remodeling, leading to abnormal transcriptional programs that promote cancer cell proliferation, invasion, and survival [22, 77, 93] (Table 1).

SMARCB1 and tumor cell proliferation and invasion

In colorectal and thyroid cancers, SMARCB1 deletion is associated with increased stem cell-like characteristics and reduced cellular differentiation [7, 22, 70]. For example, in colorectal cancer, CRISPR screening has identified SMARCB1 as a negative regulator of aberrant stem cell-like activity [22]. In thyroid cancer, SMARCB1 deficiency cooperates with oncogenic drivers such as BRAFV600E, promoting the progression of papillary thyroid carcinoma (PTC) to more invasive forms, such as poorly differentiated thyroid cancer (PDTC) or anaplastic thyroid cancer (ATC) [7]. In rhabdoid tumors, SMARCB1 deletion enhances tumor cell proliferation and promotes invasive characteristics [94]. A study by Yasumichi Kuwahara et al. demonstrated that SMARCB1 induces the expression of p16INK4A and p21CIP1/WAF1 proteins in MRT cell lines. Reduction of p21CIP1/WAF1 expression inhibits the G1 arrest induced by SMARCB1 re-expression [95].SMARCB1 deletion reduces NOXA expression, thereby weakening apoptotic pathway activity and increasing MRT cell resistance to DOX chemotherapy [96]. SMARCB1 mediates sensitivity to DNA-damaging agents not only through the intrinsic apoptotic pathway but also by regulating the level of DNA damage itself [96].These mutations activate stem cell-related gene programs while inhibiting differentiation-related genes, resulting in a more aggressive cancer phenotype [22, 94].

SMARCB1-associated transcription factors and gene regulation

SMARCB1 is involved in the regulation of the Wnt/β-catenin and Hh-GLI pathways, interacting with various transcription factors, including thyroid lineage transcription factors such as PAX8, NKX2-1, and FOXE1, to collectively regulate gene expression [7, 22]. For example, in colorectal cancer, SMARCB1 participates in suppressing aberrant stem cell-like activity by regulating the transcriptional activity of the Wnt/β-catenin pathway [22]. Loss of SMARCB1 leads to increased Wnt signaling, which enhances stem cell-like activity and impairs differentiation [22]. In gliomas, the loss of SMARCB1 leads to the upregulation of GLI1, resulting in the aberrant activation of the Hh-GLI pathway and promoting tumor cell proliferation [97].In thyroid cancer, SMARCB1 interacts with thyroid lineage transcription factors such as PAX8, NKX2-1, and FOXE1 [7]. These transcription factors are crucial for maintaining thyroid cell differentiation [7]. Deletion of SMARCB1 reduces chromatin accessibility at these transcription factor binding sites, leading to dedifferentiation and tumor progression [7].

SMARCB1 antagonizes the Polycomb Repressive Complex 2 (PRC2), which is involved in gene silencing through histone methylation [94]. Furthermore, SMARCB1 mutations are associated with dependency on other chromatin modifiers, such as EZH2, making EZH2 a potential therapeutic target for SMARCB1-deficient cancers [22, 94].

As a core subunit of the SWI/SNF complex, SMARCB1 mutations or deletions disrupt chromatin remodeling, leading to aberrant gene expression and promoting cancer cell proliferation, invasion, and dedifferentiation. It exerts its function by regulating the Wnt/β-catenin and Hh-GLI signaling pathways, influencing key transcription factors, and counteracting PRC2. Furthermore, SMARCB1 mutations may render cancer cells sensitive to EZH2 inhibitors, presenting a novel potential target for precision oncology.

Mutations of SMARCA2/4 subunits and their impact on cancer

The tumor suppressor SMARCA4, as the core ATPase subunit of the SWI/SNF complex, is mutated in various cancers, including prostate, lung, breast, pancreatic, osteosarcoma, colorectal, ovarian, oral cancers, lymphoma, and glioma, affecting the chromatin remodeling function of SWI/SNF, which leads to altered transcriptional regulation and promotes tumor development [10, 14, 54, 77, 78, 98–104]。 SMARCA2 exhibits synthetic lethality with SMARCA4. In non-small cell lung cancer (NSCLC), degradation of SMARCA2 induces reprogramming of the enhancer landscape in SMARCA4-mutant cells, resulting in the loss of enhancer chromatin accessibility at cell proliferation-related genes [105] (Table 1).

Effects of SMARCA2/4 on tumor proliferation and invasion

Prostate Cancer: In prostate cancer, dual-target degradation of SMARCA4 and SMARCA2 significantly reduces androgen receptor (AR) and FOXA1-driven prostate cancer cell proliferation [98]. SMARCA4 co-occupies enhancer regions with transcription factors such as AR and FOXA1, maintaining high expression levels of these key oncogenes. Targeted degradation of SMARCA4 causes dissociation of these transcription factors from chromatin, significantly weakening the expression of their regulated oncogenes and slowing prostate cancer cell proliferation and invasion [88, 98].

In thyroid cancer, SMARCA2 binds to enhancers of thyroid differentiation transcription factors (TTFs) PAX8 and FOXE1, promoting their expression by enhancing chromatin accessibility [106].

Lung Cancer: Inactivation of SMARCA4 accelerates lung cancer progression, particularly in cases with KRAS and TP53 mutations, leading to increased invasiveness [99]. In lung adenocarcinoma, SMARCA4 mutations promote tumor growth by inducing dependency on oxidative phosphorylation (OXPHOS). In SMARCA4-deficient tumors, expression of PGC1-α in the OXPHOS pathway is increased, enhancing tumor cell proliferation through upregulation of PGC1-α expression [14].

Lymphoma: In B-cell lymphomas, such as follicular lymphoma and diffuse large B-cell lymphoma, loss of SMARCA4 alters germinal center dynamics, causing B cells to re-enter the germinal center, undergo excessive proliferation, and evade normal differentiation processes, thereby promoting lymphoma proliferation and invasion [10].

The role of SMARCA4 in H3K27M-mutant gliomas involves regulating chromatin openness to maintain the proliferative state of tumor stem cells and inhibit cell differentiation, thereby promoting glioma proliferation and invasion. Interaction between SMARCA4 and H3K27M promotes tumor cell proliferation and prevents differentiation into mature gliocytes, leading to the maintenance of tumor cells in a progenitor-like state [54, 101].

In triple-negative breast cancer (TNBC), SMARCA4 interacts with the long noncoding RNA (lncRNA) TGFB2-AS1, inhibiting TGFB2 and SOX2 expression, thereby enhancing tumor proliferation and invasion [100].

Interaction of SMARCA4 with Other SWI/SNF subunits and factors

Loss of SMARCA4 is often associated with mutations in other SWI/SNF subunits, such as ARID1A and ARID1B.

In lung cancer, ARID1A mutations frequently occur in conjunction with SMARCA4 loss, leading to impaired enhancer-mediated transcriptional regulation. ARID1B can compensate for the loss of ARID1A, but concurrent loss of both subunits severely impairs SWI/SNF function [3, 14]. SMARCA4 mutations also affect SWI/SNF complex assembly and function by destabilizing other subunits, such as PBRM1 and SMARCB1 [3, 98].

Research on the role of SMARCA2/4 mutations in chromatin remodeling, transcriptional regulation, metabolic control, tumor proliferation, and invasion suggests that future strategies could explore SMARCA2/4 degraders or epigenetic therapies targeting the SWI/SNF complex to develop precision treatments for SMARCA2/4-mutant cancers.

SWI/SNF complex and immune regulation

Role of the SWI/SNF complex in macrophages and T cells

Chromatin Remodeling and Regulation in T Cells

In T cells, the SWI/SNF complex collaborates with transcription factors such as PU.1, RUNX1, and BCL11B to regulate chromatin accessibility at early T cell gene loci, laying the foundation for effector T cell (Teff) function [123, 124]. During T cell development, chromatin is primed for future activation. This priming enables T cells to establish chromatin accessibility at effector loci, which is critical for T cell differentiation into functional subsets [124]. The SWI/SNF complex also regulates the epigenetic transitions of CD8 + T cells, with PBAF playing a protective role by maintaining a pool of T cells that are depleted of stem-cell-like progenitors, which is crucial for immune therapy responses [49](Table 2).

Chromatin remodeling and regulation in macrophages

Different variants of the SWI/SNF complex (cBAF, ncBAF, PBAF) have distinct functions in macrophage responses to bacterial endotoxins (LPS), regulating chromatin accessibility and enhancer activation, thereby influencing the expression of inflammatory genes [123]. Upon LPS stimulation, BAF, PBAF, and ncBAF complexes are relocalized to chromatin-accessible sites. The BAF complex primarily participates in chromatin opening at potential enhancers and the deposition of H3K27ac [123], NcBAF complex: Mainly responsible for the activation of inflammatory response genes, particularly those that cooperate with transcription factors of the AP-1 and NF-κB families, and associated with the activation of interferon-stimulated genes (ISGs) [123]. The NcBAF complex collaborates with STAT family proteins (STAT1, STAT2) to promote the deposition of H3K27ac and nascent transcription at active enhancers.

PBAF complex: Typically associated with the repression of enhancers, particularly in the absence of PU.1 [123](Table 2).

Effect of SWI/SNF mutation on tumor immunotherapy

SWI/SNF mutations, commonly observed in cancer, have profound implications for cancer immunotherapy.

Loss of PBAF significantly enhances tumor control when combined with PD-1 blockade therapy. This finding suggests that targeting the PBAF complex may improve CD8 + T cell immune responses against tumors [49]. The BAF complex drives Tex Prog cell differentiation into effector-like Tex cells, while PBAF inhibits this process, making the balance between BAF and PBAF a key regulatory point during Tex subset development [49].

In cancers with SWI/SNF mutations, loss of chromatin remodeling function can impair immune cell recruitment, reduce antigen presentation, and alter tumor immunogenicity. These changes reduce the effectiveness of immune checkpoint inhibitors, as tumors with SWI/SNF deficiencies may evade immune detection. In contrast, targeting the PBAF subunit, particularly in the context of T cell exhaustion, in combination with immunotherapy, may improve tumor control [49, 124]. Loss of PBAF significantly enhances tumor control when combined with PD-1 blockade therapy [49]. Targeting the PBAF complex can enhance CD8 + T cell immune responses against tumors. The BAF complex drives Tex Prog cell differentiation into effector-like Tex cells [49], while PBAF inhibits this process, making the balance

Table 2 The SWI/SNF complex in macrophages and T cells

Subunit Name	Immune Cells	Anti-Tumor Immune Signaling Pathway/Target Gene	Associated Cancer	Relevant Drugs/Inhibitors	References
MATR3	CD4 + T cells	Epigenetic Regulation, TOX	Hepatocellular Carcinoma	Epigenetic Modulators	[125]
PBRM1 ARID2	CD8Tcell	IFN-γ, mTORC1	Melanoma	无	[44]
SMARCB1	CD8 + T cells	LSD1	Ovarian Cancer	SP-2577	[103]
BRD9	Macrophages	IFN, STAT1,STAT2,IRF9	Various Cancers	BRD9 inhibitors (I-BRD9, BI-9564), Dexamethasone	[122]
DPF2	Macrophages	NRF2-dependent anti-inflammatory pathways	Hematopoietic Cancers,	NRF2 activators	[126]

between BAF and PBAF a key regulatory point during Tex subset development [49].

In summary, SWI/SNF-mutant cancer cells may evade immune surveillance by reducing antigen presentation and inhibiting immune cell recruitment. The loss of the PBAF complex enhances the anti-tumor efficacy of PD-1 inhibitors and increases CD8 + T cell responses to tumors. The BAF complex promotes the conversion of Tex cells into effector-like T cells (Tex Eff), whereas the PBAF complex inhibits this process, making the BAF-PBAF balance a critical regulatory point for T cell exhaustion. Further investigation into the role of the SWI/SNF complex in different immune cells, combined with clinical patient data, could provide precise insights for cancer immunotherapy.

The relationship between SWI/SNF complexes and DNA repair pathways

SWI/SNF complex in DNA repair pathway

The SWI/SNF complex plays a crucial role in DNA repair pathways, including base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), and non-homologous end joining (NHEJ).

Base excision repair (BER): BER is responsible for correcting small, non-helical base lesions. The SWI/SNF complex promotes the removal and replacement of damaged bases by increasing DNA accessibility through its ATP-dependent nucleosome remodeling function [2]。.

Nucleotide excision repair (NER): NER repairs large, helix-distorting lesions, such as thymine dimers induced by ultraviolet light. The SWI/SNF complex aids in nucleosome removal, preventing its obstruction at damaged sites and facilitating the binding of repair proteins for excision and synthesis. Specifically, the BRG1 (SMARCA4) subunit of SWI/SNF is crucial for the recruitment of NER factors [13, 127]。.

Homologous recombination (HR): In HR, the SWI/SNF complex promotes the repair of DNA double-strand breaks (DSBs) by enhancing chromatin relaxation at the break sites. Subunits such as SMARCA4 and ARID1A are recruited to DNA damage sites, facilitating HR-mediated repair and reducing nucleosome density at the damage site. SMARCA4 also promotes chromatin remodeling to allow the recruitment of HR proteins, such as BRCA1 [2].

Non-homologous end joining (NHEJ): NHEJ requires rapid access to DNA ends, and SWI/SNF facilitates the binding of NHEJ factors, such as Ku70/80, by displacing nucleosomes from the DNA ends [2, 127](Table 3).

Table 3 The SWI/SNF complex in DNA repair

Subunit	DNA repair pathway	Signaling Pathway/Target Gene,	Associated Cancer,	DNA Damage Type	References.
ARID1A	NHEJ, HR	RAD21, CTCF, HDAC1-RSF1	osteosarcoma, breast cancer	DSBs	[75]
ARID1A/B, BRG1	HR	Promotes end resection of DNA to facilitate RAD51 binding to DNA to promote HR.	Osteosarcoma-U2OS, colon cancer-HCT116	DSBs	[128]
SWI/SNF	HR	RPA, ATR	Lymphoblastic Lymphoma	DSBs	[129]
ARID1a	HR	P53BP1, PARP1	cervical cancer	DSBs	[130]
ARID2	HR, NHEJ	BRCA1, RAD51, 53BP1	Hepatocellular Carcinoma	DSBs	[131]

The SWI/SNF complex maintains genomic stability

The SWI/SNF complex suppresses cancer by participating in DNA damage repair and regulating the accessibility of transcription factors. Mutations in SMARCB1, SMARCA4, and ARID1A are commonly found in rhabdoid tumors, ovarian cancer, and clear cell renal cell carcinoma [2]. Loss of function of SMARCA4, ARID1A, or PBRM1 leads to impaired DNA repair, accumulation of DNA damage, and increased genomic instability [13, 98]. ARID1A mutations disrupt HR, leading to increased reliance on NHEJ, which in turn results in error-prone DNA repair, chromosomal instability, and uncontrolled cell proliferation [2, 13].

In cancer, SWI/SNF mutations confer vulnerability, including increased sensitivity to DNA-damaging agents such as PARP inhibitors, particularly in ARID1A-mutant tumors, as these mutations exacerbate DNA repair defects [2, 98].

Mutations in the SWI/SNF complex lead to genomic instability, homologous recombination (HR) repair defects, and increased sensitivity to PARP inhibitors, offering potential strategies for DNA repair-targeted therapy.Future research should integrate patient data and combination therapy strategies to optimize treatment for SWI/SNF-mutant cancers.

SWI/SNF complexes in precision medicine

Targeted strategies in cancer treatment

Different subunits of the SWI/SNF complex, such as ARID1A and ARID1B, provide precise targeting pathways in cancer therapy. By exploiting the deletion or mutation of these subunits in cancer cells, highly selective anti-tumor therapies can be achieved, thereby reducing the impact on normal cells [15, 114].

In lung cancer, SWI/SNF mutations, particularly in SMARCA4, enhance dependence on oxidative phosphorylation (OXPHOS), making OXPHOS inhibitors a potential therapeutic target [14]. Furthermore, tumors with

ARID1A mutations may exhibit increased sensitivity to drugs such as PARP inhibitors, and ARID1A mutations could serve as predictive biomarkers for targeting DNA damage repair pathways [51, 132].

Small molecule inhibitors Novel small molecule inhibitors targeting mutations in core members of the SWI/SNF complex, such as SMARCA4 and ARID1A, are under development. These drugs may inhibit the proliferation and invasiveness of cancer cells by altering chromatin structure or regulating downstream signaling pathways associated with the SWI/SNF complex [2].BRD9 is associated with immune responses, suggesting its potential application in enhancing tumor immune responses [21]. Targeting the interaction between POU2AF2 and the SWI/SNF complex in small cell lung cancer may pave the way for new therapeutic approaches [22, 139]. In preclinical models, the selective SMARCA2 degrader PRT3789 exhibits strong synthetic lethality in SMARCA4-mutant cancers. Studies indicate that combining PRT3789 with immunotherapies, such as pembrolizumab, can enhance immune responses and further improve treatment outcomes [14, 51].

Synthetic lethality of SWI/SNF mutations

The principle of synthetic lethality is that when one gene is inactivated, the activity of another related gene becomes critical. Inhibiting the related gene simultaneously results in cell death.

Synthetic lethal effect of BRM/SMARCA2 and BRG1/SMARCA4

SMARCA2 (BRM) and SMARCA4 (BRG1) are functionally similar and exhibit functional redundancy in many cell types. In lung adenocarcinoma and ovarian cancer, SMARCA4 mutations are prevalent, and cancer cells rely on SMARCA2 to maintain chromatin remodeling and gene expression. Inhibition of SMARCA2 prevents these cancer cells from remodeling chromatin, leading to gene expression dysregulation and cell death [14, 43, 51, 93]. Targeting this dependency in therapy is known as the "synthetic lethality" strategy. Depletion of SMARCA2 in SMARCA4-deficient cancer cells leads to selective tumor cell death while sparing normal cells, causing cell cycle arrest, senescence induction, and elevated overall H3K9me3 levels [43, 51, 93]. Sasikumar Kotagiri developed YD23 through structure-activity relationship (SAR) studies, a potent and selective proteolysis-targeting chimera (PROTAC) targeting SMARCA2 [105]. It was found that YD23 exhibits potent tumor growth inhibition in SMARCA4-mutant xenografts [105].

Synthetic lethal effect of ARID1A and ARID1B

ARID1A and ARID1B are complementary subunits of the SWI/SNF complex, involved in regulating gene expression, particularly by modulating the interaction between promoters and enhancers to control gene transcription [41]. Under normal conditions, these two subunits can partially compensate for each other. If ARID1A is inactivated by mutation, cells rely on ARID1B to maintain the chromatin remodeling function of the complex [41, 132]. Wang Z has shown that in ARID1A-mutant cancer cells, targeting ARID1B effectively inhibits the function of the SWI/SNF complex, disrupting the regulation of gene expression and ultimately inducing cell death [41]. This phenomenon forms the basis for synthetic lethality, where the simultaneous loss of ARID1A and ARID1B leads to irreversible damage in cancer cells [41]. ARID1B-targeting inhibitors selectively inhibit ARID1B activity in ARID1A-mutant cancer cells, resulting in cancer cell death. In gastric and endometrial cancers, inhibition of ARID1B has shown significant antitumor effects [41, 93]. In breast cancer, ARID1B mutations are associated with increased dependence on ARID1A, where the loss of ARID1A promotes uncontrolled tumor growth. ARID1B deficiency impairs chromatin accessibility and transcriptional regulation of tumor suppressor genes, conferring invasive proliferation to cancer cells [1, 70]. In ARID1A/ARID1B double-knockout liver and skin, aggressive carcinogenesis occurs following dedifferentiation and excessive proliferation [41].Co-mutations of ARID1A and ARID1B are more common in endometrial, gastric, and ovarian cancers, leading to synthetic lethality and chromatin remodeling disruption [41, 133].

Clinical trials of SWI/SNF complexes

FHD-286 [8] targets BRM/BRG1, leading to impaired chromatin remodeling and subsequent suppression of oncogene transcription [8] [134].FHD-286 exhibits potent antiproliferative activity in models of acute myeloid leukemia (AML) and uveal melanoma [8, 134]].A Phase I clinical trial (NCT04891757) primarily evaluates the safety and tolerability of FHD-286 in AML patients [36, 134]. While full trial results are yet to be released, preliminary data suggest that FHD-286 holds promise as a potential targeted therapy [8] [134].In SMARCB1-deficient solid tumors (e.g., rhabdoid tumors and chordomas), EZH2 sustains the dedifferentiated state of cells by antagonizing the SWI/SNF complex [9, 10, 135, 136]. Functional mutations or loss of the SWI/SNF complex enhance EZH2 dependency, rendering tumors sensitive to EZH2 inhibitors [9, 10, 135, 136].

Cancers with SWI/SNF complex mutations exhibit specific metabolic or genetic dependencies, which can serve as critical breakthroughs for precision therapy.The synthetic lethality strategy is the central mechanism of SWI/SNF-targeted therapy, offering a novel approach for selective tumor eradication.Targeted small-molecule inhibitors of the SWI/SNF complex have demonstrated promising therapeutic potential but require further optimization and clinical validation.These findings provide

new research directions for SWI/SNF-targeted cancer therapy and may pave the way for future advancements in precision medicine.

Conclusion and perspectives

Mutations in SWI/SNF subunits are closely associated with various cancers, making drugs targeting these mutations potential therapeutic strategies.

Studies have shown that SWI/SNF inhibitors, such as BRM014, can enhance sensitivity to standard chemotherapy in certain cancer types, particularly through significant effects on the G1 checkpoint, which is associated with cell cycle regulation [137]. The combination of OXPHOS inhibitors with other metabolic pathway inhibitors targets the energy metabolism vulnerability in SWI/SNF-mutant tumors [14]. This combination therapy helps overcome resistance and improves overall treatment efficacy. Mutations in the SWI/SNF complex often lead to genomic instability, providing a potential opportunity for the use of DNA repair inhibitors or immunotherapies. The ability of the SWI/SNF complex to regulate the tumor immune microenvironment, particularly in modulating immune cell infiltration and immune evasion, enhances its potential as a target for immunotherapy [138]. DNA damage-associated immune activation triggered by ARID1A loss suggests its potential application in enhancing the efficacy of immune checkpoint inhibitors, providing a foundation for the development of personalized treatment strategies. The synthetic lethality between ARID1A and ARID1B, as well as the synthetic lethality between BRM/SMARCA2 and BRG1/SMARCA4, offers new possibilities for future precision medicine and combination therapies [41, 93]. Moreover, BRD9 is critical for the survival of tumors driven by SMARCB1 mutations. BRD9 inhibitors have shown effective anti-tumor activity in these cancers [93].

Although studies have demonstrated that mutations in key SWI/SNF subunits are associated with cancer progression, the feasibility of targeting PBRM1, the sensitivity of SMARCB1-deficient cancers to EZH2 inhibitors, and the synthetic lethality of SMARCA2/4 lack clinical validation, making it difficult to assess their potential applications in precision medicine.Current research on SWI/SNF-related immunotherapy primarily focuses on T cells and macrophages, with limited exploration of other immune cells such as NK cells, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs).

Many cancer therapies, including targeted therapies, face challenges related to drug resistance. For instance, cancer cells may evade SWI/SNF-targeted therapy by upregulating alternative chromatin remodelers. However, this study does not explore resistance mechanisms or potential counterstrategies, which could impact the long-term efficacy of these novel therapies.

Targeted therapy of chromatin remodeling factors may affect gene regulation in normal cells, increasing the risk of side effects. Long-term use of SWI/SNF-targeting drugs may lead to the development of resistance or affect chromatin regulation in normal cells, necessitating further studies to balance efficacy and safety [75, 114, 137, 138]. The diversity of roles played by different SWI/SNF subunits in various cancer types adds complexity to targeted therapies. It is crucial to further investigate the specific functions of these subunits in tumors to optimize treatment strategies.(Fig. 3).

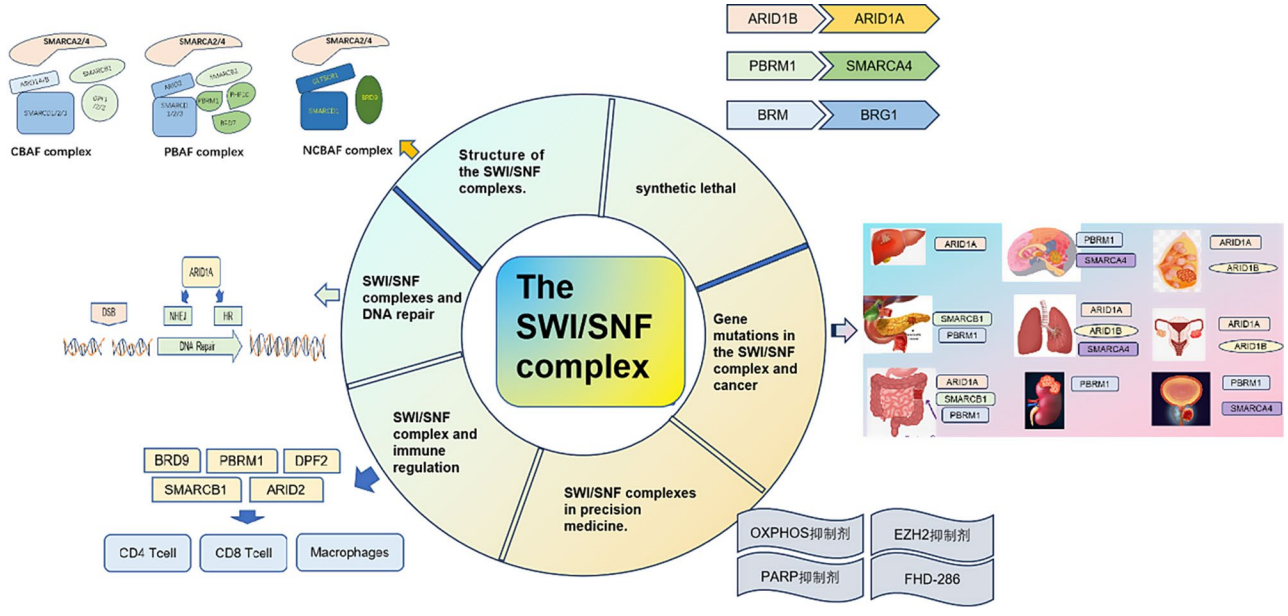

Fig. 3 The role of the SWI/SNF complex in cancer biology

Author contributions
Feng-Xiang Hao and Bin Zhao took the lead in writing the manuscript. Ying Zhang and Jia-Yi Hou discussed the contents and edited the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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