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Abstract

To activate or repress specific genes, chromatin is constantly modified by chromatin-remodeling complexes. Among these complexes, the SWItch/Sucrose Non-Fermenting (SWI/SNF) complex, also referred to as BRG1-Associated Factor (BAF) complex, moves the nucleosome along chromatin using energy provided by ATP hydrolysis. In mammalian organisms, the SWI/SNF complex is composed of 10-15 subunits, depending on cell type, and a defect in one of these subunits can have dramatic consequences. In this review we will focus on the alterations identified in the SWI/SNF (BAF) complex subunits that lead to cancerous pathologies. While SMARCB1 was the first mutated subunit to be reported in a majority of malignant rhabdoid tumors, the advent of next-generation sequencing allowed the discovery of mutations in various SWI/SNF subunits within a broad spectrum of cancers. In most cases, the mutation leads to a loss of expression or to a truncated subunit unable to perform its function. Even though it is now commonly acknowledged that approximately 20% of all cancers present a mutation in a SWI/SNF subunit, some cancers are associated to a specific alteration of a SWI/SNF subunit, which acts either as tumor suppressor genes or as oncogenes, and therefore constitute diagnostic or prognostic biomarkers. Consistently, therapeutic strategies targeting SWI/SNF subunits or the genes affected downstream have been revealed to treat cancers.

Keywords

SWI/SNF complex, BAF complex, Chromatin Assembly and Disassembly, SWI/SNF-deficient pathology, BAF-deficient pathology

Main text

A. Overview

DNA, which measures approximately two meters in length within each cell, is compacted into chromatin in the nucleus. This highly compacted chromatin must be relaxed for subsequent replication, repair or transcription. The structure of chromatin is reorganized by histone modification enzymes (by acetylation or methylation) or ATP-dependent nucleosome remodelers, which move nucleosomes along DNA using energy derived from ATP hydrolysis. Among the ATP-dependent remodelers, SWI/SNF (BAF) complexes have been the most extensively studied. SWI/SNF have between 5,000 – 10,000 binding sites over the entire genome [1] and thus affect many genes and pathways, including neuronal development [1] or hormone signaling [2]. Because of their key roles in the regulation of gene expression, alterations in SWI/SNF complexes impact diverse cellular functions directly linked to cancers. SMARCB1 was the first cancer-associated subunit to be unveiled in malignant rhabdoid tumors (MRTs) [3], prior to the discovery by next-generation sequencing of other SWI/SNF mutated subunits in a wide array of cancers. Eventually, the mutation rate of SWI/SNF subunits is almost equivalent to that of *TP53*, the single-most mutated gene in cancer (19% and 26%, respectively) [4,5]. As described in Table 1, some of the SWI/SNF subunits are more frequently mutated than others. These mutations, which can be either heterozygous or homozygous and present in somatic and/or germline cells, often lead to the loss-of-expression or to a truncated, non-functional protein. Additionally, most SWI/SNF mutations are present at low frequencies and are distributed across gene coding sequences, with no apparent site preference [4,6]. However, while this is true for most cancers harboring mutations in SWI/SNF subunits, there is few cancers in which the SWI/SNF alteration is pathognomonic and defined as the "driver" of tumorigenesis. This includes MRT and AT/RT, Small Cell Carcinoma of the Ovary (SCCOHT), Synovial sarcomas or SMARCA4-Deficient Thoracic Sarcomas (SMARCA4-DTS). In this

review of the vast and increasing literature depicting the role of SWI/SNF in cancers, we will explore subunit by subunit the alterations of SWI/SNF that are thought to lead to oncogenesis and describe their associated tumor types. But before, we need to expose the anatomy of the SWI/SNF complexes.

B. The SWI/SNF complexes

The saga of the SWI/SNF complexes discovery originated in 1984 by the concomitant identification in *Saccharomyces cerevisiae* of six new genes involved in mating-type switching, namely, *HO* and *SWI 1-5* [7] and five new genes (*SNF 2-6*) involved in sucrose fermentation [8]. But it was 8 years later that a study from Peterson and Herskowitz demonstrated that some SWI and SNF genes were similar and that some of them were bound together in a complex that modulates the expression of genes and named SWI/SNF [9]. The subsequent depiction of this complex in other species demonstrated that it is evolutionarily conserved from yeast to human [10,11], although it is mainly a transcription activator in yeast [12,13] whereas it activates or represses gene transcription in mammals [14]. Also, the mammalian SWI/SNF complexes comprise 10-15 subunits among the 29 subunits characterized thus far, a number and variety of subunits much larger than in yeast (Figure 1A) [5,10]. The composition of these mammalian complexes was first unraveled in 1996 through the initial purification of 12 proteins that co-immunoprecipitated together with BRG1 (therefore called BRG1-Associated Factors or BAF) [15] and still continues to be enriched as demonstrated by the recent identification through a proteomic screen of additional subunits, including BCL7A/B/C, BCL11A/B, BRD9 and SS18 (SYT) [5]. Amongst all the subunits described, only two subunits possess a catalytic activity. These are two mutually exclusive catalytic ATP-dependent helicases, named Brahma (BRM) and Brahma-related gene 1 (BRG-1), encoded by *SMARCA2* and *SMARCA4*, respectively. These two subunits contain 6 conserved domains: a QLQ domain, a proline-rich domain, a small helicase/SANT-associated domain, a DNA-dependent ATPase domain, a retinoblastoma

(RB)-binding domain (LxCxE) and a Bromo domain (Figure 1B). The Bromo domain interacts with the acetylated histone and participates in the binding and the stability of the SWI/SNF complex onto the DNA [16]. The LxCxE domain binds to members of the RB tumor suppressor family [17], while the QLQ domain is implicated in protein-protein interactions. Finally, the helicase and DExDc domains separate DNA double strands [18], a catalytic activity that requires ATP hydrolysis. The presence of one of these two subunits is mandatory for the ATP-dependent functions of the complex [19–21]. SWI/SNF complexes also contain a set of core subunits required for nucleosome mobility, namely, BAF155 (*SMARCC1*), BAF170 (*SMARCC2*) and BAF47 (*SMARCB1*). Adding to these subunits, the SWI/SNF complexes present 7-10 accessory subunits involved in the targeting of specific loci and thus responsible for the relative specific set of genes targeted by the different complexes [7–10] (Figure 1A). Eventually, each subunit contains specific domains (bromodomains, chromodomains, DNA-binding domains, ARID, Zing finger, etc.) required for the interaction with DNA or histones and essential for the remodeling activities of the complex (for recent reviews see [10,22,23]).

The mammalian complexes are composed of precise sets of subunits, yielding a great diversity of SWI/SNF complexes, which in vertebrates are divided into 2 sub-classes: The BRG/hBRM-associated factors (BAF) complexes that specifically contain BAF250A/B, BAF45D and SS18subunits and the Polybromo-associated BAF (PBAF) complexes that exclusively contain BAF200, BAF180, BAF45A, BRD7 and only one of the ATPases, SMARCA4 [15,24,25] (Table 2). Taking into account variations of the accessory subunits, Wu and collaborators estimated that hundreds of versions of SWI/SNF complexes may exist [15,26]. This diversity is essential to the differentiation during embryogenesis and development. Studies performed in mice [27–38], *Caenorhabditis elegans* [39] or Xenopus [40,41] showed striking evidence of the effect of modifications in the composition of SWI/SNF complexes in neural development, from embryonic stem (ES) cells to post-mitotic neurons

(Table 2 and [1] for a recent review). A switch in SWI/SNF subunits also affects several other cell fate decisions, such as the skeletal, cardiac muscle and hematopoietic differentiations [10,42–46].

The variety of SWI/SNF complexes allows for their specialization in modulating specific gene expression. Therefore, depending on the cellular background, SWI/SNF complexes have been implicated in a variety of physiological roles, such as the regulation of hormonal pathways and their crosstalk [2,47], hepatic lipid metabolism [48] or the regulation of cell cycle progression. Although SWI/SNF and polycomb complexes are functional antagonists [49,50], the mechanisms underlying SWI/SNF complex activities remain poorly understood. Two recent studies shed new light on these mechanisms in both physiological and pathological contexts. The first study characterized the role of SWI/SNF complexes in the regulation of lineage-specific enhancers [51]. Alver and co-workers revealed that SWI/SNF complexes directly bind to p300 histone acetyltransferase and thus regulate the active H3K27Ac mark on the targeted genes. Interestingly, this SWI/SNF regulation is less present in super-enhancer or transcribed regions but displays strong activity in typical distal enhancers with enrichment in the genes involved in differentiation and development. This study led to the hypothesis that the loss of SWI/SNF subunits induces tumorigenesis by acting on the acetylation of the typical enhancers of genes implicated in differentiation and development. The second study characterized the opposing functions of SWI/SNF and polycomb complexes [52]. Although the specific antagonism between SMARCB1 from SWI/SNF complexes and EZH2 from the polycomb repressive complex 2 (PRC2) was known [50], the precise mechanism was not yet characterized. Using an inducible system allowing for targeting SWI/SNF onto a precise promoter, Kadoch and co-workers demonstrated that the SWI/SNF complex rapidly removes both PRC1 and PRC2 complexes from their chromatin binding sites, consequently increasing the chromatin accessibility for transcriptional factors at these sites [52]. These studies were

particularly informative about the role of SWI/SNF under physiological conditions and provided an explanation for SWI/SNF complex deficiency in some cancers, such as SMARCA4-DTS, MRT or synovial sarcoma, as we will see in the next section.

C. SWI/SNF complex alterations in cancer

SWI/SNF complexes can be altered in a number of different ways in a number of different cancerous pathologies. In this section, we will review the principal subunits, how they are altered and in which cancers they are involved.

Loss of SMARCB1 (BAF47) activity in various cancers

SMARCB1 encodes the ubiquitously expressed nuclear protein BAF47 (or Snf5). *SMARCB1* is instrumental in epigenetic regulation and cell cycle progression and has been implicated in several signaling pathways, including the regulation of oncogenes [53–58]. *SMARCB1* is one of the most potent tumor suppressor genes [55,57,58], and its loss-of-function has been described in several tumors (Table 1).

The first implication of *SMARCB1* in cancer was reported in 1998, in MRTs, in which this gene is incapacitated in virtually all cases either by genomic deletions or truncating mutations [3]. Subsequently, using whole-exome sequencing, Lee and co-workers demonstrated that the bi-allelic loss-of-function of *SMARCB1* is the only recurrent genetic events occurring in MRT diseases [59], which was further confirmed by the very low mutational burden observed in these tumors [60]. MRT is a rare and extremely aggressive cancer of early childhood (typically diagnosed under the age of 2 years, although it may occur at any age), and it is frequently metastatic. Consequently, prognosis is poor with a mortality rate of 80% within the first year [61]. MRTs have three privileged locations, the central nervous system (tumors are then referred to as atypical teratoid/rhabdoid tumor or AT/RT) [62], the kidneys (also called rhabdoid tumor of the kidney or RTK) [63] and soft tissue (sometimes referred in this site as

MRT) [64], although any site can be affected [65,66]. Pathologically, MRTs are composed of sheets of undifferentiated round to epithelioid tumor cells that display monomorphic vesicular nuclei. MRTs have high-grade features with extensive necrosis and high mitotic activity. Typically, tumor cells display so-called "rhabdoid features", defined as paranuclear eosinophilic inclusions, a feature which was initially considered to represent rhabdomyoblastic differentiation [67]. However, rhabdoid features are primarily focal and are not pathognomonic of MRT.

The functional impact of *SMARCB1* deficiency in these tumors was initially unraveled in 2008, when Kia and colleagues demonstrated that re-expression of *SMARCB1* in MRT cells led to the re-expression of CDKN2A via a PRC2 complex-mediated loss of DNA methylation at its locus [68]. In 2010, Wilson and co-workers broadened this observation by demonstrating that the loss of *SMARCB1* increases the abundance of the PRC2 subunit EZH2, enforcing repression of its targets [69]. Hence, in MRTs, , the *SMARCB1*-deficient SWI/SNF complexes, which induces higher EZH2 expression, can no longer unbind PRC2 complexes resulting in the repression of the *CDKN2A* tumor suppressor gene and consequently in an increase of proliferation [52]. Finally, looking at a more genome wide effect, the group of Kadoch very recently demonstrated that the re-expression of *SMARCB1* in MRT cells had a profound impact on increasing BAF and PBAF occupancy on enhancers and bivalent promoters, respectively [70].

Loss of *SMARCB1* most often results from somatic inactivation but is occasionally associated with germline mutations (for a recent review [22]). In the rhabdoid predisposition syndrome type 1 (OMIM#609322), carriers of germline *SMARCB1* alterations are mainly prone to the development of MRTs, although chondrosarcomas have also been reported [54,71,72]. Germline mutations of *SMARCB1* also predispose to multiple schwannomas and meningioma in the context of familial schwannomatosis syndrome [73,74]. Affected patients develop tumors

in the spinal, peripheral or cranial nerves, which are benign but may still induce neurological complications [75]. *SMARCB1* mutations account for half of all reported familial schwannomatosis cases. In these cases, mutations are mostly located in exon 1 [76,77] and SMARCB1 typically conserves its ability to control the cell cycle, accounting for the less aggressive phenotype of tumors developed in this setting [78].

In addition to MRTs, *SMARCB1* plays also a critical role in epithelioid sarcoma (EPSR), presenting mutation rates exceeding 80-90% [79–83]. In 1994 Cordoba and co-workers highlighted the implication of chromosome 22 in EPSR with the characterization of a t(8;22)(q22;q11) translocation, but rather connected it to the Ewing sarcoma translocated region on chromosome 22q11 [84]. Several groups subsequently documented a loss of SMARCB1 expression in EPSR mostly resulting from homozygous deletions of the gene [79,82,85]. EPSR is an indolent tumor with a high rate of recurrence and metastasis. This condition predominantly affects young adults and invades the soft tissue. Originally described as restricted to distal extremities, EPSR has now been reported in several anatomical regions [67]. Depending on the localization of the tumors, 2 types of EPSR have been described: the conventional-type, mostly located in the fingers, hands, forearms or feet and the proximal-type occurring in the upper extremities as well as in the pelvis, vulva, penis or spine [86]. Moreover, histopathological differences discriminate these two subtypes, since conventional EPSR presents plump epithelioid and spindled cells with a multinodular proliferation and typically a single and central nucleolus [87], whereas proximal EPSR is characterized by large cells with an epithelioid cytomorphology and frequent rhabdoid cytoplasmic inclusions [86].

More recently, *SMARCB1* truncations following unbalanced translocations were described in renal medullary carcinoma (RMC)[88,89,90]. RMC is a rare and highly aggressive carcinoma primarily affecting young men with sickle cell traits. The prognosis is poor with a survival period of several months, partly due to the late diagnosis of the pathology, often

associated with metastasis [91–94]. Tumors cells originating from the renal medulla have a highly atypical nucleus and dense eosinophilic cytoplasm that may contain rhabdoid inclusions [67,88]. During diagnosis, the loss of SMARCB1 is used to discriminate RMC from collecting duct carcinoma (CDC) [88]. Despite the few RMC cases studied, SMARCB1 loss-of-function is thought to induce *cyclin D1* that leads to a progression through the G1 phase of the cell cycle and to cellular proliferation. This hypothesis relies on the observation that *cyclin D1* is expressed in the nucleus of neoplastic cells [88].

To date, the last tumor type described in the literature as harboring a loss of *SMARCB1* is a subtype of sinonasal carcinoma [95–97]. Sinonasal carcinomas represent 5% of head and neck carcinomas, affecting patients in their fifth decade and are associated with a 5-year survival rate of approximately 50% [98]. SMARCB1-deficient sinonasal carcinoma, underlined by *SMARCB1* deletions, represents approximately 10% of sinonasal carcinomas [99]. As in MRT, their genome seems to be highly stable as demonstrated in the only case assessed by next-generation sequencing [100], suggesting that loss of SMARCB1 is likely the driving event of tumorigenesis. This cancer is an aggressive malignancy with a median survival time of 15 months, as patients often present an advanced T4 tumor stage at diagnosis. These poorly differentiated/undifferentiated tumors may nevertheless display a basaloid phenotype or focal rhabdoid features (for a review, see [97]).

Finally, poorly differentiated pediatric chordomas displaying a common loss of *SMARCB1* underlined by chromosome 22q11 deletions have been described [101]. *SMARCB1*-deficient chordomas occur only in pediatric patients, displaying methylome profiles distinct from those of conventional chordomas and from MRT patients [104].

Displacement of SS18 in synovial sarcoma

SS18 is the last characterized SWI/SNF subunit to date. Using a proteomic approach, Kadoch and Crabtree identified SS18 as a new core subunit of the BAF complex [102]. SS18 (formerly known as SYT) was first identified in synovial sarcoma (SS) in which the translocation t(X;18) (p11.2;q11.2) provoked the fusion of SS18 on chromosome 18 to SSX1, SSX2 or SSX4 on the X chromosome [103]. This chromosomal translocation results in the fusion of the SS18 C-terminus to the 78 C-terminal amino acids of the SSX protein. Kadoch and Crabtree elegantly demonstrated that the SS18-SSX fusion protein competes with the normal SS18 subunit for incorporation into the SWI/SNF complex. As a result, and likely owing to the larger size of the fusion protein, the BAF47 subunit is expulsed from the synovial sarcoma BAF (ssBAF) complex. The eviction and subsequent degradation of BAF47 should result in a loss-of-function, as seen in MRTs. However the authors demonstrated that SS18-SSX incorporation within the SWI/SNF complex leads to a gain-of-function of the complex, with enhanced chromatin occupancy and the robust eviction of the PRC. The ssBAF is indeed redirected towards different genomic loci, probably triggered by the SSX moiety of the fusion protein that binds DNA at specific sites [104]. The ssBAF complex can thus bind to and activate the SOX2 oncogene [52,102]. To date, this example is the only evidence of the acquired oncogenic properties of the SWI/SNF complex as opposed to its predominant role as a tumor suppressor. Synovial sarcoma is a rare soft tissue sarcoma affecting young adults (mean age of 32 years) that may locate in any anatomical site but with a preference for extremities, head and neck as well as the abdominal wall. Prognosis is poor with a 5-year survival rate of 50-80% [105]. There are two major subtypes of synovial sarcoma, the biphasic and the monophasic spindle cell types, along with less frequent subtypes presenting morphological and immunohistochemical heterogeneity.

Loss-of-function of catalytic subunits (BRG-1 and BRM) in cancer

SMARCA2 and *SMARCA4* encode the 2 mutually exclusive ATPase subunits of the complex, BRM and BRG-1, respectively. While *SMARCA2* mutations are primarily implicated in neurological disorders rather than in cancers [10], *SMARCA4* is considered a tumor suppressor [106]. Mutations in *SMARCA4* are recurrent in 2 types of cancers: the small cell cancer of the ovary hypercalcemic type (SCCOHT) [107] and SMARCA4-deficient thoracic sarcomas (SMARCA4-DTS) [108].

SCCOHT is a rare aggressive type of ovarian cancer predominantly affecting young women [109]. Most tumors are composed of round poorly differentiated cells arranged in sheets and microcystic areas. Half of the cases contain larger tumor cells with vesicular nuclei dotted with conspicuous nucleoli, also known as "large cell" variants, with features reminiscent of MRT [109]. Focal cytoplasmic rhabdoid features may also be observed [109]. These tumors are characterized by biallelic *SMARCA4* inactivating mutations (including truncation, frameshift or deletion) often targeting the helicase catalytic domain and leading to the loss of expression of the protein [107,110,111]. Furthermore, in nearly half the cases of SCOOHT, SMARCA4 mutations have been identified in germline cells and may occur in the context of rhabdoid tumor predisposition syndrome 2 (OMIM# 613325) [107,112].

SMARCA4-DTS are associated with recurrent *SMARCA4* mutations leading to a BRG-1 loss of function [108,113]. Concomitantly, mutations of *TP53* are observed in 2/3rd of cases. These tumors, composed of sheets of round to epithelioid cells harboring vesicular nuclei, display high-grade features with extensive necrosis and hemorrhage. This malignancy, primarily occurring in young males with a smoking habit, is extremely aggressive with limited response to chemotherapy and a rapid local progression, leading to a poor prognosis, with a median survival time of 7 months..

Beside these two tumor types, in which a *SMARCA4* loss of function is observed in 100% of cases, *SMARCA4* is also mutated in a broad range of cancers with varying frequencies,

including Burkitt's lymphomas [114], lung adenocarcinomas [115–117] or esophageal adenocarcinomas [118] (see Table 1), with the majority of the mutations targeting the helicase catalytic domain. In these tumors, knowing how *SMARCA4* mutations are contributing to the oncogenesis is still to be investigated.

SMARCA2 is rarely mutated in human cancers, except in adenoid cystic carcinoma (ACC) [119]. ACC primarily originates from the salivary glands but can also be found in several other anatomical sites, including the breasts, lacrimal glands, lungs, brain, trachea, and paranasal sinuses. ACC is of poor prognosis due to a high metastatic rate [119]. The tumor is typically composed of ductal and myoepithelial cells with a cribriform pattern. Using whole-genome and exome sequencing of 60 ACC patients, Ho and co-workers showed that *SMARCA2* is the most frequently mutated gene and 35% of the identified mutations were found in SWI/SNF subunit genes. However, the role of *SMARCA2* mutations in ACC tumorigenesis needs to be further addressed, as ACC is characterized by recurrent gene fusions involving the *MYB* and/or *MYBL1* oncogenes considered as the driver events of these tumors [120].

Lastly, mutations in the catalytic subunits may also be found in poorly differentiated carcinomas of the gastrointestinal tract including: colon, small bowel, stomach and distal esophagus. These carcinomas comprise glandular areas together with poorly differentiated solid areas in which tumor cells may have rhabdoid features [95,121]. These undifferentiated gastrointestinal carcinomas (UGC) mostly display *SMARCB1* or *SMARCA4* inactivation although *SMARCA2* and *ARID1A* alterations have also been reported. Interestingly, the undifferentiated component displays rhabdoid features, providing a link between rhabdoid morphological features and SWI/SNF deregulation. SWI/SNF alterations in these tumors represent secondary genetic events acquired at a late stage of tumorigenesis. *SMARCA2* and *SMARCB1* are the most frequent SWI/SNF mutated subunits in UGC (77% and 50% of the cases, respectively). While all cases presenting a *SMARCB1* mutation also harbor a mutation in

the *SMARCA2* subunit, mutations affecting *SMARCA2* and *SMARCA4* are mutually exclusive, and the same is true for *SMARCB1* and *SMARCA4* [121]. Notably, these 4 SWI/SNF subunits are the only subunits tested for mutations in these cancers.

In keeping with BRG-1 and BRM being the mandatory catalytic, mutually exclusive, subunits of SWI/SNF, the team of Charles Roberts demonstrated that in SMARCA4-deficient tumor cells, *SMARCA2* was up-regulated and my therefore complement the loss of BRG1 within SWI/SNF complexes [122]. Targeting BRM in SMARCA4-deficient tumors thus represent an interesting therapeutic approach [123–125]. Nevertheless, we and others observed that SCCOHT and SMARCA4-DTS cells presented an intriguing common feature: the concomitant loss of SMARCA4 and SMARCA2 expression, the later not being supported by any gene alteration [108,123,126]. Moreover, treatment of SCCOHT cells with the histone deacetylase (HDAC) inhibitor trichostatin A restores the expression of SMARCA2, suggesting a mechanism of epigenetic silencing of *SMARCA2* or an indirect inhibitory effect on SMARCA2 mRNA degradation [123]. Unlike the synthetic lethality observed in other SMARCA4-deficeint tumors, in SCCOHT the re-expression of SMARCA2 abolishes cell proliferation.

Despite different clinical settings, MRT, SCCOHT and SMARCA4-DTS tumors harbor similar features: MRTs and SCCOHTs present very simple genome and epigenome (SMARCA4-DTS tumor genome is rather complex), SCCOHTs and SMARCA4-DTS share the common loss of SMARCA2 expression, all these tumors present somehow rhabdoid features and clustering analyses demonstrated that expression profiles of these three tumor types are quite correlated [108,112,127,128]. The deregulation of genes involved in embryonic stem cell transcriptional program, such as SOX2 that is upregulated in both AT/RTs [129] and SMARCA4-DTS [108], is a common trait of these tumors. In keeping with the inability of an ATPase-lacking SWI/SNF to displace PRC complexes from the chromatin [52], the repression

of lineage specific genes might be the results of the persistence of PRC2 at these loci.. This hypothesis is supported by the demonstration that EZH2 inhibition abolishes proliferation of both SCCOHT and MRT cells [130].

Involvement of the SWI/SNF accessory subunits in cancer

SWI/SNF accessory subunits are of tremendous importance for conferring the specificity of a given complex in a given tissue or cell. Disease-causing mutations are therefore also found in some accessory SWI/SNF subunits. Among these subunits, *SMARCE1* was found mutated in 100% of familial multiple spinal meningioma cases [131–133], leading to the consideration of this gene as a tumor suppressor. Meningiomas are slowly developing tumors with a cranial or spinal localization. Loss of SMARCE1 (BAF57) only occurs in the spinal form and is associated with a clear-cell histological morphology [131]. This clear subtype is more aggressive and has a tendency to spread to the CNS where it forms metastases [133]. Notably, the development of the disease occurs earlier in men (between 2 and 10 years of age) than in women (between 14 and 30 years of age). Although the underlying reason remains unknown, a hormonal role has been suggested in the growth of meningioma [132], consistent with the role of SMARCE1 in steroid hormone responses [47].

BAF250a plays a critical role in tumorigenesis. Its encoding gene, *ARID1A*, is one of the most commonly affected SWI/SNF genes in human cancers. *ARID1A* is mutated in a wide variety of neoplasms, such as hepatocellular carcinoma [134,135], lung adenocarcinoma [117], gastric cancers [136–138], bladder cancers [139,140] or cholangiocarcinomas [141] (Table 1). More importantly, *ARID1A* is considered a tumor suppressor gene in ovarian clear cell carcinomas (OCCC) [142] in which this gene is mutated in half of the cases [6,142]. OCCC is an aggressive form of ovarian cancer with a poor prognosis and a resistance to standard

platinum-based chemotherapy [143–145]. OCCC are composed of hobnail cells with a clear cytoplasm. Similar to observations in ovarian cancer, mutations in *ARID1A* occur more frequently in endometrial clear cell tumor subtypes than in the serous subtype [146]. Accordingly, *ARID1A* is mutated in almost 40% of endometrial cancers, and even if the mechanism is not yet clear, the *ARID1A* mutation has been linked to the progression of benign endometriosis to carcinoma [6]. Remarkably, *ARID1B*, encoding the BAF250b subunit that is mutually exclusive with BAF250a, is rarely mutated in cancer, except in childhood neuroblastoma [147].

SMARCC2 is scarcely mutated in cancers (Table 1), except in gastric and colorectal cancers, in the context of microsatellite instability [148]. Kim and co-workers observed a repeat sequence in exon 8 of *SMARCC2*, which is a hotspot for frameshift mutations, present in 9% and 15% of gastric and colorectal cancers, respectively. This mutation leads to a codon stop and thus a loss-of-function of SMARCC2 (BAF170). However, the role of this mutation in these cancers has not yet been fully determined, and further studies are needed.

SWI/SNF cancerous pathologies without genomic or epigenetic alterations of SWI/SNF

SWI/SNF subunits have also been implicated in tumorigenesis, without harboring alterations in their coding sequence, particularly when a subunit is targeted by epigenetic silencing (as described for instance with *SMARCA2* silencing in SCCOHT and SMARCA4-DTS). Unaltered SWI/SNF complexes have also been involved in tumorigenesis via their interactions with long non-coding RNAs (lncRNA). Two mechanisms have been described for a lncRNA to perturb SWI/SNF activities: the lncRNA can either directly interacts with the SWI/SNF complex, antagonizing its activities, or force the recruitment of the SWI/SNF complex at some specific loci [23]. In prostate cancer, the overexpressed *SChLAP1* lncRNA

interacts with SMARCB1 [149] and consequently diverts SWI/SNF from some of its target genes, leading to tumor cell invasion and to the promotion of metastasis [149,150]. In contrast, in hepatocellular carcinomas, the *lncTCF7* lncRNA recruits the SWI/SNF complex to the promoter of the *TCF7* gene, increasing TCF7 expression and leading to the activation of the WNT signaling pathway and promotion of tumor progression [151].

SWI/SNF complexes interact with numerous cofactors at specific loci [152]. Hence, based on the same interacting/recruiting models than with the lncRNA, it may be possible that alterations of specific cofactors could lead to the deregulation of the SWI/SNF complexes. We may therefore underestimate the number of cancers presenting a SWI/SNF functional alteration.

D. Targeting SWI/SNF activities in clinical applications

Based on next-generation sequencing studies, deregulation of SWI/SNF subunits in tumorigenesis is increasingly demonstrated in a much wider array of cancers than previously thought, impacting diagnosis, as well as therapeutic and prognostic markers in these cancers. With regards to diagnosis, inactivating mutations of core subunits lead to the loss of expression of corresponding subunits which are used to confirm the histopathological diagnosis of tumors underlined by recurrent SWI/SNF alterations, such as MRT, epithelioid sarcomas, SCCOHT and SMARCA4-DTS, to name but a few. In the case of prognosis, SMARCE1 has been proposed as a key pro-metastatic factor in prostate cancer, with high expression levels of SMARCE1 associated with a dramatic increase in the migratory capacity of tumor cells *in vitro* and *in vivo* [153]. Similarly, SMARCE1 is a marker of poor prognosis in endometrial carcinomas [154].

Several therapeutic strategies have been devised to exploit the vulnerability of tumor cells harboring SWI/SNF deregulation. First, due to the functional antagonism between SWI/SNF complexes and PRC2, SMARCB1-deficient MRT and SMARCA4-deficient SCCOHT present

an increase in PRC2 activity [69,155], which can be inhibited with specific inhibitors targeting EZH2, the catalytic subunit of PRC2 responsible for the methylation of lysine 27 of histone H3. EZH2 inhibition potently arrests rhabdoid tumor growth both *in vitro* and *in vivo* [69,155]. Phase 2 clinical trials are ongoing to determine whether these findings are applicable in human patients. Interestingly, EZH2 inhibitors may act in synergy with etoposide, a topoisomerase II (Topo II) inhibitor, in a subset of *SMARCA4*-deficient neoplasms [156]. This synergistic activity may be related to the physical interaction of SWI/SNF complexes with Topo II during the cell cycle [157]. Indeed, upon Topo II inhibition in SMARCA4-wild type cell lines *in vitro*, *SMARCA4* transcript levels increase to compensate for a decrease in Topo II activity [156]. The authors speculated that this compensatory mechanism is abrogated in the case of *SMARCA4* mutations, thereby accounting for the synergistic effect of their combination. Moreover, *SMARCB1* inactivation leads to *cyclin D1* upregulation both *in vitro* and *in vivo* [158,159]. Thus, phase 1/2 clinical trials are currently ongoing with ribociclib (LEE011), a cyclin-dependent kinase (CDK) 4/6 inhibitor [160]. Finally, in the context of *SMARCA4* inactivation, tumor cell survival relies on the activity of SMARCA2, the alternative ATPase of SWI/SNF complexes. Inhibition strategies targeting SMARCA2 have been demonstrated as successful synthetic lethal strategies in SMARCA4-deficient tumors both *in vitro* and *in vivo* [19,161]. However, this strategy is questioned by the subset of SMARCA4-inactivated tumors displaying concomitant loss of SMARCA2, namely, SCCOHT and SMARCA4-DTS [108,123]. Moreover, although their precise tissue lineage remains unknown, a minor subsets of lung adenocarcinomas may present a dual loss of SMARCA4 and SMARCA2, and importantly, these patients have a worse prognosis than those with expressing SMARCA4/A2 [162,163]. The next step is to understand whether targeting SMARCA2 with a specific peptide in SMARCA4-deficient cancers will effectively lead to the tumor cell death or if these cancer cells will be able to adapt and resist to such treatments.

Finally, SWI/SNF subunits could also be used as predictors of therapeutic response. Indeed, in 2008, it was shown that the response of steroid treatment in pediatric acute lymphoblastic leukemia was correlated with the level of expression of 3 SWI/SNF subunits (*SMARCB1*, *SMARCA4*, *ARID1A*): lower expression was associated with higher treatment response [164]. Similarly, *SMARCE1* expression can be used as a marker of drug response in ovarian cancer and in lung cancer: the sensitivity to cisplatin, doxorubicin, and 5-fluorouracil in ovarian cancer seems to be associated with low *SMARCE1* expression [165], whereas low *SMARCE1* expression is associated with resistance to *MET* and *ALK* inhibitors in non-small cell lung cancers [166].

E. Concluding remarks

The SWI/SNF complex subunits are implicated in a wide variety of cellular functions, both in a physiological and pathological context. Unraveling their implication in pathologies should result in the development of new therapeutics targeting mutated SWI/SNF subunits. However, these mutations predominantly result in SWI/SNF complex loss-of-function under pathological conditions, and therapeutic strategies should thus focus on restoring their normal cellular functions. To this end, improving the current understanding of the mechanisms underlying the loss of these subunits and how this loss leads to a pathology, as well as determining which genes are targeted by SWI/SNF or in which pathways these proteins are implicated is of utmost importance.

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Author contributions

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Tables

Table 1: SWI/SNF subunits alterations in cancers. Cancers in which an alteration of SWI/SNF is thought to be driving oncogenesis are indicated in gray.

Genes	Cancer type	%	Genetic alteration in the SWI/SNF subunits	References
SMARCB1	Malignant rhabdoid tumor	100%	biallelic inactivation	[3,167]
	Epithelioid sarcoma	80% - 90%	homozygous deletions	[79,80,85]
	Renal medullary carcinoma	100%	loss of heterozygosity	[88,168]
	Rhabdoid tumor predisposition syndrome 1	100%	heterozygous germline mutation	[169]
	Familial schwannomatosis	45%	non-truncating splice-site mutations and missense mutations in exon 1	[76,78]
	Undifferentiated chordomas with notochordal differentiation that typically arise in the axial spine (=atypical chordomas)	100%	Heterozygous mutations or deletion, loss of expression	[170]
	Synovial sarcoma	> 95%	Expulsion of SMARCB1 from complex by SS18-SSX	[102]
	Sinonasal carcinomas	<10%	Homozygous (~75%) or heterozygous (~25%) deletion	[96,97,171]
SMARCA2	Small cell cancer of the ovary, hypercalcemic type	100%	no mutation - loss of expression	[123]
	SMARCA4- deficient thoracic sarcoma	100%	no mutation - loss of expression	[108]
	undifferentiated carcinomas in gastrointestinal tract	77%	unknown	[121]
SMARCA4	Ovarian small cell carcinoma of the hypercalcemic type	91.2%	biallelic inactivating mutations	[107,111,172]
	SMARCA4-deficient thoracic sarcoma	100%	mostly nonsense and frameshift mutations	[108]
	Rhabdoid tumor predisposition syndrome 2	100%	heterozygous germline mutation	[173]
ARID1A	Ovarian clear cell carcinomas	49.1%	somatic truncating or missense mutations	[6,142]
	Gastric cancers	18.7%	inactivating mutation mostly	[136–138]

	Childhood neuroblastoma	5.6%	mutation with loss of heterozygosity	[147]
	Endometrial cancers	39%	somatic truncating or missense mutations	[6,174]
	Lung adenocarcinoma	9.8%	Truncating mutations	[117]
	bladder cancers	17%	Somatic mutations	[140]
	Breast cancer	2.5%	mutation	[175–177]
	Cholangiocarcinomas	18.8%	mutation	[141]
	hepatocellular carcinoma	15%	mutation	[134,135]
ARID1B (BAF250b)	Childhood neuroblastoma	7%	hemizygous intragenic deletions, or splice-site or missense mutations	[147]
ARID2 (BAF200)	Non-small cell lung cancer	8.2%	mutation (loss of function) or homozygous deletion	[178]
SMARCC2	Gastric cancers with microsatellite instability	9.4%	heterozygous frameshift mutations	[148]
	Colorectal cancers with microsatellite instability	14.6%	heterozygous frameshift mutations	[148]
SMARCE1	Familial multiple spinal meningiomas	100%	heterozygous mutations in germline - complete loss of BAF57	[131–133]
BAF180	breast cancer	No data	truncating mutations associated with loss of heterozygosity	[179]
SS18	Synovial sarcoma	100%	SS18-SSX fusion	[103]
PBRM1	Clear cell renal cell carcinomas	20-40%	truncating mutations	[180]
BCL7a	Non-Hodgkin lymphomas	19.7%	mutation	[5]
	Multiple myelomas	21.7%	mutation	[5]
BCL11b	T cell acute lymphoblastic leukemias	20–25% pediatric, 5% adult	mostly missense or frameshift mutations	[181,182]

Table 2: Subunits composition of the different SWI/SNF complexes.

The composition of SWI/SNF subunits varies according to cell type and during neuronal development. Some subunits are characteristic of the complex (shown in red) and correspond to the signature subunits.

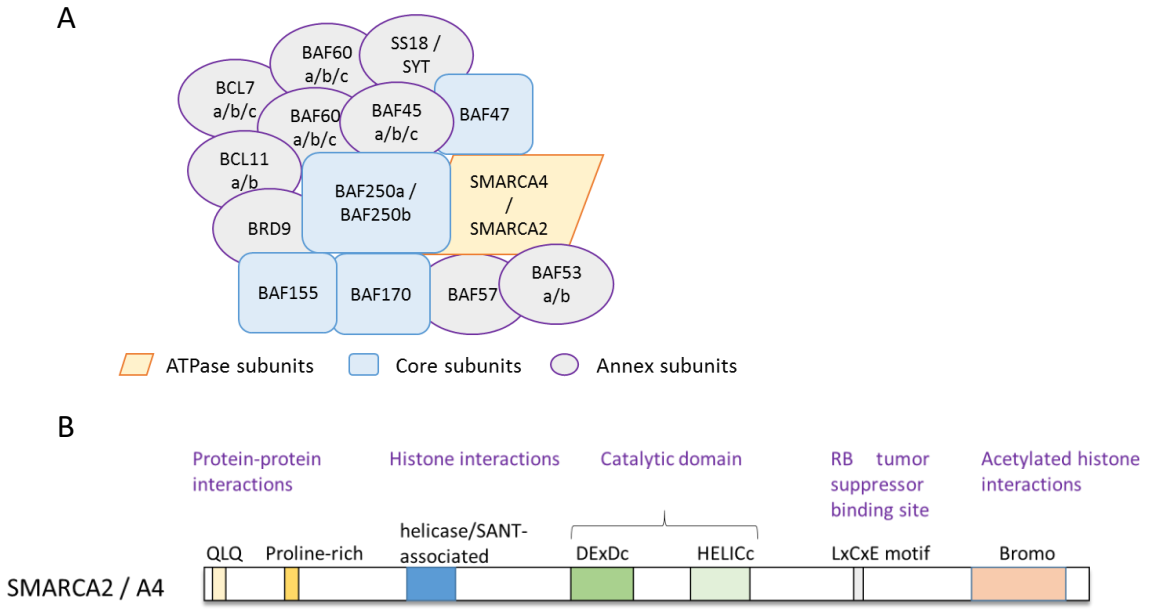
	BAF COMPLEX	**PBAF COMPLEX**	**ESBAF COMPLEX**	**NPBAF COMPLEX**	**NBAF COMPLEX**
CATALYTIC SUBUNITS	BRM / BRG-1	BRG-1	BRG-1	BRG-1 / BRM	BRG-1 / BRM
CORE SUBUNITS	BAF47 BAF155 BAF170	BAF47 BAF155 BAF170	BAF47 BAF155 -	BAF47 BAF155 BAF170	BAF47 BAF155 BAF170
ACCESSORY SUBUNITS	ARID1A / 1B - BAF57 BAF60a/ b / c BAF45a / b / c BAF53a / b SS18 BRD9 BCL7a / b / c BCL11a / b	ARID2 BAF180 BAF57 BAF60a/ b / c BAF45a / b / c BAF53a / b - BRD7 - -	ARID1A / 2 - / BAF180 BAF57 BAF60a BAF45a BAF53a SS18 BRD7 / BRD9 BCL7a / b / c BCL11a / b	ARID1A /1B /2 - / BAF180 BAF57 BAF60a BAF45a BAF53a SS18 BRD7 / BRD9 BCL7a / b / c BCL11a / b	ARID1A /1B /2 - / BAF180 BAF57 BAF60a / c BAF45b / c BAF53b CREST BRD7 / BRD9 BCL7a / b / c BCL11a / b

Figure Legends

Figure 1: BAF complex assembly

A. Schematic of the subunits composing BAF complexes. The complexes are composed of catalytic subunits (orange), core subunits (blue) and accessory subunits (purple). The subunits are arranged in an arbitrary manner.

B. Schematic of the domains of the catalytic subunits. The catalytic subunits SMARCA2 and SMARCA4 are composed of 6 conserved domains, all of which have a specific function (in purple). The arbitrary size of the domains does not reflect their actual size.



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