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Mammalian SWI/SNF Complexes in Cancer: Emerging Therapeutic Opportunities

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Abstract

Mammalian SWI/SNF (BAF) chromatin remodeling complexes orchestrate a diverse set of chromatin alterations which impact transcriptional output. Recent whole-exome sequencing efforts have revealed that the genes encoding subunits of mSWI/SNF complexes are mutated in over 20% of cancers, spanning a wide range of tissue types. The majority of mutations result in loss of subunit protein expression, implicating mSWI/SNF subunits as tumor suppressors. mSWI/SNF-deficient cancers remain a therapeutic challenge, owing to a lack of potent and selective agents which target complexes or unique pathway dependencies generated by mSWI/SNF subunit perturbations. Here, we review the current landscape of mechanistic insights and emerging therapeutic opportunities for human malignancies driven by mSWI/SNF complex perturbation.

mSWI/SNF complex composition and canonical functionality

A single eukaryotic cell contains roughly 3 billion base pairs of DNA that are highly compacted to fit into a 5-micron nucleus. Such density of genetic information is achieved through the formation of progressively condensed chromatin structures, nucleosomes, that harbor 146 bases of DNA stably wrapped around a single octamer of histone proteins [1,2]. The stability and compactness provided by this nucleosomal structure safeguards the genome; however, temporal and spatial DNA accessibility necessitates entities such as chromatin remodeling complexes (CRCs), which are macromolecular machines capable of remodeling nucleosome architecture. CRCs are multi-subunit assemblies composed of a core ATPase that is fueled by ATP hydrolysis to regulate nucleosomal structures, and peripheral, non-catalytic protein subunits which confer specialized, non-redundant functions. Remodeling activity has been shown to facilitate the accessibility of transcription factors to functional DNA elements (enhancers, promoters, replicons), and subsequently stimulate

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context-specific gene expression and repression, as well as DNA replication, recombination, and repair[3].

Eukaryotes have evolved four distinct families of CRCs (SWI/SNF, ISWI, CHD, INO80), which exhibit a high degree of conservation from humans to yeast, particularly among the ATPase subunits [3]. Despite the supposed conserved function across the four families of chromatin remodelers, mSWI/SNF complexes have been the most strongly implicated in disease, with over 20% of human cancers harboring mutations in the genes encoding mSWI/SNF subunits [4–6]. mSWI/SNF complexes are further subdivided into two main complexes referred to as BAF (BRG1 or BRM-associated factors) and PBAF (Polybromo-associated BAF), which differ based on distinct subunit composition (Figure 1). Mutations in BAF and PBAF subunits appear to drive different malignancies; moreover, mSWI/SNF complexes have been shown to function as both tumor suppressors and oncogenes [7]. *SMARCB1*, *ARID1A* and *SMARCA4* are the most well-studied subunits, owing to their early-identified, clear genetic links to disease and their recently-uncovered high mutation frequencies in specific cancer types. The results of these human genetic studies have inspired the investigation of novel therapeutic strategies. Loss-of-function mutations of the mSWI/SNF subunits most often result in protein loss and subsequent disruption of complex integrity and composition. Consequently, cancer-specific subunit-deficient complexes result in altered regulation of distinct target gene sets, spawning new cellular dependencies or synthetic lethalities that can be exploited for targeted therapeutic approaches. Here, we review the most current and actionable therapeutic angles that can be explored to address neoplasms driven by mutations in core members of mSWI/SNF chromatin remodeling complexes.

Synthetic lethality: a tangible path toward targeted therapies for mSWI/SNF-driven cancers

Synthetic lethality is broadly defined as the combination of two genetic events (i.e., mutations) that result in loss of cell fitness [8]. Various synthetic lethal relationships have been reported in mSWI/SNF-driven cancers in which loss of one subunit (e.g., SMARCB1 [9], ARID1A [10,11], SMARCA4 [12–14]) confers unique dependency on the presence of another functional mSWI/SNF subunit, particularly subunit paralogs, or increased dependency on an downstream gene or cellular pathway. As restoration of gene products in affected tissues is not clinically tractable, targeting cancers driven by loss of tumor suppressor genes remains a challenge in cancer therapy [15,16]. The genomic era has enabled routine exon sequencing of human tumor specimens [6], and as a consequence, synthetic lethal screening efforts employing both genetic manipulation and small molecules have jumped to the forefront of precision cancer therapy [17–19]. The discovery of synthetic lethal relationships hallmark to cancers driven by mSWI/SNF complex perturbation may suggest the use of targeted therapies in cases where drugs already exist for the dependent molecular pathway(s). However, chromatin regulators are generally responsible for more global effects on transcription, and hence are often less reliant on any single downstream gene or pathway. Consequently, synthetic lethal relationships between subunits within the mSWI/SNF complex or between mSWI/SNF subunit loss and aberrantly activated signaling

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pathways will prompt the discovery of new agents across various neoplasms for which targeted therapeutics have not to date been identified.

Intra-complex synthetic lethal relationships between paralogous subunits

SMARCA4/SMARCA2

The results of synthetic lethal screening efforts have revealed that cancers bearing protein loss of one mSWI/SNF subunit exhibit uniquely strong dependency on the presence of a remaining, intact paralogous subunit to maintain their proliferative fitness. Synthetic lethal screening efforts using RNAi libraries in SMARCA4-deficient non-small cell lung carcinoma (NSCLC) cell lines identified SMARCA2 as the top synthetic lethal dependency required for cell line proliferation [13,14]. SMARCA4 and SMARCA2 are mammalian homologs of the SNF2-like ATPases in yeast and Drosophila, which use ATP hydrolysis to power the remodeling activity of CRCs [20]. SMARCA4 protein inactivation or loss-of-function point mutations [21] have been reported across neoplasms of various tissue types, including the lung [22–25], blood (Burkitt lymphoma) [21,26], brain (pediatric medulloblastoma) [21,27], ovary [28,29], pancreas [30], and others. Whether this specific intra-complex synthetic lethal relationship between paralog subunits holds true across a wide range of cancer types remains to be determined. However, the discovery of SMARCA2 as an actionable target has informed a potential approach in SMARCA4-deficient lung cancers, especially those that may lack the canonical molecular targets such as EGFR/RAS/PI3K activating mutations.

ARID1A/ARID1B

Dependency on a remaining paralog subunit upon single paralog loss is further demonstrated with the ARID1A-ARID1B pair of subunits, further demonstrating the partially redundant nature of paralog subunits within mSWI/SNF complexes [31]. The AT-rich interactive domain-containing protein 1A (ARID1A) is only found in BAF complexes and not PBAF complexes. Genome wide sequencing efforts have discovered somatic loss-of-function mutations in ARID1A across a range of gynecologic cancers [32], in approximately 30% of ovarian endometrioid carcinomas (OEC) and roughly 60% of ovarian clear-cell carcinomas (OCCC) [33,34]. Furthermore, saturation analysis of cancer genes reveals ARID1A to be one of the top genes to be frequently mutated among three or more tumor types [35]. Interestingly, ARID1A mutations are frequently monoallelic, indicating that haploinsufficiency may also play an important role in the oncogenic process [34,36].

Future Opportunities

Subunit-specific degradation can be realized through modern strategies in chemical biology such as those using ligand-dependent protein degradation of target biomolecules. Such approaches are already being exploited in settings in which a high-affinity small molecule capable of selectively binding the target of interest is tethered to a module that is able to recruit an E3 ubiquitin ligase to induce specific degradation of the targeted protein [37–39]. Efforts are currently underway to modify mSWI/SNF bromodomain-specific small molecules for protein degradation approaches. Such strategies will require additional biochemical studies before they are considered for further preclinical and clinical

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development, for example, determining whether targeted subunits in isolation or full complex assembles are degraded. While SMARCA2 and ARID1B are the most efficient vulnerabilities of SMARCA4-mutant and ARID1A-deficient cancers, respectively, to date small molecule based inhibitors have been challenging to identify owing to high degree of similarity between paralogs. Moreover, ARID1B loss has been recurrently linked to intellectual disability syndromes [40], thus ARID1B-specific degradation would have to be targeted only to affected tissues. In addition, caution would be required in patient identification; for example, SCCOHT, is a SMARCA4-deficient cancer (genetically) with concomitant loss of SMARCA2 (at the mRNA and protein level) leaving no ATPase subunit to deplete or inhibit [41]. mSWI/SNF-deficient neoplasms seem to recurrently retain dependence on the residual complex, which, in the case of paralogs, is assembled exclusively with the remaining paralog. Targeted chemical biology approaches such as small molecule-inducible protein subunit degradation represent a possible yet currently unexplored avenue for mSWI/SNF-driven cancer therapy.

Synthetic lethality between other protein complexes and signaling pathways

SMARCB1-loss and EZH2 inhibition

The discovery of recurrent, biallelic inactivation of *SMARCB1* in malignant rhabdoid tumor (MRT) by Versteege and colleagues in the late 1990's provided the original evidence for the uniquely potent tumor suppressive function of mSWI/SNF complexes [42,43]. MRT is a rare, highly aggressive pediatric cancer with a remarkably low burden of secondary mutations, that to date lacks effective therapeutic approaches[44]. Roberts and colleagues reported elevated expression of EZH2 (enhancer of zeste homolog 2) in SMARCB1-deficient cells [9] and showed that depletion of EZH2 in MRT cell lines resulted in apoptosis [9]. Over the past several years, studies have shown that xenograft-based mouse models of MRT respond to small molecule inhibition of EZH2 [45]. Potent and specific EZH2 inhibition has also been demonstrated in various preclinical studies of hematopoietic malignancies such as lymphoma [46–49]. Preclinical proof of concept of small molecule-mediated EZH2 inhibition has been validated in SMARCB1-deficient solid tumors [45,50]. EZH2 functions as the core enzymatic subunit of the polycomb repressor complex 2 (PRC2), which is responsible for the trimethylation of histone H3 at lysine 27 (H3K27me3), a mark associated with genomic transcriptional repression [51–54]. Both the mSWI/SNF and the PRC2 complex are crucial effectors of genomic transcription; their activating and repressive functions, respectively, are tightly regulated during development [55]. The mSWI/SNF complex has been shown to antagonize the polycomb complex, hinting at a co-evolved transcriptional role [9,56–59]. The synthetic lethal relationship between SMARCB1 loss and PRC2 inhibition represents one of the most actionable dependencies that can be rationally targeted with current inhibitory agents against both EZH2 and EED [49,60]. As the ongoing human clinical trials come to term, the prospect of using EZH2 inhibitors as a mainstay in SMARCB1-deficient cancers will become clear (Table 1).

In addition to MRT, genetic studies have uncovered SMARCB1-loss in a number of other solid tumors including atypical teratoid/rhabdoid tumors (AT/RT), epithelioid sarcomas

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(ES), epithelioid malignant peripheral nerve sheath tumors (EMPNST), various SMARCB1-deficient carcinomas (e.g. myoepithelial carcinomas, sinonasal basaloid carcinoma), schwannomas, and very rare cases of multiple meningiomas [61–65]. Whether the loss of SMARCB1 is universally concomitant with elevated expression of EZH2 in every SMARCB1-deficient neoplasm remains to be determined as new studies emerge. Interestingly, an exhaustive survey of the genomic and epigenetic landscape of AT/RT uncovered three epigenetically distinct AT/RT subgroups in addition to inactivation of SMARCB1 [62]. The primary AT/RT samples showed wide genetic uniformity with specific epigenetic differences in three major pathways termed ATRT-TYR, ATRT-SHH and ATRT-MYC. As expected, EZH2 expression was elevated in all three subgroups [62]. Most importantly, this degree of granularity in deciphering the heterogeneous nature of AT/RT can further diversify targeted therapies in the clinic. This finding suggests that EZH2 inhibition could potentially synergize with pathway-dependent inhibitors in each respective AT/RT subgroup where drugs already exist. Of note, two small molecule inhibitors of smoothened (SMO), a key effector regulating SHH signaling, were recently approved by the federal drug administration (FDA) [66]. AT/RT-MYC on the other hand, showed MYC target gene upregulation with bromodomain-containing protein 4 (BRD4), a transcriptional co-activator [62], targeted to MYC enhancers. Bromodomains are protein modules that bind acetyl lysines on chromatin serving as readers of epigenetic states and recruiters of transcriptional apparatus [67–70]. Bromodomain inhibition has been established and validated in various hematopoietic cancers [71,72] and has been shown to reduce MYC target gene expression [73–75]. Hence, BRD4 inhibition in the ATRT-MYC subgroup may represent a viable path forward. SMARCB1-deficient AT/RTs are thus particularly primed for drug combination studies pairing EZH2 inhibitors with molecular probes of the SHH pathway to downregulate hedgehog signaling or BRD4 inhibitors to attenuate expression of MYC target genes.

SMARCA4-deficient thoracic sarcomas bear concomitant loss of SMARCA2

Over the past two years, sequencing studies of solid tumors revealed that two tumor types, small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) and SMARCA4-deficient thoracic sarcomas (SMARCA4-DTS) feature genetic loss of SMARCA4 [28,76–79] with concomitant silencing of SMARCA2. Immunohistochemical staining of SCCOHT tumor samples showed reduced or absent nuclear SMARCA2 protein [79], indicating that not all cancers that feature loss of SMARCA4 will benefit from a SMARCA2 ATPase inhibitor. Intriguingly, unsupervised hierarchical clustering of transcriptional profiles of these tumor types denoted that SMARCA4-DTS profiles were most closely aligned with MRT and SCCOHT, highlighting the mechanistic similarity of mSWI/SNF ATPase loss and BAF47 (SMARCB1/hSNF5) loss [79]. However, cell of origin may also contribute to the striking similarities in gene expression profiles. These findings represent the first demonstrations of SMARCA4-deficient cancers (SMARCA4-DTS and SCCOHT), which correlate with SMARCB1-deficient MRT. SMARCB1 loss is hallmark to ~98% of MRT; the remaining 2% have been reported to have SMARCA4 genetic loss with SMARCA2 silencing. These results suggest that EZH2 inhibition should be explored in SMARCA4-DTS and SCCOHT cell lines and murine pre-clinical models to establish whether this approach may show efficacy in these tumor types (Table 1).

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Pathway vulnerabilities in ARID1A-deficient cancers

In addition to the striking intra-complex dependency (ARID1B) in ARID1A-deficient tumors, novel synthetic lethal targets that are not members of the mSWI/SNF complex have also been identified, with studies exploring the tractability of EZH2 [10], YES1 [11], PARP [80], ATR [81] and PIK3CA [82] pathway inhibition. It is interesting to note that SMARCB1-deficient tumors such as MRT and AT/RTs showed increased sensitivity to EZH2 inhibition. However, the ovarian clear-cell carcinoma (OCCC) cell lines lacking ARID1A described thus far do not show upregulation of EZH2 [10], suggesting that the molecular dependencies caused by SMARCB1 loss in MRT are different in ARID1A-loss cancers. In addition, EZH2 was not ranked among the top vulnerabilities identified in shRNA-based dropout screening set published by Helming et al (Figure 2B) [31]. Strikingly, Kim and co-authors showed that the viability of mSWI/SNF-deficient (ARID1A, SMARCA4 and PBRM1 mutated) cancer cell lines primarily depended on a structurally intact PRC2 complex as opposed to the enzymatic activity of EZH2 [83]. On that account, further studies are warranted to determine whether EZH2 enzymatic inhibition or PRC2-specific destabilization will amount to a specific vulnerability across a broader set of ARID1A-deficient cancers.

mSWI/SNF complexes have long been implicated in DNA damage repair [84,85]. Recently, various studies have demonstrated that ARID1A deficient cancer cells exhibit enhanced vulnerability to inhibitors of DNA repair pathways [80,81]. While DNA checkpoint inhibition warrants greater pre-clinical exploration, the PIK3/AKT pathway has garnered significant interest in the field. A recent report has converged on the PIK3/AKT pathway as a vulnerability for ARID1A-mutant neoplasms [82]. Notably, both catalytic subunits of PIK3, PIK3CA (p110) and PIK3R2 (p85), are featured among the highest vulnerabilities across a set of ARID1A-deficient cells within shRNA-based dropout screening data sets (Figure 2B). PIK3CA activating mutations have been recurrently seen in ARID1A-deficient OCCC patients [86,87]. This raises the possibility that ARID1A-loss cooperates with activating PIK3CA mutations for OCCC oncogenesis. Furthermore, knock down of ARID1A in breast cancer and fibroblast cell lines increased sensitivity to PIK3 and AKT inhibition. Interestingly, OCCC lines that have retained proper expression of ARID1A have been shown to be less sensitive to PIK3 and AKT inhibition [82]. PIK3CA is known to play an essential role in tumor development across various tissue types [88]; PIK3CA inhibition is a clinically tractable option due to the wide availability of PIK3 pathway drugs [89].

In fact, there are more than 30 inhibitors targeting various nodes of the PIK3/AKT pathway with some rapidly moving toward FDA-approval [90]. Whether PIK3CA is the most tangible target to treat ARID1A-deficient cancers is still unknown; consequently, further research will be required to mechanistically exploit the role of ARID1A-loss in tumorigenesis.

Directly targeting protein domains of the mSWI/SNF complex

ATPase and bromodomain inhibition

The increasingly apparent role of mSWI/SNF complexes in human disease, coupled with recent successes in the development of bromodomain inhibitors, have inspired the discovery

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of PFI-3, a potent and specific small-molecule inhibitor of the bromodomain modules on SMARCA2, SMARCA4 and PBRM1 (Figure 3) [91]. However, despite engaging various key subunits of the mSWI/SNF complex (in both BAF and PBAF complexes), PFI-3 has failed to show anti-proliferative responses in cancer cell lines [92]. PFI-3 demonstrated proper engagement of its cellular targets but was unable to disengage endogenous SMARCA2-containing mSWI/SNF complexes from chromatin, likely owing to the number of other DNA-binding and chromatin-binding domains on mSWI/SNF complexes [93]. Vangamudi et al., established the ATPase activity of SMARCA2/4 as the pertinent biologically active target by demonstrating that an ATPase-dead mutant of SMARCA2/4 fails to rescue the proliferation of SMARCA4-deficient lung cancer cell lines, while both a SMARCA2/4 wild-type and a bromodomain-dead mutant construct were able to maintain cellular viability [93]. With these results, targeted inhibition of the ATPase domain of SMARCA2 has become widely recognized as the most viable approach for the treatment of a subset of SMARCA4-deficient cancers (e.g. 10-20% of NSCLC cases) [93].

Various SMARCA4 deficiencies manifest as tumor suppressor mechanisms [28,79], but a recent finding in neuroblastoma (NB) highlighted the ATPase as an oncogene [94]. Jubierre et al., showed overexpression of SMARCA4 in stage 4 NB patients was associated with worst outcomes [94]. Experiments both in cell culture and xenograft mouse models using a range of NB cell lines demonstrated apoptotic cell death upon shRNA-mediated knockdown of SMARCA4 [94]. This discovery did not evaluate whether the oncogenic effects were mediated by the catalytic activity of SMARCA4 or within the context of an intact and fully functional mSWI/SNF complex. As future work establishes this distinction, the toxicity and potential therapeutic window of SMARCA4 or SMARCA2 ATPase inhibition needs to be explored in pre-clinical murine models. Moreover, the ATPase domains of SMARCA4 and SMARCA2 are essentially identical (Figure 3), making identification of target-specific small molecule chemical probes exceedingly challenging. Small molecule probes that are potent but unable to discriminate between the ATPases of SMARCA4 and SMARCA2, may still be clinically effective in specific mSWI/SNF-driven cancer types.

The bromodomain-containing accessory subunits, BRD9, PBRM1 and BRD7 (PBAF-specific) have been linked to acute myeloid leukemia (AML), clear-cell renal cell carcinoma (ccRCC) and breast cancer respectively [95–97]. Moreover, BRD9/7 and PBRM1 feature bromodomains that are liable to small molecule inhibition (Figure 3). Unlike the acetyl readers found on SMARCA4 and SMARCA2, the bromodomain of BRD9 has been demonstrated to be a tangible target in AML [95]. Although BRD9 is rarely mutated in human cancers and is expressed rather ubiquitously, it is vital to leukemia maintenance, particularly in AML [95]. While studies have begun to shed light on the role of the mSWI/SNF complex in leukemia maintenance, due to the combinatorial complexity of mSWI/SNF complexes, the proper subunit module responsible for AML maintenance remains unresolved [98]. A number of potent small molecule inhibitors of BRD9 have been recently reported (Figure 3), and future work in this area is warranted to establish whether BRD9 is critical to cells other than AML cells. This will further resolve whether BRD9 inhibition impedes remodeling activity of the mSWI/SNF complex across the genome or whether this is a specific response, occurring at MYC-driven enhancers loaded with BRD9 protein not tethered to the mSWI/SNF.

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Targeting the unique oncogenic property of SS18-SSX in synovial sarcoma

The mSWI/SNF complex is broadly depicted as a tumor suppressor [99,100], with genetic loss of one subunit often perturbing the complex integrity and composition, which results in transcriptional deregulation of genes that regulate cellular proliferation [101]. However, mSWI/SNF complexes can also be oncogenes, noted most strongly in synovial sarcoma, in which a unique gain-of-function mutation confers oncogenic functionalities. Synovial sarcoma is a highly aggressive and rare cancer which occurs in the extremities of pediatric and young adult patients [102] and is uniformly characterized by an in-frame fusion of the mSWI/SNF subunit SS18 to the C-terminal end of SSX1 or SSX2 and rarely SSX4 [103–105]. SS18-SSX is most often the only genetic aberration (in an otherwise stable genomic background) and specific knockdown of the fusion protein rapidly induces cell death in SS cell lines. Moreover, recent studies have shown that SS18-SSX competes the endogenous SS18 protein and consequently evicts SMARCB1 away from the mSWI/SNF complex [102]. In the presence of SS18-SSX, SMARCB1 is unable to bind the complex and is degraded by the proteasome [102], which can be detected by immunohistochemical analyses. SS18-SSX-specific degradation represents a challenging yet highly impactful therapeutic avenue. Ongoing clinical trials are investigating the tractability of EZH2 inhibition in SS due to the low levels of SMARCB1. In addition, further synthetic lethal screening efforts, both with shRNA/CRISPR-Cas9 and small molecule libraries represent additional opportunities toward the identification of unique pathway sensitivities that result from the activity of the oncogenic SS18-SSX-containing SWI/SNF complex.

Conclusions and Future Outlook

Emerging data from modern human genetic and functional genomic studies have implicated mSWI/SNF complexes as exciting but challenging drug targets. Synthetic lethal screening efforts have unmasked new potential avenues to treat cancers driven by mSWI/SNF perturbations. Further mechanistic studies will be required to determine whether the dependencies conferred by subunit loss are consistent across different tissue types harboring loss of the same subunit. Paradoxically, mSWI/SNF subunits have been implicated as oncogenes in various neoplasms (e.g. synovial sarcoma, NB, TNBC, etc). As demonstrated, mSWI/SNF mutations are manifested through diverse and context-specific modalities, which will require cancer-specific approaches to achieve targeted therapies. Moving forward, several mSWI/SNF subunit mutations co-occur with known oncogenic genomic aberrations (e.g. PIK3CA, KRAS, BRAF and more), thus comprehensive rescue experiments must be thoughtfully considered to determine specific synthetic lethalities. For instance, a drug targeting an essential gene or pathway might effectively reduce the proliferative capacity of several cell types in which mSWI/SNF mutations are frequent, yet that alone does not suffice to imply synthetic lethality. The identification of therapeutic approaches for the broad range of human cancers that are driven by mSWI/SNF complex perturbation represents a burgeoning field ripe for new discoveries. As further sequencing studies and functional genetic screening efforts are completed, additional cancer subtypes predicted to benefit from mSWI/SNF-specific drug development will be uncovered.

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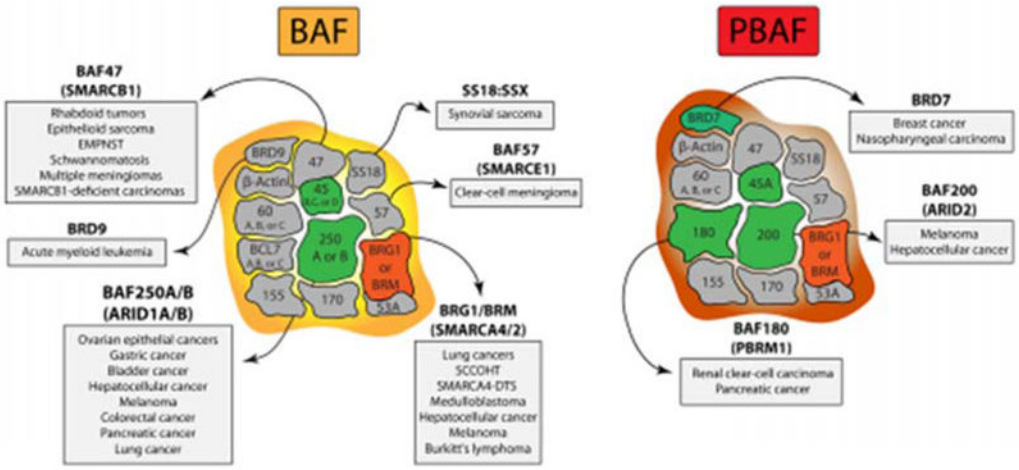

Figure 1. mSWI/SNF chromatin remodeling complexes in human cancer

Mammalian SWI/SNF complexes are separated into two separate forms: BRG1/BRM associated factor (BAF or SWI/SNF-A) and polybromo-associated BAF (PBAF or SWI/SNF-B). BAF and PBAF share numerous subunits, including both ATPases BRG1 and BRM (depicted in red). BAF and PBAF differ from one another by incorporation of key peripheral subunits (depicted in green). Mutations in the genes encoding mSWI/SNF complex subunits are present in over 20% of human cancers, with specific subunits mutated in specific malignancies, as shown [4–6].

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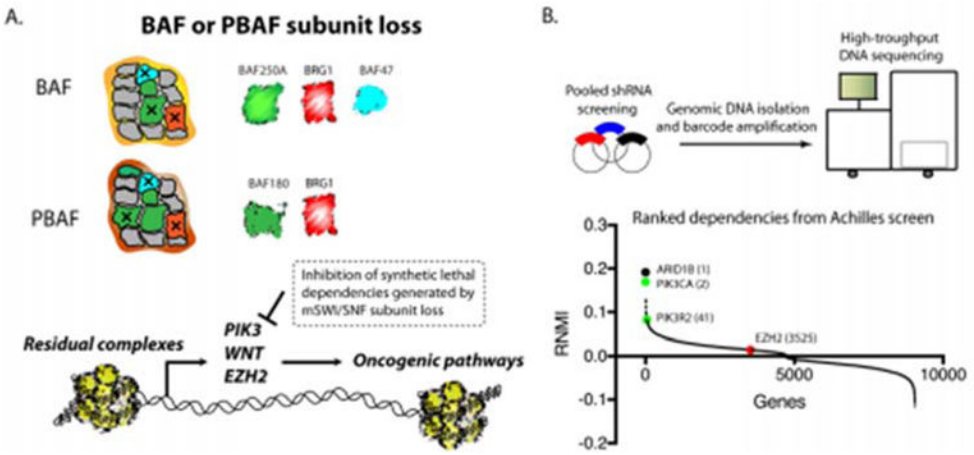

Figure 2. Genetic perturbation to genes encoding mSWI/SNF subunits gives rise to cancer-specific vulnerabilities

(**A**) Loss of BAF or PBAF subunits results in subunit(s)-deficient complexes resulting in transcriptional deregulation across distinct oncogenic pathways. Inhibition of resulting synthetic lethal dependencies represents a viable therapeutic avenue, using existing agents where available. (**B**) Rank gene list depicting specific vulnerabilities in ARID1A-deficient cells from an RNAi screen from [30]. ARID1B (black dot) is the top vulnerability in ARID1A-deficient cells, followed by PIK3 pathway genes (green dots). EZH2 (red dot) does not score as a top dependency in the dataset reported in [30]. Genes are ranked by RNMI (Ranked Normalized Mutual Information) score.

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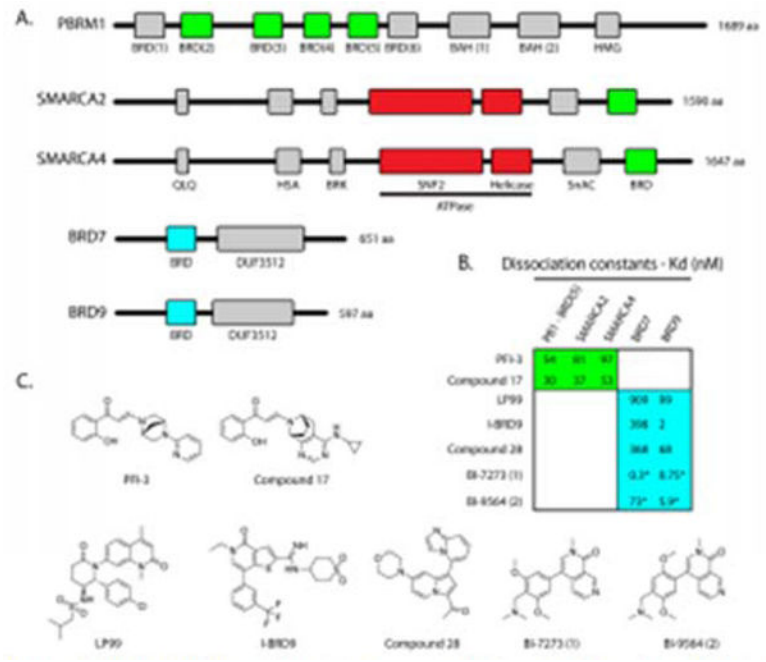

Figure 3. mSWI/SNF subunits contain several bromodomains with existing, potent small molecule probes

(**A**) Schematic of five mSWI/SNF subunits (PBRM1, SMARCA2, SMARCA4, BRD7, and BRD9) depicting the prevalence of bromodomains across proteins of the chromatin remodeling complex. In green, are bromodomains inhibited by PFI-3 [92] and Compound 17 [91]; in blue are bromodomains inhibited by LP99 [106], I-BRD9 [107], Compound 28 [108], BI-7273(1) and BI-9564(2) [109]. (**B**) Dissociation constants or Kd (nM) of each small molecule to their respective targets are tabulated. Values with (*) were calculated based on BROMOscan inhibitor binding platform. Remaining values were determined by isothermal titration calorimetry (ITC). (**C**) Chemical structures of bromodomains inhibitors targeting PBRM1, SMARCA2, SMARCA4, BRD7 and BRD9.

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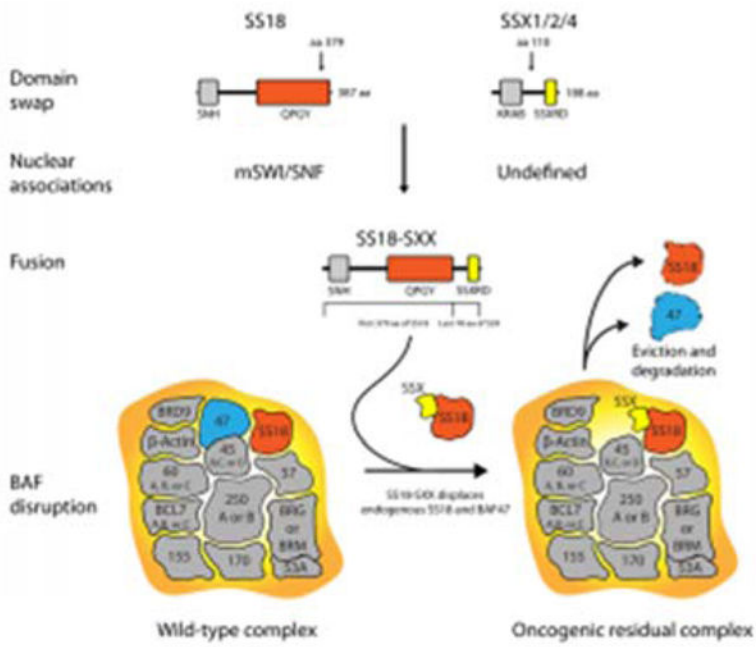

Figure 4. The SS18-SSX fusion protein hallmark to synovial sarcoma renders mSWI/SNF complexes oncogenic

Synovial sarcoma is driven by the t(X;18) chromosomal translocation which results in the fusion of the first 379 amino acids (aa) of SS18 to the last 78 aa of SSX1, 2, or 4. The ensuing SS18-SSX fusion protein dominantly replaces wild-type SS18 in BAF complexes and results in the inability of BAF47 (SMARCB1 or hSNF5 or INI1) to properly assemble. The oncogenic residual complex is targeted to new genomic loci leading to oncogenic gene expression and proliferation.

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Table 1

Early-phase clinical trials evaluate vulnerabilities identified in cancers with mSWI/SNF complex subunit deficiencies

EZH2 inhibition is currently being evaluated in various SMARCB1-deficient cancers, including malignant rhabdoid tumor (MRT), AT/RT, and epitheliod sarcoma (EpS). Dasatinib, which targets both BCR/ABL and Src family tyrosine kinases, is being evaluated in patients with ovarian, fallopian tube, endometrial, and peritoneal cancers; in this set, ARID1A (BAF250A) immunoreactivity (via immunohistochemical analyses) is being recorded to correlate ARID1A mutation status with treatment outcome. Following preclinical studies, EZH2 inhibitor clinical trials in SMARCA4-DTS patients could be warranted given the genetic and transcriptional similarities to MRT [79]. Selective small molecule ATPase inhibitors of SMARCA2 have yet to be reported. Note: While there are various ongoing clinical trials involving the cancers listed here, only those trials with explicit monitoring of mSWI/SNF subunit mutation status (i.e. genetic sequencing, IHC staining) are included in this table.

Gene	Protein	Associated Neoplasms (%)	Associated Vulnerabilities	Clinical Trials	References
SMARCB1 (hSNF5)	BAF47 INI1	Malignant rhabdoid tumor (>95%) Atypical teratoid/rhabdoid tumor (>95%) Epithelioid sarcoma (~93%) Epithelioid malignant peripheral nerve sheath tumor (50%) Schwannomatosis/multiple meningiomas SMARCBl-deficient carcinomas (e.g.Myoepithelial carcinoma) Ovarian clear cell carcinoma (46–57%) Ovarian endometrioid	EZH2; SHH; MYC; TYR; SMARCA4	NCT02601937 NCT02601950	[9,42–44, 50, 61–65, 83]
ARID1A	BAF250A	carcinoma (30%) Endometrial endometrioid carcinoma (39–44%) Breast (13–35%) Pancreatic cancer (33–45%)	ARID1B; PIK3/AKT; EZH2; YES1; PARP; ATR	NCT02059265	[10, 11, 31–36, 80–83]
SMARCA4	BRG1	Non-small cell lung cancer (10–35%) SMARCA4-deficient rhabdoid tumors SCCOHT SMARCA4-DTS Medulloblastoma (5–10%) Burkitt's lymphoma (15%) Neuroblastoma	SMARCA2; PIK3/AKT; EZH2	None	[12–14, 21–30, 76–79, 83, 93,94]