Received: 1 October 2020 | Revised: 6 December 2020 | Accepted: 7 December 2020

DOI: 10.1111/cas.14768

REVIEW ARTICLE

Cancer Science WILEY

The role of the SWI/SNF chromatin remodeling complex in pancreatic ductal adenocarcinoma

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Funding information
Uehara Foundation, Grant/Award Number: 201720143; Takeda Foundation, Grant/Award Number: 201749741; Mochida Foundation, Grant/Award Number: 2017bvAg; Mitsubishi Foundation, Grant/Award Number: 201910037; Princess Takamatsu Cancer Research Fund, Grant/Award Number: 17-24924; Grants-in-Aid KAKENHI, Grant/Award Number: JP19H03639; Japan Agency for Medical Research and Development, Grant/Award Number: 20cm0106177h0001 and 20gm6010022h0003

Abstract

ATP-dependent chromatin remodeling complexes are a group of epigenetic regulators that can alter the assembly of nucleosomes and regulate the accessibility of transcription factors to DNA in order to modulate gene expression. One of these complexes, the SWI/SNF chromatin remodeling complex is mutated in more than 20% of human cancers. We have investigated the roles of the SWI/SNF complex in pancreatic ductal adenocarcinoma (PDA), which is the most lethal type of cancer. Here, we reviewed the recent literature regarding the role of the SWI/SNF complex in pancreatic tumorigenesis and current knowledge about therapeutic strategies targeting the SWI/SNF complex in PDA. The subunits of the SWI/SNF complex are mutated in 14% of human PDA. Recent studies have shown that they have context-dependent oncogenic or tumor-suppressive roles in pancreatic carcinogenesis. To target its tumor-suppressive properties, synthetic lethal strategies have recently been developed. In addition, their oncogenic properties could be novel therapeutic targets. The SWI/SNF subunits are potential therapeutic targets for PDA, and further understanding of the precise role of the SWI/SNF complex subunits in PDA is required for further development of novel strategies targeting SWI/SNF subunits against PDA.

KEYWORDS

BAF, chromatin remodeling complexes, epigenetics, pancreatic ductal adenocarcinoma, SWI/SNF

1 | INTRODUCTION

There is mounting evidence to support the substantive role of epigenetic regulators in the development and progression of cancer. ATP-dependent chromatin remodeling complexes are a group of epigenetic regulators that alter the assembly of nucleosomes and regulate the accessibility of transcription factors to the DNA, thus leading to dynamic regulation of gene expression.[1] These complexes play crucial roles in stem cell maintenance, development, and cancer. They are divided into four distinct families: SWI/SNF, ISWI, CHD, and INO80, and all of them are evolutionarily conserved from yeast to humans. The SWI/SNF chromatin remodeling complex changes chromatin accessibility by chromatin repositioning, nucleosome ejection, and histone dimer eviction (Figure 1A).

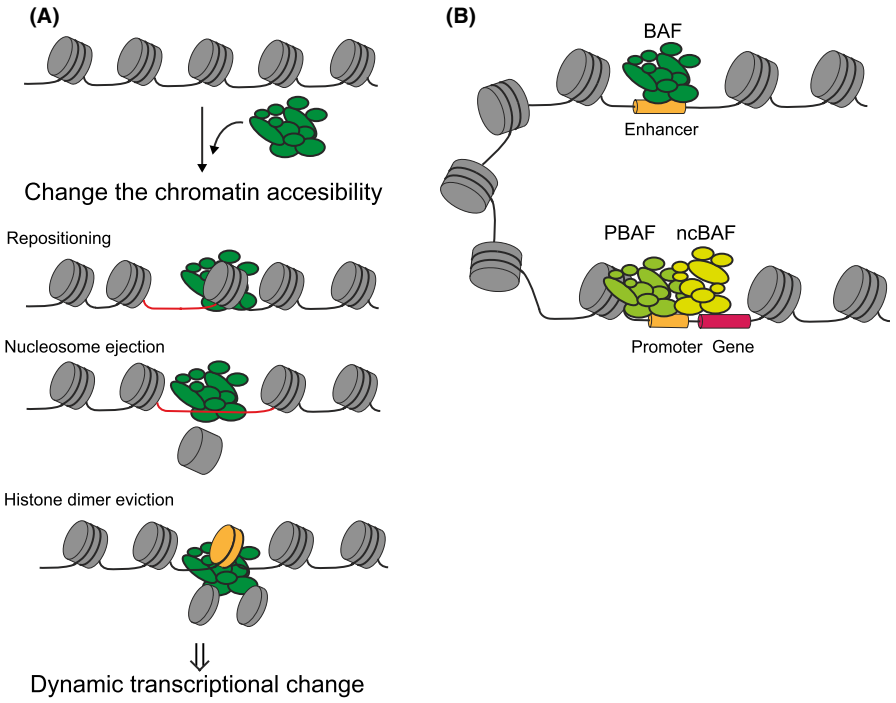

FIGURE 1 A, The SWI/SNF complex controls the transcription by changing the chromatin accessibility. B, BRM/BRG1-associated factor (BAF) complex mainly interacts with enhancer regions, while polybromo-associated BAF (PBAF) and noncanonical BAF (ncBAF) interact with promoter regions

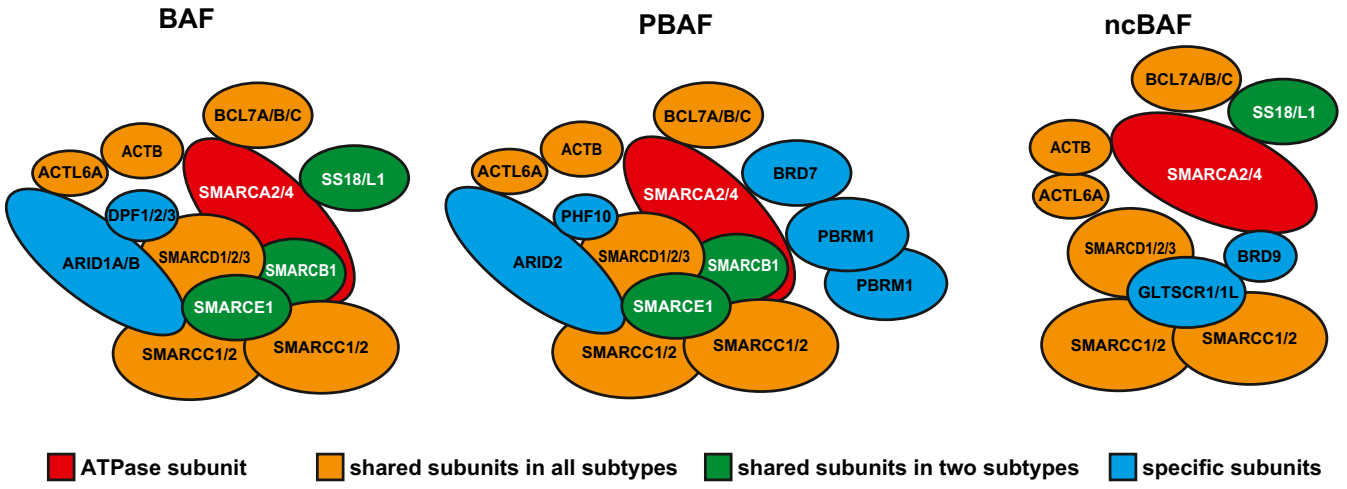

FIGURE 2 Subunits of three major subclasses of the SWI/SNF complex. BAF, BRM/BRG1-associated factor; PBAF, polybromo-associated BAF; ncBAF, non-canonical BAF

ISWI and CHD control nucleosome maturation, assembly, and spacing, whereas INO80 conducts histone removal and replacement.[2] In particular, the SWI/SNF complex is known to control transcription by activating promoter/enhancer regions by partially regulating acetylated histone H3 K27 (H3K27ac), which is a marker of active promoter/enhancer.[3-5] Recent whole-exome and whole-genome sequencing studies have shown that the SWI/SNF complex was most frequently mutated in these four families and harbored mutations in more than 20% of human cancers, implying their important roles in cancer development and progression.[6,7] In this review, we summarize the recent discoveries regarding the emerging roles of the SWI/SNF complex in pancreatic ductal adenocarcinoma (PDA) initiation and progression and discuss potential treatment strategies targeting subunits of the SWI/SNF complex.

2 | THE SUBUNITS OF THE SWI/SNF COMPLEX AND THEIR INVOLVEMENT IN HUMAN CANCER

The SWI/SNF complex contains 12-15 subunits and comprises three main groups: the BRM/BRG1-associated factor (BAF) (SMARCA2/SMARCA4-associated factor in humans), polybromo-associated BAF (PBAF), and **non-canonical** BAF (ncBAF) complexes[8] (Figure 2). They have several common subunits, including SMARCA2/4, SMARCB1,

SMARCC1/2, SMARCD1/2/3, SMARCE1, ACTL6A/B, β-actin, BCL7A/B/C, and SS18/L1. In these subunits, SMARCA4 (mouse; BRG1) and SMARCA2 (mouse; BRM) are known to be enzymatic ATPase subunits that catalyze the hydrolysis of ATP. SMARCC subunits exist as heterodimers. The BAF complex features ARID1A/B and DPF1/2/3, whereas the PBAF complex lacks SS18/L1 and features PBRM1, ARID2, BRD7, and PHF10. PBRM1 is present in more than one copy per PBAF complex. The ncBAF complex, which has been recently identified, lacks SMARCB1 and SMARCE1, and features BRD9 and GLTSCR1/1L (also known as BICRA/BICRAL) subunits.[8] Recent chromatin immunoprecipitation (ChIP) sequencing studies have shown that the enhancer regions are the predominant genomic targets of the BAF complex and that the promoter regions are the predominant genomic targets of the PBAF and ncBAF complexes[3-5,9] (Figure 1B).

ARID1A is the most frequently mutated subunit in SWI/SNF subunits, which is mutated in 8% of human cancers, and ARID2, PBRM1, SMARCA4, ARID1B, and SMARCA2 are mutated in more than 2% of cases.[10-12] The mutation frequency of the SWI/SNF complex varies with cancer types, and some cancer types are deeply addicted to mutations of SWI/SNF subunits. For example, 98% of malignant rhabdoid tumors and 90% of epithelioid sarcomas have *SMARCB1* mutations,[13-15] 95% of small cell carcinomas of the ovary have *SMARCA4* mutations,[16,17] 35% of uterine endometrioid carcinomas and 46% of ovarian clear cell carcinomas have *ARID1A* mutations,[18,19] and 41% of clear cell renal cell carcinomas have *PBRM1* mutations.[20] Interestingly, although most mutations in subunits of the SWI/SNF complex are loss-of-function mutations, suggestive of their tumor-suppressive roles, SS18-SSX fusion, seen in nearly 100% of synovial sarcomas, is a gain-of-function mutation, suggesting an oncogenic role.[21,22] Thus, the SWI/SNF complex has context-dependent oncogenic and tumor-suppressive roles. The heterogeneous involvement of the SWI/SNF complex in various cancer types could be explained, in part, by the fact that the chromatin accessibility landscape of cancer is cell type–specific.[23]

3 | SWI/SNF COMPLEX AS A CANCER THERAPEUTIC TARGET

Currently, there are very few potent and selective molecules targeting the subunits of the SWI/SNF complex itself. However, in recent years, many studies have been conducted to identify synthetic lethal targets against SWI/SNF-mutated cancer to therapeutically exploit SWI/SNF dysfunction in human cancer. Synthetic lethality is defined as a combination of deficiencies in the expression of two or more genes that leads to cell death, whereas a deficiency in only one of these genes does not.[24] Synthetic lethality is a good therapeutic strategy for targeting tumor suppressor genes because re-expression of deleted genes is difficult without genome editing. One of the most famous and successful examples of synthetic lethality targeted therapy is PARP1 inhibitor for *BRCA1/2*-deficient cancer. BRCA1/2 is required for homologous recombination (HR) and acts as a tumor suppressor gene.[25] PARP inhibitor selectively kills *BRCA1/2*-mutated cells by targeting their HR deficiency.[26] The PARP inhibitor has now been approved by the US Food and Drug Administration for the treatment of patients with *BRCA*-mutant cancers including PDA.

There are three strategies to explore synthetic lethal targets of the SWI/SNF complex. The first strategy is to diminish the residual complex by targeting mutually exclusive subunits, such as SMARCA2 in SMARCA4-mutated cancer,[27] ARID1B[28] or BRD2 (as an ARID1B inhibitor)[29] in ARID1A-mutated cancer, and BRD9 in SMARCB1-mutated cancer.[9] The second strategy is to target Polycome Repressive Complex 2 (PRC2), which has the opposite role of the SWI/SNF complex. Inhibition of EZH2, a catalytic subunit of PRC2, was proposed as a synthetic lethal target for SWI/SNF-mutated cancer.[30-32] The third strategy is to target downstream mechanisms. As the SWI/SNF complex is involved in DNA damage repair pathways, PARP1[33] and ATR[34] are proposed as targets for ARID1A-mutated cancer. The SWI/SNF complex is also involved in cell cycle regulation. To target this mechanism, CDK4 and CDK6 are proposed as targets of SMARCA4[35,36] and AURKA for SMARCA4- or ARID1A-mutated cancers.[37,38] In addition, UBE2C is a target for SMARCB1-deficient cancer in part by controlling Cyclin B.[39] Metabolic vulnerabilities are other targets of SWI/SNF-deficient cancer. Oxidative phosphorylation (OXPHOS) has been proposed as a target for SMARCA4- and ARID1A-deficient cancer,[40] and the glutathione metabolic pathway, which regulates reactive oxygen species, is proposed as a target for ARID1A-deficient cancer.[41] The SWI/SNF complex activates promoter/enhancer regions by regulating H3K27ac. Histone deacetylases, HDAC2[42] and HDAC6[43] are proposed as targets for ARID1A-deficient cancer. ARID1A-deficient cancer is also vulnerable to PI3K inhibitor[44] and tyrosine kinase inhibitor dasatinib.[45] MDM2 and MDM4, which inhibit p53 function, are targets for p53-intact SMARCB1-deficient cancer.[46] Protein synthesis and the endoplasmic reticulum (ER)-stress pathway as downstream factors of Myc could also be synthetic lethal targets for *SMARCB1*-deficient cancer.[47] In another review article, these series of efforts are described in more detail.[48]

However, such synthetic lethality is context-dependent. For example, EZH2 is a synthetic lethal target of ARID1A, but additional downregulation of SMARCA4, which in turn upregulates SMARCA2, induces resistance to EZH2 by upregulating the antiapoptotic gene BCL2.[49] Furthermore, EZH2 inhibitors are not efficient for SWI/SNF-mutated cancers in the context of RAS pathway mutations.[30] Considering such context dependency, a cancer type–specific validation study is warranted.

On the other hand, some SWI/SNF subunits act as oncogenes in a specific context and would be a direct target to treat cancer. For example, SMARCA4 acts as an oncogene, at least in neuroblastoma,[50] acute leukemia,[51] and small cell lung carcinoma.[52] Although PFI-3, a bromodomain inhibitor of SMARCA4, failed to show efficacy in cancer cells, inhibition of the ATPase activity of SMARCA4 could be an alternative target.[53] Moreover, BRD9

is essential for acute myeloid leukemia and is targetable using iBRD9, a BRD9 inhibitor.[54] SS18-SSX gene fusion, which is seen in 100% of synovial sarcomas, is also a potential therapeutic target.

4 | MUTATIONS OF THE SUBUNITS OF THE SWI/SNF COMPLEX IN HUMAN PDA

PDA is one of the most aggressive cancers, in which the number of newly diagnosed patients annually is nearly equal to the mortality of that year.[55,56] This dismal prognosis is due to late diagnosis and lack of highly effective therapies. To improve its prognosis, exploring new effective therapeutic agents are warranted. PDA is considered to arise from two major precursor lesions: pancreatic intraepithelial neoplasia (PanIN) or intraductal papillary mucinous neoplasm (IPMN). PDA is genetically characterized by the so-called "Big 4" mutations: *KRAS* gain-of-function mutation (over 90%) and *INK4A/p16*, *p53*, and *SMAD4* deletion or loss-of-function mutations, and the following relatively low frequent mutations.[57] Recent large-scale sequencing efforts have identified 10 core signaling pathways of mutations, in which chromatin modification and the SWI/SNF complex are independently included.[58] Indeed, subunits of the SWI/SNF complex, including *ARID1A* (6%), *SMARCA4* (2.1%), *ARID2* (2.1%), *PBRM1* (1.8%), *SMARCA2* (0.8%), *ARID1B* (0.5%), and *SMARCB1* (0.5%), were mutated in 14% of cases by integrated analysis of four recent genomic studies using cBioPortal (Figure 3).[11,12,58-61] The relatively high mutational burden of subunits of the SWI/SNF complex in PDA implies that the SWI/SNF complex has important roles in PDA, but its precise role is not fully understood.

5 | THE FUNCTIONAL ROLES OF SUBUNITS OF THE SWI/SNF COMPLEX IN PDA

5.1 | SMARCA4/Brg1 as a context-dependent regulator

Brg1, the mouse homolog of SMARCA4, is one of the two catalytic ATPase subunits of the SWI/SNF complex. SMARCA4 expression is frequently reduced or lost in human IPMN, which is one of the two main precursor lesions of PDA,[62] and decreased SMARCA4 expression correlates with increased dysplasia in human IPMN.[63] The initial in vivo functional study of the SWI/SNF complex in pancreatic carcinogenesis focused on Brg1. The pancreatic epithelium-specific deletion of *Brg1* with $Kras^{G12D}$ mutation led to the formation of cystic neoplasms that highly resembled human IPMN, and these mouse IPMN lesions progressed to invasive PDA.[64] This IPMN-derived

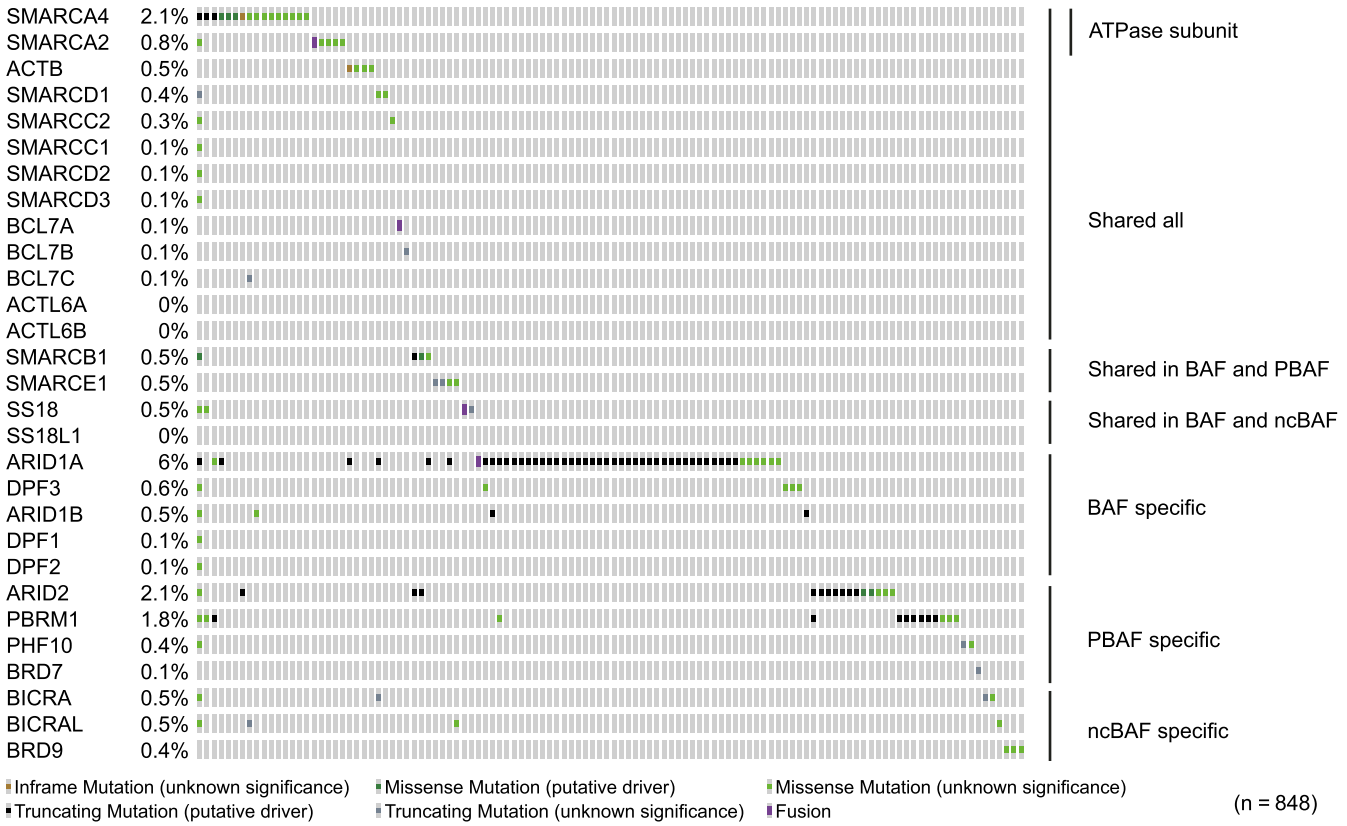

FIGURE 3 Mutational landscape of the subunits of the SWI/SNF complex in pancreatic ductal adenocarcinoma (PDA). Integrated analysis of four PDA genomic studies[58-61] using cBioPortal. BAF, BRM/BRG1-associated factor; PBAF, polybromo-associated BAF; ncBAF, non-canonical BAF

PDA mouse model by Brg1 deletion with $Kras^{G12D}$ mutation has a better prognosis for survival than the classic PanIN-derived PDA mouse model, which harbors $Kras^{G12D}$ mutation and *Tp53* heterozygous deletion and is derived from pancreatic acinar cells.[65,66] This prognostic trend is mirrored by that in human IPMN-PDA vs PanIN-PDA.[67] *Brg1* null IPMN-PDA also possesses distinct molecular signatures that support less malignant features than PanIN-PDA. Additionally, the adult pancreatic ductal cell– or acinar cell–specific deletion of *Brg1* with $Kras^{G12D}$ mutation revealed that IPMN lesions were derived from ductal cells, which have different cellular origins compared with PanIN lesions from acinar cells. This study highlights that IPMN-PDA is a biologically and molecularly distinct subset with a different cellular origin, although histologically indistinguishable from PanIN-PDA.

Furthermore, the following study showed that Brg1 blocks the initiation of ductal tumorigenesis by inhibiting the dedifferentiation of ductal cells via positive regulation of Sox9.[68] Surprisingly, Brg1-put back in *Brg1*-null mouse IPMN-PDA cell lines and *SMARCA4*-null human PDA cell lines promoted tumorigenesis in IPMN-PDA by supporting anchorage-independent growth and a mesenchymal-like landscape in part through Hmga2, which is known as an epithelial-mesenchymal transition (EMT) regulator. This study shows that Brg1 has context-dependent roles at distinct stages of PDA, such as TGF-β signaling.[69] In other words, Brg1 works as an oncogene in IPMN-PDA progression contrary to the tumor-suppressive role at its initiation.

In contrast to the tumor-suppressive role of Brg1 in the initiation of ductal cell–derived tumorigenesis, our recent work has shown that Brg1 plays an oncogenic role in the initiation of acinar cell–derived tumorigenesis.[70] Acinar cell–specific deletion of *Brg1* impaired PanIN and PanIN-derived PDA formation in the presence of *Kras* mutation and *p53* mutation, in a Sox9-dependent manner. Mechanistically, Brg1 directly binds to *Sox9* promoter regions and recruits PDX1, one of the Sox9 upstream regulators, to its promoter and enhancer regions. These data demonstrate that the BRG1/SOX9 axis is critical for acinar cell–derived PanIN-PDA formation. Furthermore, using an in vivo double recombinase system, we showed that the established PanIN also requires Brg1 for its maintenance by inhibiting apoptosis. These studies highlight the cell type–specific (opposite in ductal cell vs acinar cell) and context-dependent (opposite at early vs late stage) roles of Brg1 in PDA (Figure 4A).

5.2 | ARID1A as a tumor suppressor

ARID1A, which is one of the BAF-specific subunits, is the most frequently mutated subunit of the SWI/SNF complex in human PDA (Figure 2). ARID1A expression was absent in 22% of surgically

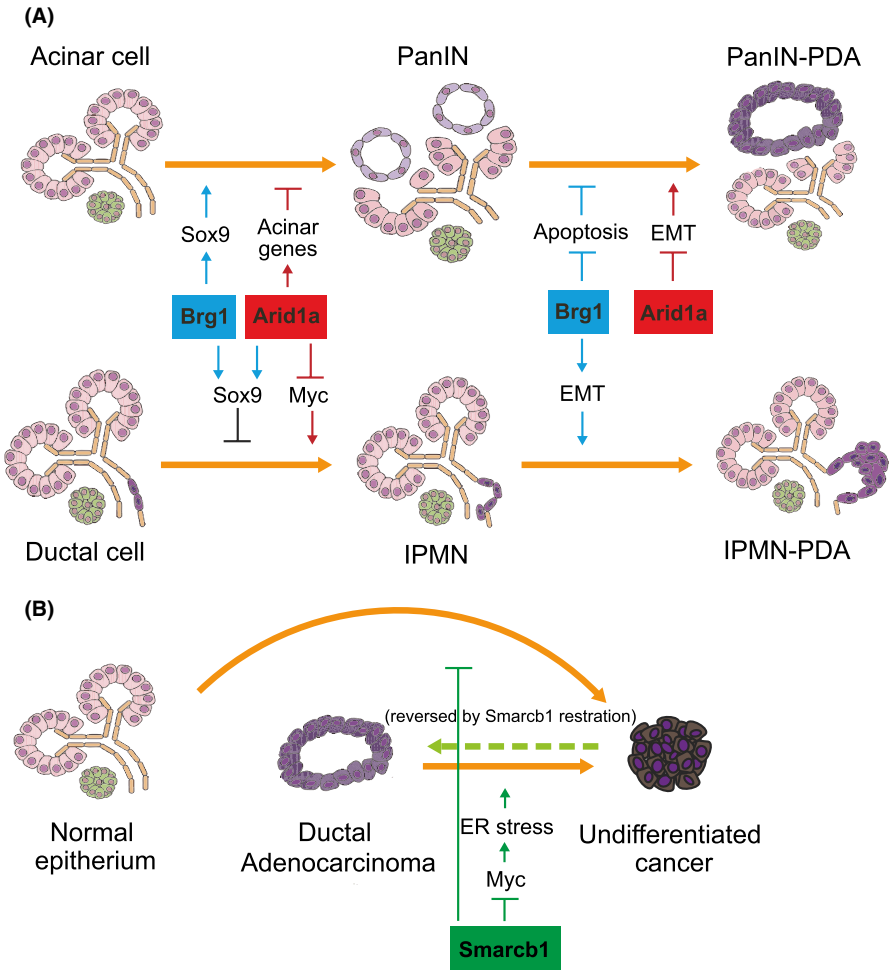

FIGURE 4 A, The role of SMARCA4 and ARID1A in pancreatic tumorigenesis. B, The role of SMARCB1 in pancreatic tumorigenesis. PanIn, intraepithelial neoplasia; PDA, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; EMT, epithelial mesenchymal transition; ER, endoplasmic reticulum

resected IPMNs and in 36% of PDA samples.[71] Protein loss and mutations of *ARID1A* correlate with poor survival of PDA patients.[72] Recently, several in vivo functional analyses of ARID1A in pancreatic tumorigenesis have been conducted.[71,73-75] Our initial study showed that pancreatic *Arid1a* deletion with a $Kras^{G12D}$ mutation forms IPMN and IPMN-derived PDA, demonstrating that *Arid1a* acts as a tumor suppressor in pancreatic tumorigenesis.[71] Furthermore, adult ductal cell– or acinar cell–specific deletion of *Arid1a* with *Kras* mutation confirmed that IPMN caused by *Arid1a* deletion was derived from ductal cells. Mechanistically, *Arid1a* loss led to the dedifferentiation and dilation of pancreatic ductal cells by partly suppressing Sox9 expression. These results highly resembled those of *Brg1* deletion; however, there were several differences between them. First, the incidence of PDA in *Arid1a*-deleted mice was significantly lower than that in *Brg1*-deleted mice. This difference could be explained by the lower mTOR pathway activation in *Arid1a*-deleted IPMN than in *Brg1*-deleted IPMN. Second, PanIN was formed in adult acinar cell–specific *Arid1a*-deleted mice, whereas PanIN was nearly abolished in *Brg1*-deleted mice. This difference suggests that *Arid1a* does not work as "cell type–specific oncogene" like *Brg1* in pancreatic tumorigenesis. Furthermore, the following studies from three other groups have provided additional insights into this issue. First, the sequential knockdown of *Arid1a* using an inducible sh*Arid1a* model in adult *Kras*-mutated pancreatic epithelium resulted in rapid and irreversible PanIN formation but did not increase PDA formation. ARID1A knockdown reduced chromatin accessibility of enhancer regions of acinar cell–identifying transcription factors and limited their expression.[75] Second, the embryonic pancreatic epithelium–specific deletion of *Arid1a* with *Kras* mutation and *p53* heterozygous deletion formed IPMN and poorly differentiated adenocarcinomas with increased EMT gene expression and stem cell identity.[73] Third, the ductal cell–specific deletion of *Arid1a* with *Kras* mutation and *p53* heterozygous deletion resulted in occasional PDA formation with increasing MYC activity and protein synthesis.[74] This study also showed that the acinar cell–specific heterozygous deletion of *Arid1a* in the context of *Kras* mutation and *p53* heterozygous deletion accelerated PanIN and undifferentiated PDA formation. These results further confirmed the tumor-suppressive role of *Arid1a* in pancreatic tumorigenesis (Figure 4A).

5.3 | SMARCB1 as a gatekeeper of EMT

SMARCB1 is a common subunit of the SWI/SNF complex. *SMARCB1* is mutated in nearly all malignant rhabdoid tumors and is frequently deleted in pancreatic undifferentiated rhabdoid carcinoma, a subtype of pancreatic undifferentiated cancer.[76] In vivo functional analysis of Smarcb1 revealed their suggestive strong tumor-suppressive function. The deletion of *Smarcb1* in the embryonic pancreas epithelium in the oncogenic *Kras* with or without *a p53*-null background markedly accelerated tumorigenesis and increased metastatic spread and mesenchymal reprogramming.[47] In vivo deletion of *Smarcb1* in established tumors through a lentiviral-based somatic-mosaic system also resulted in rapid expansion of the aggressive mesenchymal population. Moreover, in vivo *Smarcb1* restoration in *Smarcb1*-deleted aggressive cancer resulted in mesenchymal-to-epithelial reversion and indolent tumor growth, and these effects of *Smarcb1* restoration were canceled by ectopic Myc activation (Figure 4B). These results highlight the role of Smarcb1 as a gatekeeper of EMT through Myc regulation. Furthermore, the loss of *Smarcb1* drives protein synthesis and adaptive activation of the ER stress–induced survival pathway, and inhibition of these pathways showed synthetic vulnerabilities in *Smarcb1*-deleted mesenchymal tumors. This study also showed that HSP90 inhibitor, as a protein synthesis inhibitor, is a potential therapeutic agent for the mesenchymal subpopulation of PDA.

6 | SWI/SNF COMPLEX AS A THERAPEUTIC TARGET FOR PDA

Currently, there are several studies targeting synthetic lethal molecules of the SWI/SNF complex in PDA. For targeting the residual SWI/SNF complex, ARID1B was proposed as a target for ARID1A-deficient PDA.[72] For targeting the downstream molecular mechanism, a recent study showed that SWI/SNF dysfunction sensitizes human pancreatic cancer cells to DNA-damaging agents and that PDA with SWI/SNF aberrations exhibits responsiveness to platinum-based treatment regimens.[77] Furthermore, protein synthesis and the ER stress pathway were proposed as the synthetic lethal targets for *SMARCB1*-deficient PDA as described above.[47] On the other hand, to target the oncogenic property of SWI/SNF components, knockdown of SMARCA4 in human pancreatic cancer cells reversed the gemcitabine resistance in part through inhibiting phosphorylation of Akt and p21.[78]

These studies suggest that the SWI/SNF complex could be targetable for PDA as well as other cancer types. However, further in vivo functional validation studies are warranted because most pieces of these evidence are cell line–based studies.

7 | CONCLUSION

Here, we summarize the current understanding of the functional roles of subunits of the SWI/SNF complex in PDA. Although they play critical roles in both the initiation and progression of PDA, their roles are highly context-dependent. The SWI/SNF subunits themselves and their downstream mechanisms are potential therapeutic targets for PDA. Further understanding of their precise roles is required for the future development of novel strategies targeting the SWI/SNF subunits against PDA.

ACKNOWLEDGMENTS

This work was supported in part by Grants-in-Aid KAKENHI (JP19H03639), a research program as part of the Project for Development of Innovative Research on Cancer Therapeutics (P-Direct) from the Ministry of Education, Culture, Sports, Science, and Technology and the Japan Society for the Promotion of Science. It was also supported by the Japan Agency for Medical

Research and Development, the Project for Cancer Research and Therapeutic Evolution (20cm0106177h0001), and AMED-PRIME (20gm6010022h0003). It was also supported by the Princess Takamatsu Cancer Research Fund (17-24924), the Mochida Foundation (2017bvAg), the Mitsubishi Foundation (201910037), the Uehara Foundation (201720143), and the Takeda Foundation (201749741).

DISCLOSURE

The authors declare no conflicts of interest.

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How to cite this article: Tsuda M, Fukuda A, Kawai M, Araki O, Seno H. The role of the SWI/SNF chromatin remodeling complex in pancreatic ductal adenocarcinoma. *Cancer Sci*. 2021;112:490–497. https://doi.org/10.1111/cas.14768