

## Review Article

## Oncogenic roles of SMARCB1/INI1 and its deficient tumors

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SMARCB1/INI1 is one of the core subunit proteins of the ATP-dependent SWI/SNF chromatin remodeling complex, and is identified as a potent and bona fide tumor suppressor. Interactions have been demonstrated between SMARCB1/INI1 and key proteins in various pathways related to tumor proliferation and progression: the p16-RB pathway, WNT signaling pathway, sonic hedgehog signaling pathway and Polycomb pathway. Initially, no detectable SMARCB1/INI1 protein expression was found in malignant rhabdoid tumor cells, whereas all other kinds of tumor cells and non-tumorous tissue showed SMARCB1/INI1 protein expression. Therefore, immunohistochemical testing for the SMARCB1/INI1 antibody has been considered useful in confirming the histologic diagnosis of malignant rhabdoid tumors. However, recently, aberrant expression of SMARCB1/INI1 has been found in various tumors such as epithelioid sarcomas, schwannomatosis, synovial sarcomas, and so on. In addition, it has been reported that aberrant expression can be classified into three patterns: complete loss, mosaic expression and reduced expression. Although the various pathways related to mechanisms of tumorigenesis and tumor proliferation are complexly intertwined, the clarification of these mechanisms may contribute to therapeutic strategies in SMARCB1/INI1-deficient tumors. In terms of pathological classifications, SMARCB1/INI1-deficient tumors may be re-classified by genetic backgrounds.

SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1), which is also named INI1 (integrase interactor 1), is one of the core subunit proteins in the SWI/SNF (SWItch/Sucrose Non-Fermentable) ATP-dependent chromatin remodeling complex encoded at chromosomal position 22q11.2.<sup>(1)</sup> SMARCB1 was first identified as a gene essential for glucose-repressible genes in *Saccharomyces cerevisiae*.<sup>(2)</sup> Characterization of the *SMARCB1/INI1* gene revealed that it encodes glutamine- and proline-rich domains characteristic of activation domains.<sup>(3)</sup> As for the protein, a yeast 2-hybrid screen designed to identify host proteins that could interact with HIV-1 integrase first, identified the human homologue of SNF5, which was then named SMARCB1,<sup>(4)</sup> and a human polypeptide corresponding in sequence to yeast SNF5 was isolated using a yeast 2-hybrid screen in WI38 human fibroblasts.<sup>(5)</sup>

SMARCB1/INI1 is ubiquitously expressed in the nuclei of all normal cells.<sup>(6)</sup> Disruption of SMARCB1/INI1 expression in mice results in early embryonic lethality: SMARCB1/INI1-null embryos die between 3.5 and 5.5 days post-coitum.<sup>(7)</sup> SMARCB1/INI1 heterozygous-deficient mice and those with conditional ablation of SMARCB1/INI1 develop aggressive cancer including rhabdoid-like tumors and T-cell lymphomas at a median onset of only 11 weeks.<sup>(8–10)</sup>

This embryonic lethality is rapid compared with other tumor suppressors. For example, p53 inactivation leads to

cancer at 20 weeks, p19Arf loss at 38 weeks, and p16Ink4a loss at 60 weeks. Thus, the rapid onset and complete penetrance of cancer following inactivation of SMARCB1/INI1 establishes this gene as a potent and bona fide tumor suppressor.<sup>(11,12)</sup>

## Function of SMARCB1/INI1

**Role of SMARCB1/INI1 in the p16-RB pathway.** The p16 tumor suppressor protein functions as an inhibitor of CDK4 and CDK6, the D-type cyclin-dependent kinases that initiate phosphorylation of the retinoblastoma tumor suppressor protein (Rb) and activate the E2F transcription factor.<sup>(13)</sup> Rb represses gene transcription, required for the transition from G0/G1 to S phase, by directly binding to the transactivation domain of E2F.<sup>(14)</sup> Thus, p16 has the capacity to arrest cells in the G1-phase of the cell cycle.<sup>(13)</sup>

Reintroduction of *SMARCB1/INI1* into malignant rhabdoid tumor cell lines having SMARCB1/INI1 deficiency induced the accumulation of cells in G0/G1, and, in some cases, cell senescence or apoptosis.<sup>(15,16)</sup> These findings resulted from G0/G1 cell cycle arrest associated with transcriptional repression of Cyclin D1, induction of P16, and hypophosphorylation of RB.<sup>(16,17)</sup> This repression of Cyclin D1 transcription was associated with direct recruitment of HDAC activity to the Cyclin D1 promoter.<sup>(16–18)</sup>

Previous studies have suggested that *SMARCB1/INI1* suppresses tumor progression by signaling through the p16INK4a and retinoblastoma tumor suppressors to negatively regulate cell cycle progression from G0/G1 to the S-phase.<sup>(19)</sup> It was recently reported that *SMARCB1/INI1* signals via the p16INK4a-Rb-E2F pathway regulate chromosomal stability, suggesting a new function in tumor suppression for this chromatin-remodeling protein.<sup>(20)</sup>

**Role of SMARCB1/INI1 in the canonical WNT pathway.** Traditionally, WNT signaling pathways have been characterized by two large categories: the canonical WNT (or  $\beta$ -catenin-dependent) and non-canonical WNT (or  $\beta$ -catenin-independent) pathways. Biologically, the canonical WNT signaling pathway usually plays important roles regulating cell fate, proliferation and survival, and its aberrant activation is found in several types of human cancer, whereas non-canonical WNT signaling is more associated with differentiation, cell polarity and migration.<sup>(21)</sup>

SMARCB1/INI1 deficiency in the developing limb mesenchyme leads to aberrant activation of the canonical WNT pathway and to phenotypic defects consistent with WNT/ $\beta$ -catenin overexpression.<sup>(22)</sup> In SMARCB1/INI1-deficient tumors, WNT targets are elevated compared with those in the normal cerebellum, and aberrant activation of  $\beta$ -catenin target genes occurs independently of canonical WNT pathway activation.<sup>(22)</sup> Thus, SMARCB1/INI1 deficiency causes aberrant activation of the WNT signaling pathway and results in phenotypic defects consistent with WNT/ $\beta$ -catenin overexpression.<sup>(22)</sup>

**Role of SMARCB1/INI1 in the sonic hedgehog signaling pathway.** The sonic hedgehog (Shh) signaling pathway is a major regulator of cell differentiation, cell proliferation, and tissue polarity.<sup>(23)</sup> Tumorigenesis, tumor progression and therapeutic response have all been shown to be impacted by the Shh signaling pathway.<sup>(23)</sup> Hedgehog signal transduction is initiated by the binding of Hh proteins to the Patched 1 protein (Ptc1). Ptc1 inhibits the activity of a smoothened (SMO) protein that activates factors downstream of the Hh signaling pathway when those ligands are not bound to Ptc1.<sup>(24,25)</sup> SMO stimulates a signaling cascade that results in the activation of the glioma-associated oncogene homolog (GLI) family of zinc finger transcription factors (GLI1, GLI2, and GLI3), when those ligands are bound to Ptc1.<sup>(24,25)</sup>

SMARCB1/INI1 was found to localize to the upstream regions of the transcription start sites of GLI1 and Ptc1. Sh-RNA-mediated knockdown of SMARCB1/INI1 leads to upregulation of the GLI1 and Ptc1 expressions, and to activation of the Shh signaling pathway.<sup>(26)</sup> Conversely, re-expression of SMARCB1/INI1 in malignant rhabdoid tumor cell lines represses GLI1 expression.<sup>(26)</sup> Clinical cases of primary SMARCB1/INI1-deficient tumors (malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor) showed enrichment of gene expression associated with Shh signaling pathway activation and GLI1 overexpression signatures which often possess activating mutations in the Shh signaling pathway.<sup>(26)</sup> Therefore, SMARCB1/INI1 is identified as one of the top regulators of GLI1, and is a key mediator of Shh signaling pathway.<sup>(26)</sup>

**Role of SMARCB1/INI1 in the Polycomb pathway.** Activations of Polycomb proteins contribute to epigenetically based gene silencing during the developmental processes of proliferation, and it has been suggested that these proteins may serve important roles during oncogenic transformation.<sup>(27)</sup> Polycomb proteins form two distinct multiprotein repressive complexes, PRC1 and PRC2. EZH2, which is the functional enzymatic component of PRC2, is highly expressed in various cancers,

and is often correlated with tumor progression and poor prognosis, although the mechanisms underlying the upregulation of EZH2 are poorly understood.<sup>(27)</sup> EZH2 plays an important role as the catalytic subunit in PRC2 and mediates gene silencing by catalyzing the trimethylation of histone 3 lysine 27 (H3K27me3) at the promoter regions of target genes.<sup>(27,28)</sup>

SMARCB1/INI1-deficient tumor samples also express higher levels of EZH2.<sup>(27)</sup> EZH2 transcription is directly repressed by SMARCB1/INI1 in mouse embryonic fibroblasts.<sup>(27)</sup> SMARCB1/INI1 deficiency leads to broad repression of lineage-specific Polycomb-regulated genes, and this repression is dependent on the presence of EZH2.<sup>(27)</sup> SMARCB1/INI1 deficiency causes elevated levels of H3K27me3 at lineage-specific Polycomb targets.<sup>(27)</sup> Thus, SMARCB1/INI1 deficiency mechanistically leads to elevated expression and recruitment of EZH2 to Polycomb targets, the trimethylation of histone 3 lysine 27, and the ultimate repression of Polycomb genes in SMARCB1-deficient fibroblasts and cancers.<sup>(27)</sup> In SMARCB1/INI1-deficient malignant rhabdoid tumors, inhibition of EZH2 functions as a SMARCB1/INI1 surrogate and derepresses neural differentiation genes, cell cycle inhibitors, and tumor suppressors while reducing GLI1, Patch1, MYC and EZH2.<sup>(29)</sup>

**Other targets of SMARCB1/INI1.** It has been reported that the other targets of SMARCB1/INI1 are c-MYC and Aurora A. C-MYC, which is a regulator gene that codes for a transcription factor, plays a role in cell cycle progression, apoptosis and cell transformation. C-MYC is known to be significantly upregulated in SMARCB1/INI1-deficient malignant rhabdoid tumors.<sup>(30)</sup> Recruitment of the SWI/SNF complex, mediated by the interaction of INI1 with c-MYC, facilitates the transcription of a discrete subset of c-MYC target genes, especially those involved in apoptosis, which might explain the tumor-suppressor activity of SMARCB1/INI1.<sup>(31,32)</sup>

Aurora A, which is a member of a family of mitotic serine/threonine kinases, is implicated with important processes during mitosis and meiosis, the proper functionings of which are critical for healthy cell proliferation. Aurora A is a direct downstream target of SMARCB1/INI1-mediated repression in malignant rhabdoid tumor cells, and the loss of SMARCB1/INI1, which is required for their survival, leads to aberrant overexpression of Aurora A in these tumors.<sup>(33)</sup>

## SMARCB1/INI1-deficient tumors

In 1990, monosomy 22 as the only cytogenetic abnormality was found in three cases of atypical teratoid/rhabdoid tumors.<sup>(34)</sup> In 1998, positional cloning and sequence analysis of malignant rhabdoid tumors eventually identified mutations, deletions and other somatic alterations in the *SMARCB1/INI1* gene.<sup>(35)</sup> After that, aberrant expression of the SMARCB1/INI1 protein has been reported to occur in various tumors.<sup>(36–39)</sup> At present, three patterns of aberrant SMARCB1/INI1 expression- complete loss, mosaic expression and reduced expression- have been identified (Table 1).

## Complete loss groups

**Malignant rhabdoid tumor.** Malignant rhabdoid tumors are classified as tumors of uncertain differentiation. Most such tumors present at birth or develop in infancy, and occur in the central nervous system, kidney and soft tissue.<sup>(40)</sup> Almost all malignant rhabdoid tumors show complete loss of SMARCB1/INI1 expression (Fig. 1a,b).<sup>(41–44)</sup> In a small minority of cases,

**Table 1. SMARCB1/INI1-deficient tumors**

Complete loss group
Malignant rhabdoid tumor (atypical teratoid/rhabdoid tumor)
Epithelioid sarcoma
Renal medullary carcinoma
Epithelioid malignant peripheral nerve sheath tumor
Myoepithelial tumor
Extraskeletal myxoid chondrosarcoma
Pediatric chordoma
Pancreas undifferentiated rhabdoid carcinoma
Sinonasal basaloid carcinoma
Rhabdoid carcinoma of the gastrointestinal tract
Mosaic expression group
Schwannomatosis
Gastrointestinal stromal tumor
Ossifying fibromyxoid tumor
Reduced expression group
Synovial sarcoma

although SMARCB1/INI1 expression is preserved, SMARCA4/BRG1 is completely lost.<sup>(45)</sup> SMARCB1/INI1 is inactivated homozygously in the majority cases of this kind of tumor by deletions and/or mutations.<sup>(41,46)</sup> However, about 20% cases with loss of SMARCB1/INI1 protein expression also showed no alteration at either the DNA or RNA level, and the mechanism of the inactivation of the *SMARCB1/INI1* gene product was not clarified.<sup>(41,46)</sup>

**Epithelioid sarcoma.** Epithelioid sarcoma is a rare soft tissue tumor displaying an uncertain line of differentiation. Two clinicopathologic subtypes are recognized: the conventional-type, characterized by its proclivity for distal extremities and a pseudo-granulomatous growth pattern; and proximal-type, which arises mainly in the proximal extremities or truncal regions, and consists of nests and sheets of large epithelioid cells.<sup>(47)</sup> Complete loss of SMARCB1/INI1 expression is found in 76–100% cases of proximal-type and 81–93% cases of conventional-type epithelioid sarcoma.<sup>(48–52)</sup> The ratio of gene alteration at either the DNA or RNA level causing SMARCB1/INI1 protein inactivation varies widely between 0% and 58% in conventional-type or between 19% and 100% in proximal-type cases.<sup>(48,52–54)</sup> In addition, it is suggested that microRNAs such as miR193a-5p, miR-206, miR-381 and miR-671-5p may have the potential to inhibit SMARCB1 mRNA in epithelioid sarcoma.<sup>(55–57)</sup>

**Pancreatic undifferentiated rhabdoid carcinoma.** Undifferentiated carcinoma of the pancreas that are predominantly (>50%) composed of rhabdoid cells is very rare with only approximately 60 cases reported previously in the medical literature.<sup>(58)</sup> Agaimy *et al.*<sup>(58)</sup> reported that 4 of the 14 this carcinoma shows the complete loss of SMARCB1/INI1 immunorexpression, and these all four cases are monomorphic anaplastic histology, whereas the remaining 10 cases are pleomorphic giant cell histology. In SMARCB1/INI1 deficient cases, three of the four cases lacked *KRAS* alterations (mutations and/or amplifications).<sup>(58)</sup>

### SMARCB1/INI1-deficient carcinoma of the sinonasal or gastrointestinal tract

SMARCB1/INI1-deficiency has been also found in extremely small numbers of carcinoma of the sinonasal or gastrointestinal tract.<sup>(59–61)</sup> Agaimy *et al.*<sup>(59–61)</sup> reported three cases of sinonasal SMARCB1/INI1-deficient basal cell carcinoma and five cases of SMARCB1/INI1-negative rhabdoid carcinoma of the gastrointestinal tract.

Age/sex of these sinonasal basal cell carcinomas were as follows: 35 years old (years)/female; 52 years/male; 28 years/female.<sup>(59)</sup> Histological features showed a few scattered rhabdoid cells, basaloid “blue” appearance, papilloma-like exophytic component, extensive pagetoid surface growth with prominent denuding features, and replacement of underlying mucous glands mimicking an inverted papilloma.<sup>(59)</sup> High-risk human papilloma virus infection was negative in all cases.<sup>(59)</sup>

Age/sex/primary site of these rhabdoid carcinomas of gastrointestinal tract were as follows: 32 years old (years)/male/large intestine; 54 years/male/esophago-gastric junction; 58 years/male/antrum; 79 years/male/cecum; 66 years/male/stomach body.<sup>(61)</sup> Histological features showed rhabdoid cells and anaplastic large ones.<sup>(61)</sup> Spindle-shaped sarcomatoid cells or medullary structures were also found in each of one case.<sup>(61)</sup>

**Other tumors.** Complete loss of SMARCB1/INI1 protein expression has been reported to occur in all renal medullary carcinomas, about half of epithelioid malignant peripheral nerve sheath tumors, some myoepithelial tumor and some extraskeletal myxoid chondrosarcomas.<sup>(6,62–65)</sup> Recently, pediatric chordoma with SMARCB1/INI1-deficiency cases have also been reported.<sup>(66)</sup> These tumors are known to have rhabdoid cells, which are characterized by the existence of a large eosinophilic inclusion within the cytoplasm, eccentric nuclei and prominent nucleoli.

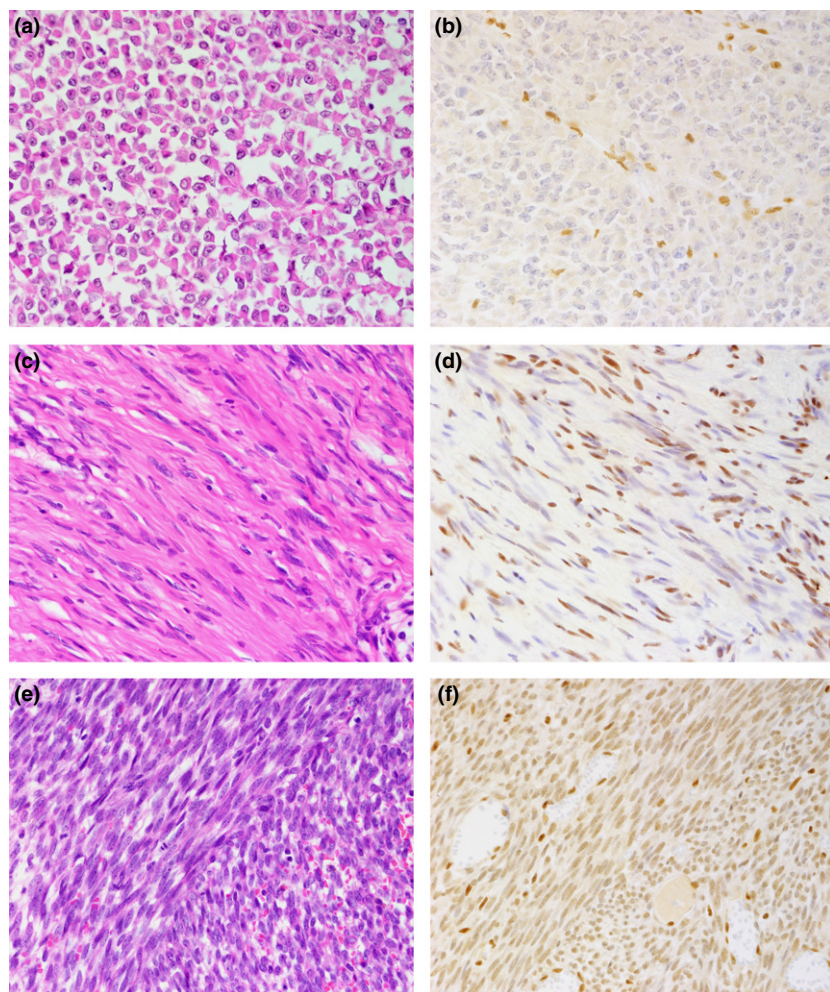
### Mosaic groups

**Schwannomatosis.** Schwannoma is benign peripheral nerve sheath neoplasms composed exclusively of Schwann cells.<sup>(67)</sup> Schwannomatosis, which is a familial or sporadic syndrome, is classified into two major categories according to the absence of vestibular schwannomas and neurofibromatosis type 2 (NF2) pathology.<sup>(68)</sup> Most cases of familial schwannomatosis (14/15; 93%) and NF2-associated schwannomas (10/12; 83%), and some cases of sporadic schwannomatosis (10/18; 55%) show mosaic patterns of SMARCB1/INI1 protein expression (Fig. 1c,d).<sup>(69)</sup> Genetically, most schwannomatosis patients show missense or splice-site mutations of SMARCB1/INI1 genes at germline.<sup>(70,71)</sup> These mutations cause the replacement of an important amino-acid residue or the in-frame deletion or insertion of amino-acid residues, resulting in the synthesis of a SMARCB1/INI1 protein with altered activity.<sup>(70)</sup>

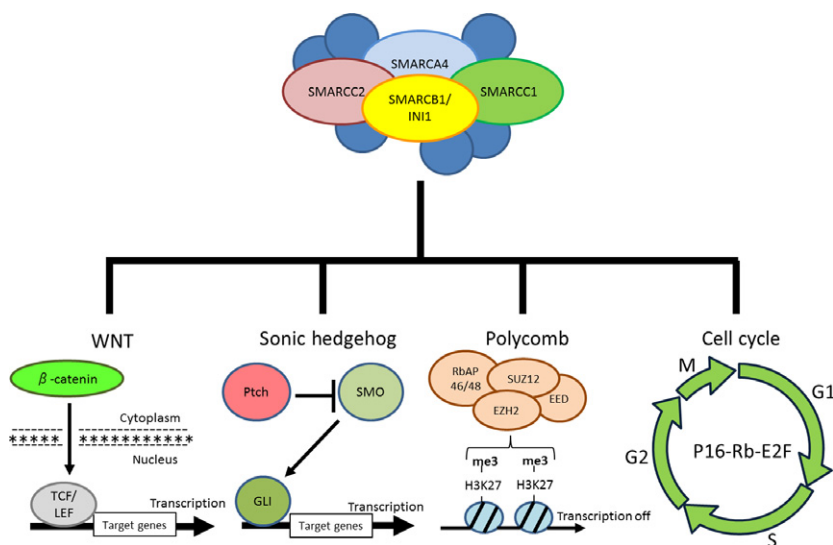
**Gastrointestinal stromal tumor.** Gastrointestinal stromal tumor (GIST), which is the specific KIT-positive mesenchymal tumor of the gastrointestinal tract, demonstrates a gain-of-function mutation of the KIT gene or the PDGFRA gene.<sup>(72,73)</sup> About half of GIST cases (17/27; 63%) show mosaic patterns of SMARCB1/INI1 protein expression.<sup>(74)</sup> Genetically, among the 27 informative cases, 19 (70%) showed LOH of at least one of the microsatellite markers on 22q11.23 including the SMARCB1/INI1 gene.<sup>(74)</sup> In another study, four of the seven metastatic GIST cases harbored a heterozygous deletion of part or the entire arm of chromosome 22, on which SMARCB1 is located.<sup>(75)</sup>

**Ossifying fibromyxoid tumor.** Ossifying fibromyxoid tumors, characterized by a lobular proliferation of small bland round cells with a peripheral shell of woven bone, are classified as tumors of uncertain differentiation.<sup>(76,77)</sup> Immunohistochemically, the mosaic pattern of SMARCB1/INI1 was noted in 14 of 19 (74%) cases.<sup>(78)</sup> Genetically, although epigenetic events such as posttranslational modifications or small deletions or mutations are not detectable by FISH, five of seven cases showed an aberrant signal in the SMARCB1/INI1 gene by FISH. Five cases showed a hemizygous deletion of both





**Fig. 1.** Hematoxylin–eosin histologic (a, c, e) and SMARCB1/INI1 (b, d, f) immunohistochemical findings. (a, b) Malignant rhabdoid tumor (2-year-old male; kidney). No nuclear expression of SMARCB1/INI1 protein is observed in tumor cells, whereas infiltrating lymphocytes or vascular endothelial cells disclose immunoreactivity (b). (c, d) Schwannomatosis (48-year-old woman; cauda equina). SMARCB1/INI1 protein expression is focally reduced with a mixture of nuclear-positive and nuclear-negative tumor cells, showing mosaic pattern (d). (e, f) Synovial sarcoma (22-year-old woman; abdominal wall). The tumor cells showed reduced expression of SMARCB1/INI1 protein compared with the positive control, which included infiltrating lymphocytes and entrapped normal tissue (f).



**Fig. 2.** Target genes and pathways implicated in the tumor suppressor activity of SMARCB1/INI1.

SMARCB1/INI1 and PANX2 (the control probe) in >50% of cells, and three of those five had a second population of cells showing two signals for SMARCB1/INI1 and one signal for the control, suggesting loss of one copy of the 22q telomeric region.<sup>(78)</sup> No cases with homozygous deletion of the SMARCB1/INI1 gene were found.<sup>(78)</sup>

### Reduced group

**Synovial sarcoma.** Synovial sarcoma, which is classified as a tumor of uncertain differentiation, has three major histological subtypes: the monophasic type, biphasic type and poorly differentiated type.<sup>(79)</sup> Genetically, a fusion of the SS18 gene to

an SSX family member as the result of a chromosomal translocation, t(X;18), is recognized.<sup>(79–81)</sup> Kohashi *et al.*<sup>(81)</sup> first identified reduced SMARCB1/INI1 immuno-expression in the majority of cases of synovial sarcoma (Fig. 1e,f). Kadoch *et al.*<sup>(82)</sup> clarified the mechanism of reduced expression of the SMARCB1 protein: SS18-SSX integrates into SWI/SNF complex, and wild-type SS18 and SMARCB1 are displaced from the complex; then SMARCB1 is proteosomally degraded.

## Conclusion

SMARCB1/INI1 plays an important role in various interwoven factors in several pathways (Fig. 2), and different cancers show different aberrant expression patterns of its protein. Although the several pathways related to mechanisms of tumorigenesis and tumor proliferation are intertwined in

complex ways, the clarification of these mechanisms may contribute to therapeutic strategies in SMARCB1/INI1-deficient tumors. In terms of pathological classification, SMARCB1/INI1-deficient tumors may be re-classified by their genetic backgrounds.

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## Disclosure Statement

The authors have no conflict of interest to declare.

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