



## Mini Review

## Targeting SMARCAL1 as a novel strategy for cancer therapy

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## ABSTRACT

SMARCAL1 is a SNF2 chromatin-remodeling protein with ATP-dependent annealing helicase activity. Recent studies have shown that SMARCAL1 is involved in DNA damage repair and cell cycle progression. Deficiency of SMARCAL1 enhances the anticancer activity of chemotherapy agents and reverses cancer cell resistance to these agents. Therefore, targeting SMARCAL1 is an attractive therapeutic approach for cancers with defects in DNA damage repair or cell cycle checkpoints. Here, we review advances in our understanding of the biochemical and cellular functions of SMARCAL1 made over the recent years and discuss the rationale for development of SMARCAL1 inhibitors as novel anticancer therapies.

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## 1. Introduction

Defects in the pathways of DNA damage repair may result in persistent genetic lesions that can lead to carcinogenesis. On the other hand, the mechanism by which chemotherapy and radiotherapy induce cancer cell apoptosis and thus cell death begins with DNA damage. Cancer cells are more sensitive to DNA-damaging agents than normal cells because of their intrinsic deficiencies in DNA damage repair. However, cancer cells have alternative pathways of DNA damage repair that can be activated by DNA-damaging chemotherapy drugs; as these repair progresses, the cells develop resistance to these drugs. Therefore, inhibiting DNA damage repair molecules could result in cell death by reversing the cells' resistance to cancer-killing drugs, an example of synthetic lethality. Dozens of DNA damage repair inhibitors have already been tested in clinical trials. Here, we summarize the functions of SMARCAL1 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1), an ATP-driven annealing helicase member of the SNF2 family, in DNA damage repair and cell cycle progression and discuss the rationale for targeting SMARCAL1 as a strategy for cancer therapy.

**Abbreviations:** ATM, ataxia telangiectasia-mutated; ATR, Rad3 related kinase; ATRIP, ATR interacting protein; chk2, checkpoint kinase 2; DSB, dsDNA break; HARP, HepA-related protein; RPA, replication protein A; SIOD, Schimke immuno-osseous dysplasia; SMARCAL1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily a-like 1; ssDNA, single-stranded DNA.

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## 2. The SMARCAL1 gene

Structurally, SMARCAL1, also known as HepA-related protein (HARP), is highly similar to the *Escherichia coli* RNA polymerase binding protein HepA [1–3]. It is a SNF2 family member of ATP-dependent chromatin-remodeling enzymes. The SNF2 molecules act in gene transcription, DNA damage repair, DNA recombination, DNA methylation, and cell cycle regulation. SMARCAL1 contains a region of 28 amino acids at the N terminus; two tandem HARP domains, both of which contain ~60 residues (residues 239–307 and residues 331–400); and a SWI/SNF helicase domain [4]. SWI/SNF proteins belong to the SNF2 subfamily whose members contain seven characterized motifs (I, Ia, II, III, IV, V, and VI) [2]. SMARCAL1 contains the conserved helicase motifs that are highly similar to those of other SNF2 family members but lacks the motif III to motif IV regions [3]. The tandem HARP domains are crucial for its annealing helicase activity [5].

The SMARCAL1 gene is ubiquitously expressed in various human and mouse tissues. Mutations in SMARCAL1 cause an autosomal recessive genetic disease, Schimke immuno-osseous dysplasia (SIOD), which is characterized by T-cell immunodeficiency and growth retardation due to skeletal dysplasia [6]. Patients with SIOD show defects in T-cell proliferation in response to mitogens such as interleukin-2, phytohemagglutinin, and concanavalin A. SIOD-associated anemia does not respond to erythropoietin, and SIOD-associated bone marrow failure does not respond to stem cell factors. The growth retardation does not improve with growth hormone supplementation. Those findings imply that SMARCAL1 is a crucial regulator of cell proliferation, cell differentiation, cell survival, or cell cycle regulation.

Unlike other members of the SNF2 family such as Rad54, ACF, and Brg1, which have DNA-unwinding activities, SMARCAL1

catalyzes the rewinding of single-stranded DNA (ssDNA) bubbles coated with replication protein A (RPA) [7]. The ATPase activity of SMARCAL1 is activated by the unique DNA structures of double-stranded DNA (dsDNA)–ssDNA junctions [8,9], including model replication forks [7]. The biological importance of SMARCAL1 in humans is revealed by its role in SIOD.

### 3. SNF2 ATP-dependent chromatin-remodeling complexes and cancer

The SNF2 complexes are present in all eukaryotes and are highly evolutionarily conserved. The purified yeast SWI/SNF complex, which has ATP-dependent activity, is a multimeric chromatin-remodeling complex important for gene regulation [7]. Among the subunits of the ATP-dependent chromatin-remodeling complexes, SWI/SNF-related ATPase provides its N- and C-terminal domains to interact with other proteins in the complex [10]. The ATPase derives specificity for chromatin domains through these interactions. Using the energy of ATP hydrolysis, the SWI/SNF ATPase alters the structure of DNA nucleosomes to remodel chromatin and open the DNA, and then it advances gene transcription and aids in DNA recombination, replication, and repair. It also regulates transcription of a series of interrelated genes involved in cell proliferation and differentiation [11].

Loss of the ATPase-dependent chromatin-remodeling complexes correlates with tumorigenesis. BRM (Brahma) and BRG1 (BRM-related gene 1) are two SWI/SNF ATPase-dependent chromatin-remodeling molecules. Four of 12 (33%) human non-small-cell lung cancer cell lines were found to have concomitant downregulation of BRG1 and BRM. Loss of both BRG1 and BRM, which depresses SWI/SNF complex activity, is more common than loss of either alone [12]. SMARCB1 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1) is a core member of the SWI/SNF chromatin-remodeling complex. SMARCB1-knockout mice are prone to cancer, with a median onset of 11 weeks. The tumors are closely similar to human rhabdoid tumors with classic rhabdoid morphology [13].

The ATPase activity of the SWI/SNF members is stimulated by dsDNA breaks. Loss of this activity results in defects in DNA damage repair. In contrast, the ATPase activity of SMARCAL1 is activated by stem loop and forked DNA structures, more by ssDNA to dsDNA transitions with a recessed 3'-hydroxyl group than by ssDNA or dsDNA breaks *in vitro* [7].

### 4. SMARCAL1 in DNA damage repair and replication

Most SNF2 family members contain DEAD-box helicase-like domains that are activated in response to DNA damage and are involved in the progression of DNA repair and replication. For example, INO80 shows genetic interactions with the DNA repair pathway for dsDNA break (DSB) repair in yeast [14]. It is involved in replication forks for proper restart of DNA replication and repair of DSBs [15–17].

In an assay of microirradiated human cell lines A172, HeLa, IMR90, and MCF7, SMARCAL1 localizes to the sites of laser-induced DNA damage, implying that SMARCAL1 acts in DSB repair. And SMARCAL1 is recruited to DNA damage sites after Mre11 (meiotic recombination 11) [18], an initial component of homologous recombination (HR) and a key early response protein for processing the DNA ends of broken chromosomes for repair [19].

In cells treated with a DNA-damaging agent or replication inhibitor, SMARCAL1 co-localizes with  $\gamma$ -H2AX, a marker of DSB, suggesting that SMARCAL1 could be recruited into sites of DNA damage [20]. SMARCAL1 is recruited to the damage foci in cells treated with hydroxyurea, which inhibits DNA synthesis and

DNA repair in damaged cells [20,21]. SMARCAL1 also is recruited to the foci generated in cells treated with camptothecin, a topoisomerase I inhibitor that interferes with DNA damage repair and replication. Postow et al. found that SMARCAL1 is phosphorylated in a caffeine-sensitive manner that is involved in stabilizing the stalled forks. Loss of SMARCAL1 enhances RAD51 association with the stalled replication forks [22].

In SMARCAL1-deleted cells,  $\gamma$ -H2AX foci accumulate and both ataxia telangiectasia-mutated (ATM) and checkpoint kinase 2 (chk2) are activated. Levels of RPA-bound ssDNA are higher during S phase than in wild-type cells [21,23]. Bétous et al. verified recently that absence of SMARCAL1 leads to MUS8-dependent DSB formation and activation of an alternate repair mechanism [24]. These findings suggest that deficiency of SMARCAL1 increases DSBs and thus that SMARCAL1 is involved in the processes of DNA damage repair and replication [25].

Ciccia et al. found that SMARCAL1-depleted cells exhibit a delay in bromodeoxyuridine incorporation after treatment with the replication inhibitor thymidine [20]. Using SMARCAL1-deficient cells, several groups confirmed that SMARCAL1 is required for resistance to DNA-damaging agents such as camptothecin, mitomycin C, aphidicolin, and hydroxyurea, indicating a possible cell cycle-specific role for SMARCAL1 [4,20,21]. Re-introduction of wild-type SMARCAL1 to fibroblasts from patients with SIOD could rescue the elevated levels of DNA damage and increase resistance to DNA-damaging agents [26].

RPA binds to ssDNA, which recruits ATM, Rad3 related kinase (ATR), and the ATR interacting protein (ATRIP) and activates ATR to start the DNA damage checkpoint and repair processes [27,28]. Thus RPA is involved in DNA replication and DNA damage repair. Several groups have found that SMARCAL1 interacts with RPA2 [20]. Yuan et al. confirmed that SMARCAL1 interacts strongly with RPA1 [4]. These findings indicate that SMARCAL1 may combine more than one site with RPA complex. Instead of converting dsDNA into RPA-bound unwound DNA, SMARCAL1 functionally binds to forked DNA *in vitro* and rewinds the regions of RPA-bound ssDNA in a plasmid context [7]. The interaction between SMARCAL1 and the RPA complex suggests that SMARCAL1 functions during these processes or plays an important role in both DNA replication and repair (Fig. 1A).

### 5. SMARCAL1 and the cell cycle

Several lines of evidence suggest that SMARCAL1 is involved in regulation of the cell cycle. E2Fs are important transcription factors regulating the cell cycle through activation or suppression of their target genes, such as cyclins and cyclin-dependent kinases. We verified that E2F6 could bind to the human SMARCAL1 gene promoter and inhibit its expression in 293T cells.

Ciccia et al. and Bansbach et al. showed that SMARCAL1 recruitment to the sites of ionizing radiation- or laser-induced DNA damage occurs only in S/G<sub>2</sub>-phase cells, indicating that SMARCAL1 may be recruited to sites of damage only in the S and G<sub>2</sub> phases of the cell cycle [20,21]. This is consistent with the presumption that SMARCAL1 recognizes ssDNA generated during resection, a process that is restricted to S and G<sub>2</sub> [29]. Localization of SMARCAL1 to the sites of DNA damage required C-terminal binding protein-interacting protein (CtIP), which promotes DNA resection to generate ssDNA ends for HR repair of DSB only during the S and G<sub>2</sub> phases of the cell cycle [20,29,30]. This indicates that SMARCAL1 recognizes ssDNA generated by damaged cells during the S/G<sub>2</sub> phases and may play a role in HR DNA repair.

SMARCAL1-depleted cells show a defect in progress from S phase into mitosis. The arrest between S-phase and mitosis occurred in 75% fewer nocodazole-treated cells than control cells.

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