

# Role of chromatin remodeling protein, ARID1A and emerging therapies in ARID1A mutated ovarian and endometrial cancer

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## ABSTRACT

Genes encoding subunits forming SWI/SNF chromatin remodeling complex have been found to inhibit malignant transformation and progression. ARID1A is one such subunit and inactivating mutations in *ARID1A* gene encoding ARID1A are found in a wide spectrum of cancer and most frequently in gynecologic cancer as in ovarian clear cell adenocarcinoma, ovarian endometrioid adenocarcinoma, and uterine endometrioid adenocarcinoma. Many reports suggest that ARID1A play a tumor suppressive role in these cancers. This review focuses on tumor suppressive role of ARID1A, its synthetic lethal partners and emerging therapies in ARID1A mutated ovarian and endometrial carcinoma.

**KEYWORDS:** ARID1A, ovarian cancer, endometrial cancer, SWI/SNF chromatin remodeling complex.

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## INTRODUCTION

The SWI/SNF complexes are evolutionary conserved, composed of many subunits and play a critical role in modulating gene expression by mobilizing nucleosomes in an ATP dependent manner (Alver et al., 2017). The SWI/SNF family of chromatin remodeling complexes was initially discovered in yeast by experiments conducted to identify mutations in genes that affect the mating-type switching (SWI) and sucrose fermentation (Sucrose Non-Fermenting - SNF) pathways (Workman and Kingston, 1998; Sudarsanam and Winston, 2000). A genetic screening in yeast suggests that the proteins of the complex are involved in histone binding and chromatin organization (Winston and Carlson, 1992). In yeast, two distinct remodeling complexes are present, SWI/SNF and a closely related complex, RSC (Cairns et al., 1994). In *Drosophila* and human, two complexes exist which are homologous to SWI/SNF and RSC, respectively. In *Drosophila* the two complexes are called BAP (Brahma Associated Protein) and PBAP (Polybromo-associated BAP) complexes, and in human, these two complexes are called BAF (Brg1 Associated Factors) and PBAF (Polybromo-associated BAF) (Tang et al., 2010). BAF complex can contain one of the two distinct catalytic subunits hBRM (human Brahma) or BRG1 (Brahma-related Gene 1) while PBAF contains only BRG1 (Tang et al., 2010). There are several core subunits that are associated with both the complexes: SMARCB1 (BAF47/SNF5), SMARCC1 (BAF155), SMARCC2 (BAF170), SMARCE1 (BAF57), SMARCD1 (BAF60A), SMARCD2 (BAF60B), or SMARCD3 (BAF60C), [PHF10 (BAF45A), DPF1 (BAF45B), or DPF2 (BAF45D); DPF3 (BAF45C); and ACTL6A (BAF53A) or ACTL6B (BAF53B) (Shain and Pollack, 2013). SWI/SNF complex had diverse roles and involved in different biological processes such as cell proliferation, cell migration, embryonic development, tissue regeneration, cell senescence, apoptosis and oncogenesis (Hargreaves and Crabtree, 2011; Wu JI, 2012). Early studies found a loss of critical subunits of SWI/SNF complexes in

cancer cell lines predicting that these complexes may be tumor suppressors. Moreover, they were found to bind the RB protein, and repressed E2F function (Dunaif et al., 1994; Trouche et al., 1997) and hence may lead to uncontrolled cell proliferation. Biallelic inactivation of BAF47 was found in 100% in a malignant rhabdoid tumor (MRT), a rare childhood cancer (Versteeg et al., 1998). Loss of BRG1 and BRM was found in several human tumor cell lines and primary tumor of lung, breast, and prostate (Weissman and Knudsen, 2009). The cancers with the highest SWI/SNF mutation rates were ovarian clear cell carcinoma (75%), clear cell renal cell carcinoma (57%), hepatocellular carcinoma (40%), gastric cancer (36%), melanoma (34%), and pancreatic cancer (26%) (Shain and Pollack, 2013). Across all tumor types, the average frequency of SWI/SNF mutations (19%) approached that of *TP53* (26%), the single-most mutated tumor suppressor gene. With the advent of exome sequencing, it appears that genes encoding subunits of SWI/SNF (BAF) chromatin remodeling complexes are collectively altered in over 20% of human malignancies, across a broad range of tumor types (Helming et al., 2014). Unlike in MRTs, in most of the cancers, only one allele of the BAF subunit has been mutated, and hence it act as dominant tumor suppressors (Kadoch and Crabtree, 2015) in MRTs. Various mechanism of tumor suppression of BAF complex have been suggested and are related to BAF-polycomb antagonism, a synergy between TopoII and BAF complexes and paralogous subunit compensation as unique synthetic lethalties (Kadoch and Crabtree, 2015).

The ARID1A protein is the largest subunit of the SWI/SNF chromatin remodeling complex. ARID1A belongs to human ARID family which is a superfamily of 15 members and contains seven subfamilies (ARID1, ARID2, ARID3, ARID4, ARID5, JARID1, JARID2). ARID1A and ARID1B belong to ARID1 subfamily. ARID1B and ARID2 are two mammalian homologs of ARID1A (Patsialou et al., 2005). ARID1A and ARID1B are associated with the

BAF complex while ARID2 with the PBAF complex (Wang et al., 1996). They are named as “ARID” as they were initially found to interact with AT-rich DNA elements. However, subsequent studies suggest that AT-rich binding is not an intrinsic property of ARID and these proteins might be involved in a wider range of DNA interactions (Patsialou et al., 2005). The main function of ARID is that they are transcription regulators and hence play a role in cell proliferation, differentiation, and development (Lin et al., 2014). Recent exome studies suggest that members of ARID family play an important role in cancer such as gastric cancer, breast cancer, ovarian cancer, lung cancer, oral cancer, malignant melanoma and many others. They are either tumor suppressor or oncogene or play a dual role as both tumor suppressor and oncogene as demonstrated in some cancers (Lin et al., 2014). *ARID1A* has highest mutation rate in human cancers and frequently mutated in gynecologic cancer, as in ovarian clear cell adenocarcinoma (46–57%), ovarian endometrioid adenocarcinoma (30%) and in uterine endometrioid adenocarcinoma (40%) (Takeda et al., 2016). In a study carried out by Yamamoto et al., loss of ARID1A was found in 61% of endometriosis-associated carcinoma compared to 43% of adenofibromatous ovarian clear cell carcinomas (Yamamoto et al., 2012). In another study, loss of ARID1A expression was observed in 13 (22%) of 59 endometrioid cancers, 17 (47%) of 36 clear cell cases, 8 (44%) of 18 contiguous endometriosis cases, and 3 (8%) of 66 benign endometriotic ovarian cysts (Chene et al., 2015). The majority of *ARID1A* mutations are inactivating or loss of function mutations (frameshift or nonsense) in these cancers, suggesting that ARID1A plays a role of tumor suppressor in these cancers. Although ARID1A mutations seem to predominate in endometrium-related carcinomas, inactivation of the ARID1A is common in the development of other human carcinomas as well such as cancers arising from kidney, breast, lung, and stomach (Wang et al., 2004; Huang et al., 2007). ARID1A suppresses hepatocellular

carcinoma cell proliferation and migration by upregulating its downstream target CDKN1A through inhibiting lncRNA MVIH suggesting that loss of function of ARID1A in hepatocellular carcinoma cells might lead to the increased activity of lncRNAs and promote cancer (Cheng et al., 2017). *ARID1A* is the third most significantly mutated gene in human colorectal cancer, with MSI type having highest frequency (~39%) (Cajuso et al., 2014; Cancer Genome Atlas Network, 2012). *Arid1a* functions as a tumor suppressor in the mouse colon. Loss of *Arid1a* impairs enhancer-mediated gene regulation, and drives tumorigenesis in colon of mice (Mathur et al., 2017). A recent report suggests that in lung cancer, ARID1A has context-dependent oncogenic and tumour suppressor role (Sun et al., 2017). Mice with liver-specific homozygous or heterozygous *Arid1a* loss were resistant to tumor initiation as loss of *Arid1a* within tumors decreased chromatin accessibility and reduced transcription of genes associated with migration, invasion, and metastasis. However, the gain of function of *Arid1a* has been shown to promote cancer initiation (Sun et al., 2017).

ARID1A and ARID1B share 66% overall similarity (Wang et al., 2004). They are often co-expressed and are mutually exclusive subunits of BAF complex. Though structurally similar, ARID1A and ARID1B play opposite roles (Nagl et al., 2007). In fact, ARID1A and ARID1B show different cell cycle kinetics. ARID1A accumulates in G0 and is down-regulated throughout the cell cycle phases and is eliminated during mitosis, whereas ARID1B is expressed at all phases including mitotic phase (Flores-Alcantar et al., 2011). ARID1A-deficient cells require ARID1B for functional SWI/SNF complex assembly and hence implicate ARID1B as a potential therapeutic target in cancers with recurrent *ARID1A* mutations (Helming et al., 2014). Loss of ARID1A in wild-type HCT116 cells results in dramatic changes in chromatin accessibility, while ARID1B knockdown does not affect. In contrast, ARID1B knockdown in ARID1A mutant cells results

in further up or down-regulation of accessibility at ARID1A-dependent and unique sites (Kelso et al., 2017). Regions sensitive to ARID1A or ARID1B loss are predominantly found at enhancers and distal regulatory sites, where ARID1A and ARID1B are required for the maintenance of active enhancer histone marks (Kelso et al., 2017). ARID1A and ARID1B are found to be altered concurrently in various cancers. Integrated genomic analyses revealed *ARID1A* and *ARID1B* alterations in the childhood cancer neuroblastoma (Sausen et al., 2013). Loss of ARID1A, ARID1B, and ARID2 Expression leads to gastric cancer progression (Aso et al., 2015). Concurrent ARID1A and ARID1B inactivation were also found in endometrial and ovarian dedifferentiated carcinomas (Coatham et al., 2016). Inactivating mutations in ARID2 have also been found in wide variety of cancers including non-small-cell lung cancer (Manceau et al., 2013), hepatocellular carcinoma (HCC) (Fujimoto et al., 2012, Li et al., 2011) gastric adenomas (Lim et al., 2016), melanoma (Hodis et al., 2012) and oral squamous cell carcinoma (India Project Team of the International Cancer Genome Consortium, 2013). Exome sequencing reveals frequent inactivating mutations in ARID1A, ARID1B, ARID2 and ARID4A in microsatellite unstable colorectal cancer (Cajuso et al., 2014) In hepatocellular carcinoma, ARID2 targets cyclin D1 and cyclin E1 to suppress hepatoma cell progression (Duan et al., 2016). Targeted next-generation sequencing aimed for molecular diagnosis of endometriosis-associated ovarian cancer identified *PIK3CA* and *ARID1A* as most frequently mutated genes and *ARID2* in the category of next recurrently mutated genes (ER TK et al., 2016). ARID1A, ARID1B, and ARID2 have a highly overlapping role in transcriptional regulation as demonstrated in human liver carcinoma (HepG2) cells (Raab et al., 2015). Using RNAi approach against combinations of ARIDs, it was revealed that ARID1A and ARID2 have frequent competitive interactions, while ARID1B and ARID2 are both required for repression and are not redundant (Raab et al., 2015). Recent

exome sequencing study in population-based samples of small bowel adenocarcinoma revealed ARID2 and BRG1 mutations (Hanninen et al., 2018).

In this review, we focused on the role of ARID1A as the tumour suppressor in ovarian and endometrial cancer. We also discuss synthetic lethal pathways/subunit in ARID1A-mutant ovarian cancers as well as current and future therapeutic strategies in ARID1A-mutant cancers particularly in ovarian/endometrial cancer.

**ARID1A as tumor suppressor in ovarian/endometrial cancer:** Functional analysis shows that ARID1A is a bonafide tumor suppressor in ovarian/endometrial cancer (Wu et al., 2014). Restoration of wild-type *ARID1A* expression in ARID1A mutant ovarian cancer cells is sufficient to suppress cell proliferation, and tumor growth in mice whereas silencing of ARID1A in non-transformed epithelial cells increases cellular proliferation and tumorigenesis (Guan et al., 2011). ARID1A induces cell cycle arrest at the G1 checkpoint. Well-known p53 target genes such as *CDKN1A* and *SMAD3* are also downstream target genes of ARID1A and ARID1A collaborate with p53 to regulate *CDKN1A* and *SMAD3* transcription and tumor growth in ovarian cancer cells. Moreover, p53 is required for ARID1A-induced p21 expression. This evidence suggests that ARID1A-containing SWI/SNF complexes required interaction with p53, leading to induction of p21 leading to cell cycle arrest (Guan et al., 2011). ARID1A also act as tumor suppressor by maintaining genomic instability as it facilitates DNA damage repair and mismatch repair. Topoisomerase II $\alpha$  (TOP2A), which decatenates newly, replicated sister chromatids interact with ARID1A and bind to chromatin, utilizing ATPase activity of SWI/SNF complexes to ensure proper chromosome segregation during mitosis. This suggests that the ability of TOP2A to prevent DNA entanglement at mitosis requires SWI/SNF complex and suggests that this activity contributes to the role of SWI/SNF subunits including ARID1A

as tumor suppressors (Dykhuizen et al., 2013). Furthermore, deficiencies in SWI/SNF and MMR proteins may synergistically deregulate DNA repair mechanisms and leads to tumorigenesis. Defects in mismatch repair (MMR) are prevalent in endometrial cancers, and it has been observed that loss of expression of ARID1A is associated with loss of expression of mismatch repair proteins and/or microsatellite instability in uterine endometrioid carcinoma (Allo et al., 2014; Bosse et al., 2013). In fact, in high-grade endometrial carcinoma, ARID1A loss accompany with mismatch repair loss and a normal p53 expression suggesting that ARID1A loss may drive tumorigenesis by an alternative oncogenic pathway to p53 alteration (Allo et al., 2014). Surprisingly, ARID1A loss is found to be more prevalent in uterine endometrioid carcinomas with sporadic Microsatellite instability (75%) as compared to uterine endometrioid carcinomas from patients with Lynch syndrome (14%) which is a germ line defect of MMR genes (Bosse et al., 2013). In 22 samples of undifferentiated endometrial carcinoma (UEC), abnormal SWI/SNF subunit expression was detected in four dedifferentiated endometrial carcinomas including three with loss of BRG1 limited to the undifferentiated endometrial tumor and one case with the loss of (SMARCB1) and ARID1A expression both. Among these 22 UEC, 13 tumors showed abnormal MMR protein expression including nine with concurrent loss of MMR genes, MLH1 and PMS2. This suggests that SWI/SNF subunit alterations may play a role in the progression and dedifferentiation of endometrial carcinoma, and deficiency of SWI/SNF and MMR protein may act synergistically in deregulating DNA repair mechanisms in these tumors (Stewart and Crook, 2015). Similar findings involving loss of SWI/SNF proteins in MMR deficient endometrial tumors have been reported by other groups as well (Karnezis et al., 2016; Baker et al., 2017). These accumulating evidence suggest that ARID1A indeed play a role in maintaining genomic instability.

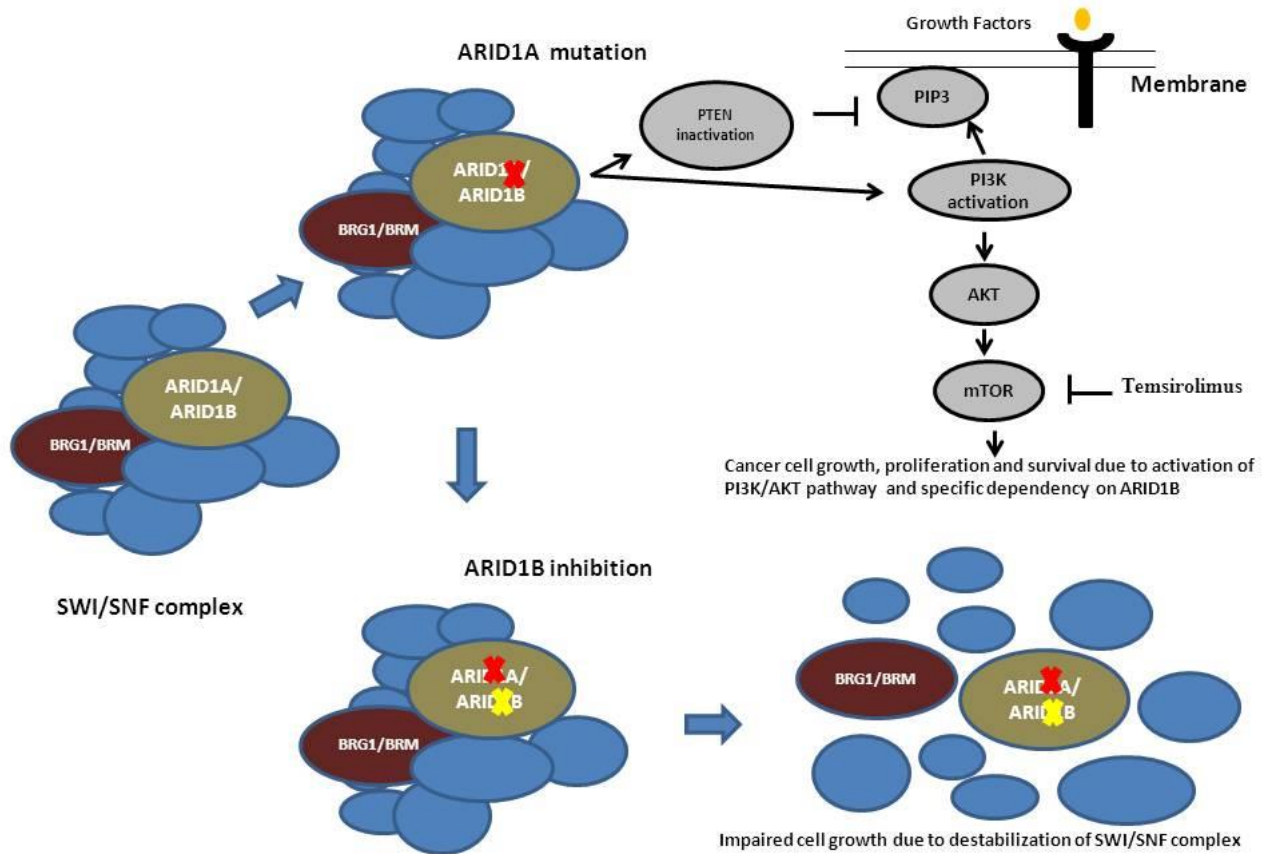
### Synthetic lethality in ARID1A-mutated ovarian/endometrial Cancer

Synthetic lethality is defined as a type of genetic interaction where two genetic events co-occur and are lethal to organism or cell. Many reports suggest that loss of ARID1A-protein expression frequently co-occurs with PI3K/AKT-pathway activation in various tumors, including ovarian clear cell carcinoma, endometrioid carcinomas, and endometrial carcinoma and ARID1A-deficient tumors show increased sensitivity to treatment with PI3K- and AKT-inhibitors (Samartzis et al., 2014; Huang et al., 2014; Yamamoto et al., 2012; Samartzis et al., 2011; Weigand et al., 2010). This suggests that there is a synthetic lethal interaction between loss of ARID1A expression and inhibition of the PI3K/AKT pathway. Activation of the PI3K/AKT pathway is mainly effected by the activation of receptor tyrosine kinases and by somatic mutations in specific components of the signaling pathway such as PTEN, PIK3CA, and AKT isoforms. Among the 42 ovarian clear-cell carcinomas, 17 (40%) tumors harbor somatic mutations of PIK3CA and majority (71%) of these were ARID1A-deficient carcinomas (Yamamoto et al., 2012). PTEN mutations are significantly found to be more frequently associated with low-grade endometrial endometrioid carcinomas (67%) as compared to low-grade ovarian endometrioid carcinomas (17%) (McConechy et al., 2014). In an Apc and Pten defective mouse ovarian cancer model, inactivation of ARID1A enhances epithelial differentiation and prolongs survival (Zhai et al., 2016). In a conditional knockout mouse model in which Arid1a and Pten were either individually deleted or in combination in the mouse ovarian surface epithelium, it was observed that after 6 months, 59.1% of double knockout mice with Arid1a and Pten developed ovarian endometrioid or undifferentiated carcinoma, whereas the remaining mice showed hyperplasia of ovarian surface epithelium (Guan et al., 2014). In contrast, Arid1a and Pten individual knockout mice did not develop ovarian lesions (Guan et al., 2014). This



suggests that mutation in *ARID1A* alone does not cause development and progression of cancer, but loss of *ARID1A* in cooperation with PI3K/AKT

pathway aberration is sufficient to drive tumorigenesis (Fig.1).



**Figure 1.** Schematic diagram showing loss of *ARID1A* drive tumorigenesis by activation of PI3K/AKT pathway and its specific dependency on *ARID1B*. Inhibition of PI3K/AKT pathway or *ARID1B* in *ARID1A* deficient tumours leads to impaired cellular proliferation in cancer cells suggesting that targeting PI3K/AKT pathway or inhibiting *ARID1B* as potential therapeutic strategy in *ARID1A*-mutatnt cancer cells.

The antagonistic roles of SWI/SNF and polycomb proteins in gene transcription have been initially revealed from genetic studies in *Drosophila* (Kennison JA and Tamkun JW, 1988). Polycomb proteins can remodel chromatin such that epigenetic silencing of genes takes place. EZH2, the catalytic subunit of polycomb repressive complex 2 is found to be overexpressed in both uterine and ovarian cancers. *ARID1A* and EZH2 are antagonistic in regulating expression of PI3K-interacting protein 1 (PIK3IP1). *ARID1A*/EZH2 directly target PIK3IP1, and EZH2 inhibition upregulated PIK3IP1 and contributes to the synthetic lethality by inhibiting PI3K/AKT signaling pathway (Bitler et al., 2015).

In a broad systematic screening approach using multiple cancer cell lines, it was revealed that *ARID1B*, whose gene product behaves in mutually exclusive fashion with *ARID1A* in SWI/SNF complexes, is the most significant gene found to be required for the survival of *ARID1A*-mutant cancer cell lines (Helming et al., 2014). Silencing *ARID1B* in *ARID1A* deficient tumors destabilizes SWI/SNF complex and impaired cellular proliferation in cancer cells (Fig.1). These results suggest that loss of *ARID1A* and *ARID1B* alleles result in a unique functional dependence. Hence, *ARID1B* may be a potential therapeutic target for *ARID1A*-mutant cancers.

## Targeted therapies in ARID1A mutated Ovarian/Endometrial Cancer

Understanding the mechanism of tumourigenesis in ARID1A mutated background in ovarian or endometrial cancer has facilitated the development of therapies against ARID1A mutant cancers. Most of these drugs work in synthetic lethal manner. Synthetic lethality is known to allow utilization of low concentrations of drugs with minimal toxicity and limited treatment resistance, and hence drugs working in synthetic lethal manner are beneficial to the patients.

Currently, molecular therapies targeting PI3K/AKT/mTOR signaling pathway and mitogen-activated protein kinase (MAPK) pathway are under investigation in a clinical trial for ovarian clear cell adenocarcinoma. A mTOR inhibitor, temsirolimus shows a potential therapeutic benefit in patients with Clear cell carcinoma of the ovary with minimum toxicity (Takano et al., 2011). Administration of sorafenib, a multikinase inhibitor, showed a partial response in a patient with stage IIIc ovarian clear cell adenocarcinoma with *PIK3CA* mutation but showed resistant to mTOR inhibitor, temsirolimus (Rahman et al., 2013).

In a high-throughput cell-based drug screening in ovarian clear cell carcinoma cell models, a synthetic lethal interaction between the kinase inhibitor dasatinib and ARID1A mutation was found. Dasatinib sensitivity is p21 and RB dependent and is characterized by an apoptotic response in ARID1A-mutant ovarian clear cell carcinoma (Miller et al., 2016). This suggests that dasatinib can be a potential therapeutic target and needs further investigations for the treatment of patients with ARID1A-mutant ovarian clear cell carcinoma.

In a recent study, using shRNA knockdown strategy it was demonstrated that ARID1A-mutated ovarian cancers cells are selectively sensitive to HDAC6 inhibition. Inhibition of HDAC6 activity using a small-molecule inhibitors triggers

apoptosis in ARID1A inactivated cells and significantly improved the survival of mice bearing ARID1A-mutated tumors (Bitler et al., 2017). This dependency of ARID1A mutated cells on HDAC6 activity was because ARID1A directly represses HDAC6 gene transcription and hence ARID1A inactivation upregulates *HDAC6* expression. Furthermore, ARID1A and p53 behaves in mutually exclusive manner and HDAC6 directly deacetylates Lys120 of p53. Thus, ARID1A mutation inactivates the apoptosis-promoting function of p53 by upregulating HDAC6 (Bitler et al., 2017). Thus, pharmacological inhibition of HDAC6 can be a promising therapeutic strategy for ARID1A mutated ovarian cancers.

Recently, enhancer of zeste homolog 2 (EZH2) inhibitors have been proposed as a novel therapeutic strategy against ARID1A-mutant clear cell carcinoma and endometrioid adenocarcinoma (Alldredge and Eskander., 2017). Bitler et al. first time show that inhibition of the EZH2 methyltransferase acts in a synthetic lethal manner in ARID1A-mutated ovarian cancer cells and that ARID1A mutational status correlated with response to the EZH2 inhibitor, GSK126 (Bitler et al., 2015). GSK126, a specific inhibitor of EZH2 triggers apoptosis in ARID1A mutated ovarian cancer cells in-vitro and caused regression of ARID1A mutated tumors in-vivo (Bitler et al., 2015).

ARID1B, a synthetic lethal partner of *ARID1A*, is also a possible target in molecular-targeted therapy. However, development of a subunit-specific inhibitor with structure and functional similarities will be a potential therapeutic approach which is challenging in this case.

With an aim to identify drugs sensitivities in *ARID1A*-mutant cancer cell lines, it was found that *ARID1A*-mutant cancer cell lines were more sensitive to treatment with the reactive oxygen species (ROS)-inducing agent elesclomol (Kwan et al., 2016). Treatment with elesclomol inhibited growth and induced apoptosis more potently in *ARID1A*-mutant ovarian cancer cells than in

ARID1A wild-type ovarian cancer cells. Knockdown of ARID1A in ARID1A wild-type ovarian cancer cells resulted in increased sensitivity to elesclomol, whereas restoration of ARID1A expression in ARID1A-mutant ovarian cancer cells resulted in increased resistance to elesclomol (Kwan et al., 2016). Hence, the study suggests a novel therapeutic strategy for *ARID1A*-mutant ovarian cancer cells by inducing oxidative stress.

To conclude, ARID1A act as a tumor suppressor in ovarian and endometrial cancer. Loss of expression of ARID1A frequently occurs in ovarian/endometrial cancer and accompanied by PI3K/AKT pathway activation in most of these cancers. Currently, therapies for ARID1A mutant cancers are limited. Although tumor suppressive genes such as ARID1A face challenges of targeted therapeutic strategies, however constant efforts towards an understanding of ARID1A mechanism of action and knowledge of molecules which shows functional dependency in ARID1A mutant cancers may help in developing effective therapeutic strategies for ARID1A deficient tumors in future.

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## Conflict of interest statement

There is no conflict of interest involved with this article.

## Authors' contributions

PS conceptualizes and prepared the manuscript. SM edited and contributed in revising the manuscript.

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