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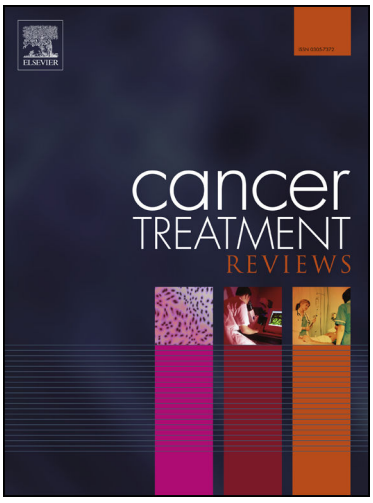

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Targeting *ARID1A* Mutations in Cancer

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Abstract

Genes encoding SWI/SNF chromatin remodeling complex subunits are collectively mutated in approximately 20% of human cancers. *ARID1A* is a SWI/SNF subunit gene whose protein product binds DNA. *ARID1A* gene alterations result in loss of function. It is the most commonly mutated member of the SWI/SNF complex, being aberrant in ~6% of cancers overall, including ovarian clear cell cancers (~45% of patients) and uterine endometrioid cancers (~37%). *ARID1A* has a crucial role in regulating gene expression that drives oncogenesis or tumor suppression. In particular, ARID1A participates in control of the PI3K/AKT/mTOR pathway, immune responsiveness to cancer, EZH2 methyltransferase activity, steroid receptor modulation, DNA damage checkpoints, and regulation of p53 targets and KRAS signaling. A variety of compounds may be of benefit in *ARID1A*-altered cancers: immune checkpoint blockade, and inhibitors of mTOR, EZH2, histone deacetylases, ATR and/or PARP. *ARID1A* alterations may also mediate resistance to platinum chemotherapy and estrogen receptor degraders/modulators.

Keywords: SWI/SNF, ARID1A, chromatin remodeling

Introduction

The AT-rich interaction domain 1A (ARID1A) protein comprises the DNA-binding subunit of SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complexes[1]. *ARID1A* alterations have been linked to oncogenesis since 1998[1]. Indeed, mutations in genes encoding subunits of SWI/SNF complexes are particularly prevalent in cancer, occurring in ~20% of all human malignancies[2]. Alterations in the *ARID1A* gene specifically, leading to loss of function of ARID1A, occur in ~6% of cancers[3].

Importantly, SWI/SNF, via its function as a chromatin remodeling complex, impacts transcription initiation and elongation. Chromatin remodeling is a critical enzyme-assisted process that enables access to DNA by remodeling nucleosome position and composition. A nucleosome is the basic structural DNA packaging unit, containing a segment of DNA wound around eight histone proteins; it resembles thread wrapped around a spool. The nucleosome is the fundamental chromatin subunit, with chromatin being a complex of DNA and protein whose primary function is packaging long DNA molecules into compact, denser structures. Therefore, chromatin remodeling dynamically modifies chromatin architecture to allow access of condensed genomic DNA to the transcription regulatory machinery, thereby controlling gene expression. The fact that chromatin remodeling complexes participate in transcription and regulation of gene expression, in combination with high prevalence of loss-of-function mutations in human cancers, point to a role as a tumor suppressor[1,4]. Indeed, SWI/SNF complexes have gained increased importance as the most frequently mutated epigenetic regulators[1,5]. This observation has ignited a search for the best manner in which to target SWI/SNF mutations, such as those affecting *ARID1A,* in patients with cancer.

1 Components of the SWI/SNF Complex

The human analogs of SWI/SNF are BRG1 and BRM-associated factors BAF and Polybromo-associated BAF or PBAF (Figure 1). SWI/SNF complexes are comprised of an ATPase, three core subunits, and an additional 8 to 11 accessory subunits that further differentiate the DNA binding specificity of each complex[1,4,6].

ARID1A and two homologous subunits, ARID1B and ARID2, are named for their AT-rich binding domain (ARID) and are the subunits responsible for binding DNA[1]. These subunits were originally thought to be mutually exclusive within an individual complex, but recent work showed the presence of multiple subunits in a small subset of SWI/SNF complexes[7]. All SWI/SNF complexes contain at least one of the three DNA binding subunits[4,6].

In humans, the two SWI/SNF ATPases are BRM (Brahma) and BRG1 (Brahma-Related Gene 1), encoded by the *SMARCA2* and *SMARCA4* genes respectively[8]. These enzymatic subunits are accompanied by BRM or BRG1-associated factors such as BAF155 (from *SMARCCA1*) and BAF170 (*SMARCC2*), which are thought to function as stabilizers and scaffolding for the ATPase and accessory subunits, while SNF5 (*SMARCB1*) contains a non-specific DNA binding domain[8]. BAF250a, BAF250b, and BAF200 (*ARID1A*, *ARID1B*, and *ARID2*) are the direct DNA-binding accessory subunits[8,9]. BAF180, also known as Protein polybromo-1 (*PBRM1*) is another accessory subunit of note, as its presence in a SWI/SNF complex is mutually exclusive with ARID1A or ARID1B[8,9]. Therefore, BAF180 will only complex with ARID2 and defines the Polybromo-associated BAF complex PBAF[8]. ARID1A/B containing complexes are termed BAF complexes and can be subdivided further by the presence of mutually exclusive accessory subunits[4,8].

The accessory factors generate several hundred possible subunit combinations in SWI/SNF complexes[9]. This combinatorial capability has been compared to the specificity of letters in a language[8,9]. The accessory subunits tailor the larger SWI/SNF complexes' binding to DNA, transcription factors, and other regulatory proteins and exponentially increase the possible specificity of the complex[9]. The diversity of vertebrate chromatin-remodeling complexes, transcription factors, and other regulatory mechanisms in transcription allow a single gene to serve a multitude of functions based on its expression pattern[9,10].

2 Functions of the SWI/SNF Complex

SWI/SNF complexes remodel nucleosomes using energy provided by the ATPase subunit, which alters the accessibility of the associated DNA to transcription factors and transcriptional machinery[1,11]. Specifically, SWI/SNF and other chromatin remodeling complexes are thought to use the energy from ATP hydrolysis to slide DNA around histones and create a loop that propagates and repositions the nucleosome[11]. This active process distinguishes nucleosome remodeling from enzymatic histone DNA modifications, such as acetylation or phosphorylation, and epigenetic modifications such as DNA methylation[4]. Additionally, chromatin remodeling complexes target and bind chromatin based on a larger set of inputs than DNA methylation or histone acetylation[9,11]. SWI/SNF core and accessory subunits provide low specificity DNA-binding domains as well as other structural motifs common to chromatin, including bromodomains, chromodomains, and plant homeodomain (PHD) domains[9,11]. The large, multi-subunit size of chromatin remodeling complexes is thought to be necessary for three-dimensional targeting of distinct histone modifications and DNA sequences of a nucleosome or perhaps even two adjacent nucleosomes[9,11]. Lessard et al. showed a rearrangement of subunit composition to be an essential step in the commitment of mammalian neural stem cells to a neuronal fate, which illustrates a critical role of SWI/SNF complexes in neural development[12].

3 Functions of *ARID1A*

ARID1A and other SWI/SNF proteins are expressed across a large majority of cell types during development and afterwards[1,4]. Knockout of *ARID1A* and several other SWI/SNF genes result in embryonic lethality, underscoring an important role in differentiation[1,4]. As mentioned, ARID1A, ARID1B and ARID2 are the SWI/SNF subunits responsible for binding DNA[1]. In addition to chromatin remodeling, ARID1A and ARID1B are also involved in double-strand break (DSB) repair pathways and localize the SWI/SNF complex to break points[13]. Knockout of either or both proteins reduces the overall activity of the nonhomologous end joining repair (NHEJ) pathway[13,14]. ARID1A is involved in homologous recombination, the dominant repair pathway in

proliferating cells[13,14]. ARID1A also participates in steroid receptor signaling via a C-terminus domain which can stimulate glucocorticoid receptor-dependent transcriptional activation[15], as well as several other pathways discussed below.

4 *ARID1A* Alterations are Frequent in Cancer

Abnormalities in genes encoding subunits of SWI/SNF complexes are found in ~20% of patients with cancer[2]. Alterations in the *ARID1A* gene leading to loss of function occur in ~6% of human malignancies[3]. *ARID1A* alterations affect protean tumor types including, but not limited to: ~45% of clear-cell ovarian cancer, ~37% of endometrial cancers, ~20-30% of gastric cancers, ~20% of bladder cancers, ~14% of hepatocellular cancers, ~12% of melanomas, ~9% of colorectal cancers, ~8% of lung cancers, ~4% of pancreas cancers and ~3% of breast cancers[16-18].

5 *ARID1A* Alterations are Associated with Epstein Barr Virus (EBV) in Human Malignancy

Epstein Barr virus was linked to cancer from its initial isolation directly from Burkitt's lymphoma cells in 1964[19]. EBV was then shown to be involved in the oncogenesis of several additional lymphomas, nasopharyngeal carcinoma, and gastric cancer[19,20]. A 2009 review of over 15,000 cases of gastric cancer estimated the prevalence of EBV positivity at 8.7%[21]. Wang and colleagues found *ARID1A* alterations in 73% of the EBV-associated subtype of gastric cancer[22]. This was largely driven by truncating mutations, though some samples showed absent or weak ARID1A protein expression despite the lack of an *ARID1A* mutation[22]. These patients were less likely to harbor a *TP53* mutation, in keeping with The Cancer Genome Atlas findings and other analyses[22-24]. *ARID1A* is also frequently mutated in the endemic variant of Burkitt's lymphoma, a disease associated with EBV infection in over 95% of cases[25,26]. Furthermore, nasopharyngeal carcinoma is known to have low levels of expression of ARID1A and is associated with EBV infection[27]. Of interest, EBV-positive gastric cancers may be especially responsive to immune checkpoint blockade[28]. The biological mechanism by which

EBV infection is associated with *ARID1A* alterations is not clear. However, similar phenomena have been seen with other viral infections. For instance, *PIK3CA* alterations can be seen in HPV positive head and neck cancers. It is conceivable that this is a clonal selection effect, though other mechanisms may be operative[29].

6 Therapeutic Targeting of *ARID1A* Abnormalities

ARID1A alterations affect multiple pathways important in cancer. Therapies targeting these pathways have shown activity in preclinical models and in patients. Several examples we discuss in the following sections include the use of immune checkpoint blockade (anti-PD-1/PD-L1) (clinical data) as well as molecules targeting the PI3K/Akt/mTor pathway, PARP inhibitors, ATR inhibitors, EZH2 inhibitors, and pan-HDAC inhibitors. *ARID1A* alterations may also be responsible for resistance to platinum agents and to estrogen receptor modulators (Table 1[3,13,14,22,24,30-53]).

7 *ARID1A* Alterations and the PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTor pathway has long been studied as a growth and survival pathway in healthy and malignant cells[33,54]. The pathway is activated through receptor tyrosine kinases, G-protein coupled receptors, cytokine receptors, and several other classes of receptors which trigger the serine/threonine kinase Akt downstream[33,54]. Akt effects many targets through direct phosphorylation or transcriptional regulation[54]. PI3K/Akt/mTor pathway alterations are common across cancers[31,40,45,55-58]. Yamamoto et al. described co-occurrence between *PIK3CA* alterations and loss of ARID1A expression, noting that 71% of *PIK3CA*-mutant ovarian clear cell carcinoma (OCCC) tumors in their set were ARID1A deficient[33,34]. Chandler et al. connected inflammation-driven tumorigenesis with ARID1A protein deficiency via interleukin-6 (IL-6) signaling[30], which can activate the PI3K/Akt/mTor pathway among others[59,60].

Further evidence of cooperation between *ARID1A* alterations and the PI3K/Akt/mTor pathway comes from nasopharyngeal carcinoma (NPC) and gastric cancer cell lines[27,32,35]. *ARID1A* knockdown by siRNA

correlated with increased Akt phosphorylation in both ovarian clear cell carcinoma and nasopharyngeal cancer cell lines[27,32]. Kim et al. also found that ARID1A loss upregulated programmed death-ligand 1 (PD-L1) expression in gastric cancer cell lines via PI3K-Akt pathway signaling[35]. One underlying mechanism of regulation of the PI3K/Akt/mTor signal may be via the PI3K-interacting protein 1 (PIK3IP1), which downregulates PI3K-Akt signaling. Indeed, ARID1A binds the *PIK3IP1* promoter, driving *PIK3IP1* expression[46]. Conversely, *PIK3IP1* expression is decreased in *ARID1A*-mutated ovarian cancer cells, which leads to PI3K/Akt/mTor pathway activation. Inhibitors of mTor such as everolimus suppress the PI3K/Akt/mTor pathway and might be useful in ARID1A-deficient cancers[33].

8 *ARID1A* Alterations and Immune Checkpoint Blockade

ARID1A alterations are associated with mismatch repair (MMR) deficiency and microsatellite instability (MSI), which in turn cause high tumor mutational burden (TMB). *ARID1A* aberrations also correlate with PD-L1 expression and EBV positivity in multiple cancers[3,18,23,37,38]. All of these factors are potential markers of disease response to immune checkpoint inhibitors[3,18,37,38,61].

In a proteomic screen, ARID1A interacted with the mismatch repair protein MSH2. Specifically, ARID1A recruited MSH2 to chromatin during DNA replication and supported mismatch repair[37]. Conversely, ARID1A inactivation attenuated mismatch repair and enhanced mutagenesis. Therefore, ARID1A deficiency may create a microsatellite instability genomic signature via its perturbed interaction with MSH2. Finally, cancers produced by an ARID1A-deficient ovarian cancer cell line in syngeneic mice exhibited high mutation load, elevated PD-L1 expression, and increased numbers of tumor-infiltrating lymphocytes. Importantly, administration of an anti-PD-L1 antibody decreased tumor burden and extended survival of mice harboring ARID1A-deficient, but not ARID1A-wild-type, ovarian cancers[37].

Although ARID1A interaction with MSH2 and resultant microsatellite instability may be relevant to responsiveness of ARID1A-deficient cancers to immune checkpoint blockade, other mechanisms may also be

operative. Indeed, recent work at our institution found that *ARID1A* alterations in a variety of human cancers were significantly associated with longer progression-free survival (PFS) after immune checkpoint inhibition, independent of TMB or MSI status[38]. While the mechanism underlying *ARID1A* mutations' correlation with immune checkpoint blockade benefit is unclear, EZH2 methyltransferase interaction with ARID1A may be implicated in immune response. Indeed, ARID1A interacts with EZH2 and suppresses EZH2-mediated interferon (IFN) responsiveness, with IFN responsiveness being crucial to immune response[62]. Sarshekeh et al. showed that *ARID1A* alteration was associated with checkpoint gene expression and other markers of immunogenicity in MSS colorectal cancer[39].

9 Targeting *ARID1A* Alterations with PARP Inhibitors

DNA encounters various assaults on its integrity throughout the cell life span. Human cells have at least five primary DNA repair pathways: mismatch repair (MMR), direct repair, base excision repair (BER), nucleotide excision repair (NER), and double-strand break (DSB) recombinational repair. Double-strand break repair includes both non-homologous end-joining (NHEJ) (used when homologous DNA is absent) and homologous recombinational directed repair, which requires extensive regions of DNA homology in another DNA duplex. Dysfunction of proteins in these pathways may cause mutagenesis.

Of particular importance, homologous recombination deficiency (HRD) can be produced by different kinds of mutations, such as those in the *BRCA* gene, and patients whose cancer cells harbor these mutations can be effectively treated with poly ADP-ribose polymerase (PARP) inhibitors[63]. PARP1 and PARP2 are enzymes activated by DNA damage that facilitate repair of single-strand breaks (SSBs), base excision repair, and homologous recombination. PARP inhibitors work to kill tumors through a synthetic lethality mechanism in cells with HRD. For instance, PARP inhibitors cause an increase in DNA SSBs, which are converted during replication to irreparable toxic DNA DSBs in BRCA1/2 defective cells[63]. DNA DSBs lead to cell death by apoptosis when the level of DNA damage is too great to warrant repair.

ARID1A alteration interferes with DNA damage repair in several ways. First, ARID1A is essential for establishing an open chromatin state upon DNA damage, a process required for the function of the NHEJ machinery. The inability of ARID1A-negative cells to mount NHEJ repair results in a partial cytotoxic response to radiation. Furthermore, PARP inhibitors act synergistically with radiation to potentiate cytotoxicity in ARID1A-negative cells in mouse models[64]. In addition, a key function of ARID1A in regulating the DNA damage checkpoint is through its recruitment to DNA DSBs via its interaction with the upstream DNA damage checkpoint kinase ATR. At the molecular level, ARID1A facilitates efficient processing of DSB to single-strand ends. By this mechanism, ARID1A deficiency sensitizes cancer cells to PARP inhibitors both in *in vitro* and *in vivo* models[14].

However, the activity of PARP inhibitors in patients with *ARID1A* alterations is not yet clear. Hu et al. screened several breast and ovarian cancer cell lines and found that ARID1A loss resulted in resistance to PARP inhibition therapy[43]. This led the authors to analyze samples of high grade serous ovarian cancer collected as part of the ARIEL2 study of the PARP inhibitor rucaparib (NCT01891344[44]). They found that patients with *ARID1A*-mutant high-grade serous ovarian cancer had a significantly shorter progression-free survival period compared to study subjects without a mutation in *ARID1A* or a gene involved in homologous recombination[43,44]. This evidence tempers earlier observations of the utility of PARP inhibitors in preclinical models. Further clinical investigation across multiple histologies will be necessary to confirm the effect of *ARID1A* alterations on the efficacy of PARP inhibitor therapy.

10 Gemcitabine and ARID1A

Kuroda et al. screened common cytotoxic agents for efficacy in ARID1A-deficient ovarian clear cell carcinoma lines and found the pyrimidine antimetabolite gemcitabine a promising possible treatment strategy[51]. They also found that growth of ARID1A-deficient ovarian clear cell xenograft models was inhibited by gemcitabine. Finally, they looked retrospectively at several patients with ovarian clear cell carcinoma and

found cases in which gemcitabine benefitted ARID1A-deficient patients for longer than comparable patients with ARID1A-proficient ovarian clear cell cancer[51].

11 *ARID1A* Alterations and EZH2 Inhibitors

Leveraging a screen of small-molecule epigenetic inhibitors, Bitler and colleagues identified an inhibitor of the enhancer of zeste homolog 2 methyltransferase (EZH2), which represses gene expression via trimethylation of histone H3 lysine 27 (H3K27Me3), as selective against ARID1A-depleted ovarian clear cell carcinoma cells[46]. Analysis of gene expression profiles identified the gene encoding PI3K-interacting protein 1 (PIK3IP1), which negatively regulates PI3K-Akt signaling, as a direct target of both EZH2 and ARID1A. *PIK3IP1* expression was reduced in *ARID1A*-mutated ovarian clear cell carcinoma cells, and EZH2 inhibition treatment or restoration of wild-type ARID1A resulted in its upregulation, suggesting that ARID1A and EZH2 antagonistically regulate *PIK3IP1* expression. Consistent with this idea, both ARID1A and EZH2 bound the *PIK3IP1* promoter in wild-type cells, with ARID1A playing a dominant role over EZH2. ARID1A, which activates *PIK3IP1* expression, usually dominates over EZH2, which suppresses *PIK3IP1*. When ARID1A is absent, EZH2 silences *PIK3IP1*. Subsequent inhibition of EZH2, in turn, reinstates the expression of PIK3IP1—and thereby the inhibition of the PI3K-Akt pathway. Importantly, EZH2 inhibitor administration induced regression and decreased the dissemination of *ARID1A*-mutated, but not *ARID1A*-wild-type, xenograft tumors, which correlated with enhanced PIK3IP1 expression and reduced Akt activation[46]. These observations indicate that suppression of EZH2 methyltransferase activity may serve as a synthetic lethal therapeutic strategy to target *ARID1A*-mutated cancers.

EZH2 communication with ARID1A may also be implicated in immune response. Mechanistically, ARID1A interacts with EZH2 via its carboxyl terminal and antagonizes EZH2-mediated IFN responsiveness. Therefore, the interaction between ARID1A and EZH2 helps define cancer IFN responsiveness and immune evasion[62].

It is unclear, however, how and if an EZH2 inhibitor strategy applies to tumors across the board. For instance, unlike in ovarian clear cell carcinoma, ARID1A-deficiency was not associated with increased sensitivity towards inhibition of EZH2 enzymatic activity or depletion of EZH2 protein in high-grade bladder cancers[47].

12 Pan-Histone Deacetylase (HDAC) Inhibitors for *ARID1A*-Altered Cancer

ARID1A mutations confer vulnerability to pan-HDAC inhibitors such as suberoylanilide hydroxamic acid (SAHA) in preclinical models of ovarian cancers[48]. This sensitivity is associated with growth inhibition triggered by the suppression of HDAC2 activity in *ARID1A*-altered cells. HDAC2 functions as a co-repressor of EZH2 to modulate the expression of EZH2/ARID1A target genes such as *PIK3IP1*. SAHA reduced the growth of the *ARID1A*-inactivated ovarian clear cell cancers in orthotopic and genetic murine models and improved the survival of mice bearing these *ARID1A*-mutated cancers[48].

13 ATR Inhibitors as a synthetic lethal strategy for *ARID1A*-Altered Cancer

ATR (Ataxia-Telangiectasia Mutated (ATM) and Rad3-related protein kinase) is a crucial element in cellular DNA damage response[65]. ATR is activated by regions of single-stranded DNA, which occur due to replicative stress, which in turn can be induced by oncogene activation. Defects in *ARID1A* sensitize cancer cells to small molecule inhibitors of the DNA damage checkpoint kinase ATR, both *in vitro* and *in vivo*[14,66,67]. Mechanistically, ARID1A deficiency leads to topoisomerase 2A and cell cycle defects, which cause an enhanced dependence on ATR checkpoint activity. In *ARID1A*-mutant cancer cells, suppression of ATR triggers premature mitotic entry & genomic instability, and hence programmed cell death. Therefore, ATR inhibitors may present a novel synthetic lethal strategy to target cancer cells harboring *ARID1A* mutations[66].

14 *KRAS* Mutant Dependency on ARID1A

Sen et al. selectively knocked out *ARID1A* in several colorectal cancer cell lines in order to assess the effect of *ARID1A* loss on cell growth. They found that two *KRAS*-mutant lines were dependent on ARID1A for proliferation[52]. In the absence of ARID1A, growth of these cell lines is severely compromised, indicating a vital role for ARID1A in this context. Mechanistically, ARID1A acts as a co-factor at enhancers occupied by AP1 transcription factors acting downstream of the MEK/ERK pathway. Therefore, upon *ARID1A* loss in *KRAS*-mutated cells, enhancers that are co-occupied by ARID1A and the AP1 transcription factors become inactive, disrupting K-RAS/AP1-dependent enhancer activity, and leading to reduced expression of the associated target genes. It is therefore plausible that targeting of the BAF SWI/SNF complex in *KRAS*-mutated colorectal cancers may offer a unique therapeutic option[52].

15 ARID1A and p53 cooperate to regulate cancer growth

In gynecologic cancers, gene expression analysis identified several downstream targets of ARID1A including *CDKN1A* (encoding p21) and *SMAD3*, which are well-established p53 target genes[68]. p53 was required and sufficient for their regulation by *ARID1A*[68]. Furthermore, *CDKN1A* acted in part to mediate growth suppression by ARID1A. Finally, the ARID1A complex interacted directly with p53 and mutations in the *ARID1A* and *TP53* genes were mutually exclusive in tumor specimens. These observations provided functional evidence to support the contention that that *ARID1A* is a tumor suppressor that co-operates with p53 to regulate growth of malignant neoplasms[68].

16 Resistance in *ARID1A*-mutant cancers

ARID1A plays a significant role in steroid receptor activity[15,69,70]. Steroid receptors (SRs) are a subfamily of the nuclear receptor superfamily, containing five classical members: estrogen receptors (ESRs), progesterone receptors (PGRs), androgen receptors (ARs), glucocorticoid receptors (GRs), and

mineralocorticoid receptors (MR)[71]. Mutations in *ARID1A* are the most common alterations of the SWI/SNF complex in estrogen-receptor-positive (ER^+) breast cancer[53]. An epigenome CRISPR-CAS9 knockout screen pinpointed ARID1A loss as an important factor determining resistance to the ER degrader fulvestrant[53]. ARID1A inactivation in cells and in patients promotes resistance to ER degraders by enabling a switch from ER-dependent luminal cells to ER-independent basal-like cells. Cellular plasticity is mediated by loss of ARID1A-dependent SWI/SNF complex targeting to genomic sites of the luminal lineage-determining transcription factors including ER, GATA-binding factor 3 (GATA3), and forkhead box protein A1 (FOXA1). ARID1A also controls genome-wide ER-dependent transcription and ER-FOXA1 chromatin interactions. Therefore, ARID1A plays a crucial role in maintaining breast luminal lineage fidelity and sensitivity to estrogen receptor modulator therapy in ER-positive breast cancer[53].

As discussed above in section 9, the evidence regarding the effectiveness of PARP inhibitors for patients with *ARID1A*-mutant cancers is mixed[14,43,44,64]. It is possible that alteration could lead to treatment resistance in certain cancers while providing an opportunity for therapeutic efficacy in others.

In many cases, cancers sensitive to PARP inhibitors are also sensitive to platinum-containing chemotherapy[72,73]. For instance, patients with *BRCA1/2*-mutated ovarian cancer have better outcomes after platinum-based therapy compared to patients without a mutation[74]. The platinum sensitivity of *BRCA*-mutated ovarian cancer is attributed to HRD in the absence of BRCA1/2 function, which results in an impaired ability of malignant cells to repair platinum-induced DSBs[72]. Of interest however, *ARID1A* alterations appear to confer clinical resistance to platinum agents in ovarian cancer[43,45,55], even though *ARID1A* alterations are associated with PARP inhibitor sensitivity preclinically[14,64]. One group examined the specific mechanisms of platinum resistance in ovarian cancer and found that multidrug resistance-associated protein 2 (MRP2) was greatly upregulated via transcriptional modifications associated with ARID1A protein loss[45]. MRP2 facilitates the ATP-dependent active membrane export of platinums, hence potentially mediating platinum resistance[45,75].

17 Germline Mutations in SWI/SNF Complexes

Germline mutations in SWI/SNF genes have recently been documented in several intellectual disability syndromes[76]. *ARID1B* haploinsufficiency was identified as the likely cause of corpus callosum abnormalities and concurrent intellectual disabilities in several patients in 2011[77,78]. Hoyer et al. then found haploinsufficiency of *ARID1B* in 0.9% of an unselected group of 887 patients with unexplained intellectual disability[79]. SWI/SNF gene alterations in *ARID1B*, *ARID1A*, *SMARCA4*, *SMARCE1* and *SMARCB1* were linked to Coffin-Siris Syndrome, a rare intellectual disability with diverse signs and symptoms including, but not limited to hypoplasia of the distal phalanx or nail of the fifth and additional digits, hypotonia, distinctive facial characteristics[80,81]. One group found SWI/SNF gene alterations in 20 of 23, or 87% of pediatric and adult patients with Coffin-Siris Syndrome[81]. Another study of patients with Nicolaides-Baraitser Syndrome, another rare intellectual disability syndrome similar to Coffin-Siris, found that 36 of 44 patients (82%) harbored a non-synonymous mutation in the *SMARCA2* gene, which is part of the SWI/SNF chromatin remodeling complex[81]. The authors point to the previously discussed role of SWI/SNF complexes in development, differentiation, and in particular neuronal differentiation[12], as the mechanism by which germline mutations in SWI/SNF genes result in these intellectual disability syndromes[76-82].

Conclusions

The ARID1A protein, by binding certain regions of DNA as part of a SWI/SNF complex, contributes to the tremendous specificity of these chromatin remodeling complexes. These complexes utilize ATP to alter nucleosome architecture in order to conceal or expose regions of DNA to transcriptional regulation, and therefore differ from enzymatic histone modifications and epigenetic modifications of DNA. Through SWI/SNF complexes' broad role in the regulation of gene expression, as well as more specific protein-protein interactions, ARID1A is connected to many important cellular pathways and processes in healthy and malignant cells.

ARID1A alterations are detected in ~6% of human cancers[3], most commonly endometroid and ovarian clear cell cancers, wherein *ARID1A* is mutated in almost 50% of tumors. These alterations lead to loss of function of the protein product and have been shown to impact numerous signals important in oncogenesis: the PI3K/Akt/mTor pathway, KRAS pathway, DNA damage repair, EZH2, and immune function (including interaction with the MSH2 mismatch repair gene product). Compounds targeting these pathways that may have activity based on preclinical mechanistic cancer models and/or based on data from patients with cancer include: immune checkpoint blockade (anti-PD-1/PD-L1) (clinical data); and inhibitors of mTor, PARP, ATR, EZH2, and HDACs (Table 1). Multiple clinical trials with various targeted agents are ongoing for cancer patients with *ARID1A*-alterations (Table 2). *ARID1A*-alterations may also be responsible for resistance to platinum chemotherapy and to estrogen receptor endocrine modulators. Understanding ARID1A function is important for more precisely matching patients whose cancers harbor *ARID1A* mutations with cognate drugs in order to optimize response and outcome[38,83-88].

Table 1: Impact of *ARID1A* Alterations and Potential Therapeutic Targets

Mechanism	Disease Models	Therapeutic Implication	Data	Comment	References
ARID1A alterations and the PI3K/Akt/mTor pathway					
Coexistent *ARID1A*-*PIK3CA* mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signaling[30]	Endometrial, ovarian, and various other cancers	Some data that wild-type ARID1A protects against inflammation driven tumorigenesis[30]	Pre-clinical	71% of *PIK3CA*-mutant ovarian clear cell carcinoma tumors are ARID1A deficient IL-6 inhibitors could potentially be tried in ARID1A deficient cancers[30]	30,46
ARID1A alterations can increase Akt phosphorlyation[32]		mTor inhibitors such as everolimus inhibit this pathway[33]	Pre-clinical	ARID1A and EZH2 associate with the PIK3IP1 promotor; PIK3IP1 suppresses the PI3K/Akt/mTor signal. ARID1A, which activates *PIK3IP1* expression, dominates over EZH2, which reduces *PIK3IP1* expression. When ARID1A is absent, EZH2 silences *PIK3IP1*.	32-34
***ARID1A* alterations sensitize tumors to immune checkpoint blockade**					
ARID1A alterations found in 73% of EBV-positive gastric cancer[22] and associated with high PD-L1 expression[35]	Gastric Cancer	Gastric cancers with EBV are more responsive to immune checkpoint blockade[36]	Clinical	*ARID1A* alterations found in 83% of MSI-high and 11% of EBV-negative MSS gastric cancers[22]	22,35,36
ARID1A recruits MSH2 to chromatin during DNA replication. Conversely, ARID1A inactivation compromised mismatch repair and increased mutagenesis[14]	Pan-cancer	Immune checkpoint blockade is associated with better outcomes across *ARID1A*-mutated cancers[37,38]	Clinical	Response to checkpoint blockade is independent of MSI status or TMB	14,37,38
ARID1A alteration is associated with higher tumor mutational burden in multiple cancers[3,38,39]	MSS CRC and multiple other cancers	These cancers or subtypes could be more susceptible to immunotherapies[3,38,39]	Pre-clinical and post-hoc analysis		3,38,39
ARID1A alterations and sensitivity/resistance to PARP inhibitors and platinum resistance					

DNA Repair Pathway involvement[14,37]	Ovarian clear cell carcinoma, cancer cell lines	May mediate sensitivity to PARP inhibitors[13,14,40-42]	Pre-clinical, Early phase trials		13,14,37,40-42
Unknown mechanism of resistance[43]	Breast and ovarian cancer cell lines and high grade serous ovarian cancer	May mediate resistance to PARP inhibitors[43,44]	Pre-clinical, post-hoc analysis		43,44
ARID1A loss leads to upregulation of MRP2, which controls transport of platinum out of cells[45]	Ovarian clear cell carcinoma	May mediate resistance to platinums[45]	Pre-clinical		45
ARID1A alterations and EZH2 inhibitors					
Synthetic lethality by inhibiting EZH2 histone methyltransferase activity in *ARID1A*-mutated cancers	Ovarian clear cell carcinoma cell lines	Some pre-clinical data that inhibition of EZH2 could be effective in ovarian cancer[46]. However, in bladder cancer, this was not demonstrated[47].	Pre-clinical	Mediated through PI3K/Akt pathway[46]	46,47
ARID1A alterations and HDAC inhibitors					
ARID1A mutation confers sensitivity to pan-HDAC inhibitors such as SAHA. This correlated with enhanced growth suppression induced by the inhibition of HDAC2 activity in ARID1A-mutated cells. HDAC2 interacts with EZH2 in an ARID1A status-dependent manner[48-50]	Mouse models of ovarian clear cell carcinoma	Some pre-clinical data that HDAC inhibitors such as SAHA could be effective[48-50]	Pre-clinical		48-50
ARID1A alterations and Gemcitabine					
Gemcitabine may be effective against *ARID1A*-mutant cancers through an unknown mechanism	Ovarian clear cell carcinoma lines & xenograft models, and patients with OCCC	Gemcitabine may be effective against *ARID1A*-mutant cancers[51]	Pre-clinical, and post-hoc analysis		51
ARID1A alterations and other targets: _ATR, KRAS, TP53,_ Estrogen Receptor					

Synthetic lethal strategies for ARID1A loss by targeting ATR	Ovarian clear cell carcinoma and other cancer cell lines	Potential target for synthetic lethality approaches based on use of ATR inhibitors[1,40,66,67]	Pre-clinical		[1,40,66,67]
ARID1A is involved in K-RAS downstream (nuclear) signaling[52]	Colorectal cancer	Knockout of ARID1A containing remodeling complexes could have activity in *KRAS*-mutated CRC[52]	Pre-clinical		[52]
ARID1A is involved in p53 target gene expression and may upregulate p53 protein expression or stability[24,31,46]	Various	Some exclusivity among wild type *TP53* and *ARID1A* mutations suggest restoring wild type p53 could provide benefit in a combinatorial approach[31]	Pre-clinical		[24,31,46]
ARID1A inactivation in cells and in patients promotes resistance to ER degraders by enabling a switch from ER-dependent luminal cells to ER-independent basal-like cells[53]	ER+ Breast cancer	ARID1A loss determined resistance to fulvestrant, an ER degrader	Pre-Clinical		[53]

Abbreviations: EBV = Epstein Barr virus; ER = estrogen receptor; HDAC = histone deacetylase; MRP2 = multi-drug resistance-associated protein 2; MSI = microsatellite instability; MSS = microsatellite stable; SAHA = suberanilohydroxamic acid; TMB = tumor mutational burden

Table 2: Selected Clinical Trials for *ARID1A*-altered Cancer

Study Title	Cancer Types	Intervention	ClinicalTrials.gov Identifier
Phase II Study of Tazemetostat in Solid Tumors Harboring an ARID1A Mutation	Solid tumor with *ARID1A* mutation	Tazemetostat (EZH2 inhibitor)	NCT05023655
PD-1 Combined With Dasatinib for as Third-line Treatment for ARID1A Mutation Advanced Non-Small Cell Lung Cancer	Non-Small Cell Lung Cancer with *ARID1A* mutation	Toripalimub (anti-PD1 antibody) and Dasatinib (multi-kinase inhibitor)	NCT04284202
ATr Inhibitor in Combination With Olaparib in Gynaecological Cancers With ARID1A Loss or no Loss (ATARI)	Gynecological Cancers with *ARID1A* mutation	AZD6738 (ATR inhibitor) and Olaparib (PARP inhibitor)	NCT04065269
Nivolumab for the Treatment of Patients With Metastatic Urothelial Cancer With ARID1A Mutation and Stratify Response Based on CXCL13 Expression	Urothelial Cancer With *ARID1A* mutation	Nivolumab (anti-PD1 antibody)	NCT04953104
Olaparib in Treating Patients With Metastatic Biliary Tract Cancer With Aberrant DNA Repair Gene Mutations	Biliary Tract Cancer With Aberrant DNA Repair Gene Mutations (including *ARID1A* mutation)	Olaparib (PARP inhibitor)	NCT04042831

Graphical Abstract: Potential Therapeutic Targets for *ARID1A* Alterations

Caption: Multiple potential therapeutic targets exist for cancers with *ARID1A* alterations. There is evidence that *ARID1A* alterations lead to resistance to platinum-based chemotherapy, and mixed evidence regarding the efficacy of PARP inhibitors.

Figure 1: Components of the SWI/SNF Complexes

Figure 1: The SWI/SNF complex binds to histone bound DNA using either ARID1A, ARID1B, or ARID2 as the primary binding protein. Three core SMARC proteins and an ATPase subunit are necessary for function across all possible combinations of SWI/SNF proteins. The ATPase provides the energy necessary to remodel chromatin and alter the expression of target genes. Various other subunits provide a great deal of combinatorial complexity and specificity to the complex.

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Highlights

- About 20% of cancers harbor SWI/SNF chromatin remodeling complex gene alterations.
- ARID1A is a SWI/SNF subunit responsible for binding DNA.
- ~6% of cancers have loss-of-function alterations in *ARID1A.*
- *ARID1A* alterations correlate with improved clinical outcome after immunotherapy.
- ARID1A impacts PI3K/AKT/mTOR, DNA damage, EZH2, and other signals.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

JM has no disclosures to report.

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