INNOVATIONS JOURNALS

Review Article

Therapeutic Role of Synthetic Lethality in *ARID1A*-Deficient Malignancies

Kyaw Z. Hein,[1] Bettzy Stephen,[2] Siqing Fu[2]

[1]Department of Internal Medicine, HCA Florida Westside Hospital, Plantation, FL, USA
[2]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Address correspondence to Kyaw Z. Hein (kyawzawhein123@gmail.com).

Sources of Support: None. Conflicts of Interest: None.

Submitted: Dec 16, 2022; First Revision Received: Apr 28, 2023; Accepted: Sep 21, 2023

Hein KZ, Stephen B, Fu S. Therapeutic role of synthetic lethality in ARID1A-deficient malignancies. *J Immunother Precis Oncol.* 2024; 7:41–52. DOI: 10.36401/JIPO-22-37.

This work is published under a CC-BY-NC-ND 4.0 International License.

ABSTRACT

AT-rich interaction domain 1A (ARID1A), a mammalian switch/sucrose nonfermenting complex subunit, modulates several cellular processes by regulating chromatin accessibility. It is encoded by *ARID1A*, an immunosuppressive gene frequently disrupted in a many tumors, affecting the proliferation, migration, and invasion of cancer cells. Targeting molecular pathways and epigenetic regulation associated with ARID1A loss, such as inhibiting the PI3K/AKT pathway or modulating Wnt/β-catenin signaling, may help suppress tumor growth and progression. Developing epigenetic drugs like histone deacetylase or DNA methyltransferase inhibitors could restore normal chromatin structure and function in cells with ARID1A loss. As *ARID1A* deficiency correlates with enhanced tumor mutability, microsatellite instability, high tumor mutation burden, increased programmed death-ligand 1 expression, and T-lymphocyte infiltration, ARID1A-deficient cells can be a potential therapeutic target for immune checkpoint inhibitors that warrants further exploration. In this review, we discuss the role of *ARID1A* in carcinogenesis, its crosstalk with other signaling pathways, and strategies to make ARID1A-deficient cells a potential therapeutic target for patients with cancer.

Keywords: ARID1A, PARP, EZH2, PIK3CA, synthetic lethality

INTRODUCTION

In 1998, it was discovered that mammalian switch/sucrose nonfermenting (SWI/SNF) complexes are associated with cancer.[1] Twenty percent of all cancer types are associated with mutations in the 29 genes that make up the SWI/SNF complex, suggesting that this complex plays a crucial role in carcinogenesis and that genetic disruption of this complex may lead to tumor development.[2–4] Of note, molecular alterations to AT-rich interaction domain 1A (*ARID1A*) are found in approximately 10% of human malignancies, making it the most frequently mutated gene in the complex.[5] *ARID1A* is located on chromosome 1p36.11 and is a region of the genome frequently lost in cancer.[6]

ARID1A mutations are prevalent in various cancers, including gynecologic, gastrointestinal, pancreatic, breast, urothelial, renal cell carcinoma, and non–small cell lung cancer (NSCLC).[7–10] ARID1A contributes to signaling via key molecular pathways, such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), phosphatase and tensin homolog, tumor protein p53, and protein phosphatase 2 scaffold subunit A alpha.[11] In hepatocellular carcinoma, *ARID1A* displays a dual role, with its gain of function triggering tumor initiation and loss promoting tumor progression.[12,13] ARID1A loss predicts poor overall survival in gastric cancer and suggests potential sensitivity to programmed death-1–programmed death-ligand 1 (PD-1–PD-L1) immune checkpoint therapies.[14–16] ARID1A is essential for maintaining the integrity of pancreatic acinar cells and is a barrier to transformation and epithelial-mesenchymal transition in the pancreas.[17] Loss of *ARID1A*, in the presence of the *KRAS* mutation and P53 loss, the most common molecular alterations in pancreatic ductal adenocarcinoma, exacerbates the aggressive behavior of pancreatic ductal adenocarcinomas.[17] In breast cancer, *ARID1A* mutations are linked to cancer aggressiveness, prognosis, epigenetic regulation, and cell invasion through interactions with the *RAB11FIP1* gene.[9,18–23] In renal cell carcinoma, *ARID1A* silencing leads to increased cell proliferation and reduced cell death, with lower expression levels correlating with poor prognosis.[24,25] *ARID1A* mutations are also identified in cancers of unknown primary origin, melanoma, colorectal cancer, and NSCLC.[8,10,26,27] While the role of ARID1A in colorectal cancer remains unclear, its loss

in NSCLC has been linked to poorer survival rates, indicating its potential as a valuable prognostic marker.[28–30] Because *ARID1A* mutations are found in many cancer types and interact with other critical molecular pathways, an understanding of the association between these aberrant signaling pathways could lead to the use of a synthetic lethal strategy in which the simultaneous inactivation or alteration of two genes leads to cell death, while the inactivation or alteration of either gene alone does not.[31,32]

This article aimed to review the role of *ARID1A* in cancer biology, its interaction with other signaling pathways, and the potential therapeutic strategies for targeting ARID1A-deficient cells, including epigenetic drugs and immune checkpoint blockade therapies.

FUNCTIONS OF *ARID1A*

ARID1A regulates gene transcription by directly controlling cancer-related gene expression or indirectly by recruiting or activating histone-modifier enzymes.[33,34] This regulates immunologic response, chromatin arrangement, cell differentiation, and development.[33–35] *ARID1A* may behave as a tumor suppressor or oncogene, depending on the cancer type and stage.

Tumor Suppressor Gene

ARID1A, also known as BAF250a, is a key component of the SWI/SNF complex, belonging to the BRG1-associated factor (BAF) subclass.[36–38] Inactivation or silencing of ARID1A has been associated with dysregulated transcriptional programs, cell cycle control, DNA damage response, checkpoint signaling, regulation of p53 targets, and telomerase activity in various types of tumors.[39,40] ARID1A inhibits carcinogenesis by binding to yes-associated protein and transcriptional co-activator with PDZ-binding motif. This linkage prevents yes-associated protein/transcriptional co-activator with PDZ-binding motif from binding to the TEA-domain transcription factor, which is required to activate downstream target genes responsible for cellular proliferation.[41] The posttranslational acetylation of Lys120 in the DNA-binding domain of p53 regulates apoptosis without impacting cell cycle control. [42] However, *ARID1A* mutations upregulate HDAC6, which deacetylates Lys120 on P53.[43] This process inhibits P53's proapoptotic action and promotes cancer. The upregulation of HDAC6 expression is also one of the consequences of ARID1A inactivation, which leads to deacetylation of Lys120 of P53. This posttranslational modification that is proapoptotic in nature and specifically governs apoptosis without affecting the regulation of the cell cycle. The inhibition of P53K120Ac by *ARID1A* mutations leads to the suppression of the apoptosis-promoting function of P53, thereby facilitating the advancement of cancer. Cell proliferation was observed to be elevated in cell lines carrying wild-type (WT) ARID1A with shRNA-mediated suppression of ARID1A but had no impact on ARID1A-null cells.[44] However, restoring *ARID1A* in cells where it had been removed markedly reduced proliferation, providing more evidence for its function as a tumor-suppressor gene.[44]

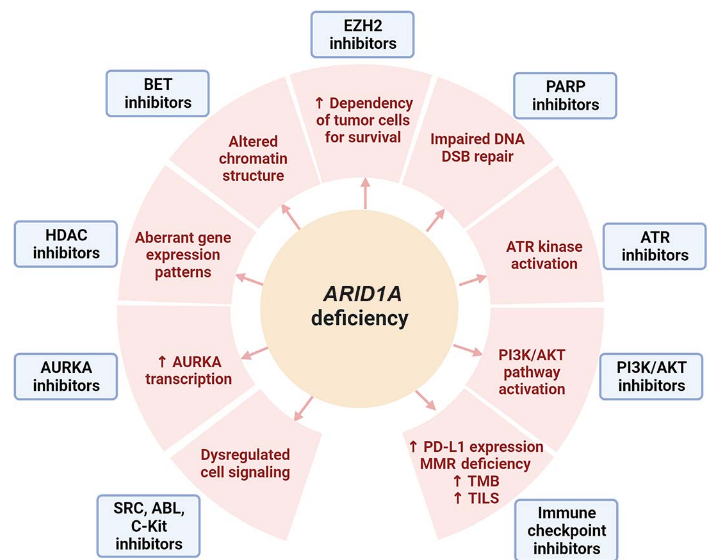

Figure 1. Therapeutic targets in *ARID1A*-deficient malignancies. ABL: Abelson murine leukemia viral oncogene homolog 1; ATR: ataxia telangiectasia and Rad3-related protein; AURKA: Aurora kinase A; BET: bromodomain and extra-terminal motif; C-KIT: KIT proto-oncogene receptor tyrosine kinase; DSB: double-strand break; EZH2: enhancer of zeste homolog 2; HDAC: histone deacetylase 6; PARP: poly (ADP-ribose) polymerase 1; PD-L1: programmed death-ligand 1; SRC: proto-oncogene tyrosine-protein kinase; TILS: tumor-infiltrating lymphocytes; TMB: tumor mutation burden.

Oncogene

ARID1A exhibits context-dependent activity in various cancer models.[39,45] ARID1A has tumor-promoting properties in the early stages of transformation.[46] Hepatocellular carcinoma tumors overexpressed ARID1A in 83% of cases relative to healthy liver tissue, and higher *ARID1A* expression levels have been associated with poorer prognosis.[47,48] WT *ARID1A* was also found in primary endometrial cancer tumors, but metastatic subclones from the same patient harbored detrimental mutations.[11] Loss of *ARID1A* in mice with *APC* mutations slowed the progression of ovarian cancer and delayed the onset of colon cancer.[49] Sun et al[46] suggested the significance of taking stage, dosage, and tissue context into account when assessing ARID1A's role and formulating treatment plans to modify the epigenetic machinery in cancer.

THERAPEUTIC STRATEGIES TO TARGET *ARID1A* MOLECULAR ALTERATIONS IN CANCER

Understanding the biology of *ARID1A* has led to the identification of potential targets for therapeutic interventions to treat *ARID1A* deficient cancers (Fig. 1). Several biomarker-based studies (Table 1) to evaluate cancer therapeutics in *ARID1A*-deficient malignancies are ongoing.

Table 1. Biomarker-based clinical trials to evaluate therapeutics targeting *ARID1A* molecular alterations in cancer

Target	Interventional agent	ClinicalTrials.gov ID	Disease setting	Study phase	Estimated enrollment (*N*)	Study Status
EZH2	Tazemetostat	NCT05023655	Advanced or metastatic solid tumor harboring *ARID1A* mutation (except epithelioid sarcoma)	II	40	Recruiting
PARP	Bevacizumab and/or niraparib	NCT05523440	Recurrent endometrial cancer and/or ovarian cancer with *ARID1A* mutation	II	92	Not yet recruiting
PD-1	Nivolumab	NCT04957615	Metastatic or unresectable solid tumors with *ARID1A* mutation and CXCL13 expression	II	30	Recruiting
PD-1	Nivolumab, Diagnostic laboratory biomarker analysis	NCT04953104	Metastatic urothelial cancer with *ARID1A* mutation and CXCL13 expression	II	30	Not yet recruiting
PD-L1, CTLA-4, HDAC	Durvalumab, tremelimumab, belinostat	NCT05154994	*ARID1A*-mutated metastatic or unresectable, locally advanced urothelial carcinoma	I	9	Recruiting
ATR, PARP	AZD6738 and/or olaparib	NCT04065269	Gynecological cancers with ARID1A loss	II	40	Recruiting
Aurora A	JAB-2485	NCT05490472	Advanced solid tumors, such as ER+ breast cancer, triple-negative breast cancer, *ARID1A*-mutant solid tumors and small cell lung cancer	I /IIa	102	Not yet recruiting
Tyrosine kinase	Dasatinib	NCT02059265	Recurrent or persistent ovarian, fallopian tube, endometrial, or peritoneal cancer	II	35	Active, not recruiting
PARP	Olaparib	NCT04042831	Metastatic biliary tract cancer with aberrant DNA repair gene mutations	II	36	Recruiting
PD-L1, MLH1, MSH2, MSH6, PMS2	Platinum regimens	NCT04872036	Urothelial carcinoma		66	Completed
BET	PLX2853	NCT03297424	Advanced malignancies	Ib	49	Completed
PD-1 Tyrosine kinase	Toripalimub and dasatinib	NCT04284202	*ARID1A*-mutation advanced non–small cell lung cancer	II	30	Unknown

ADID1A: AT-rich interaction domain 1A; ATR: ataxia telangiectasia and Rad3-related protein; BET: bromodomain and extra-terminal motif; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; EZH2: enhancer of zeste homolog 2; HDAC: histone deacetylase 6; PARP: poly (ADP-Ribose) polymerase; PD-1: programmed death-1.

Synthetic Lethality

The application of synthetic lethality as a strategy for developing cancer therapeutics was introduced after the efficacious employment of poly (ADP-ribose) polymerase 1(PARP) inhibitors in patients with ovarian cancer with *BRCA* mutations.[50–54] Synthetic lethal strategy is used to target molecular alterations in gene pairs, which, when simultaneously inactivated, produces cell death.[31,32] This strategy is widely used in cancers with loss-of-function molecular alteration in tumor suppressor genes. As cross-talk between *ARID1A* and other signaling pathways have been implicated in carcinogenesis, numerous therapeutic targets, such as PARP, enhancer of zeste homolog 2 (EZH2), PIK3CA, the glutathione metabolic pathway, and histone deacetylase 6 (HDAC6), have been investigated for the treatment of *ARID1A*-deficient cancers.[55–62]

Ataxia telangiectasia and Rad3-related protein inhibitors

ARID1A regulates the DNA damage response (DDR) mechanism, which detects DNA damage and coordinates cellular responses.[63] The ATR/checkpoint kinase 2 pathway, which is triggered by single-strand breaks (SSBs), and the ataxia telangiectasia-mutated/checkpoint kinase 1 (Chk1) pathway, which is activated by double-strand breaks (DSBs), serve as key DNA damage response regulators.[64] ATR prevents premature mitotic entrance by activating the G2 checkpoint in the presence of DNA damage.[65] Cell division cycle 25C (CDC25C) is an essential component of the G2/M transition, and its activity is regulated by Aurora kinase A (AURKA) and the ARID1A/ATR/CHK1 pathway.[65,66] In colorectal cancer cells with *ARID1A* mutations, interruption of the ARID1A/ATR/CHK1 pathway promotes tumor cell proliferation by increasing CDC25C activity.[65] In models with *ARID1A* mutations associated with elevated levels of checkpoint kinase 2, the inhibition of ATM results in the accumulation of cytosolic DNA and the activation of the cGAS/STING signaling pathway.[67] This process increases the infiltration of T cells into ARID1A-deficient cells, contributing to enhanced immune response.

Subsequently, Williamson et al[68] investigated the therapeutic potential of ATR inhibitors in ARID1A-deficient malignancies. Researchers discovered that ARID1A-deficient cancer cells were more sensitive to ATR inhibitors than their WT counterparts, possibly because of their inability to recover from replication stress.[68] Significantly, ATR inhibition prevented the growth of ARID1A-deficient tumor xenografts in mice with minimal toxicity to healthy tissues.[68] These results demonstrate the potential of ATR inhibitors as a synthetic lethal therapy for tumors with ARID1A deficiency, highlighting the need for further research and development of ATR-targeting molecules for cancer treatment.

PARP inhibitors

PARP1 is best known for detecting DNA SSBs.[69] Activated PARP1 mediates recruitment of the SSB repair (SSBR) machinery for DNA repair. Subsequently, PARP1 dissociates from the site to allow the repair machinery to access DNA. This allowed PARP1 to be released from DNA to another location to initiate the SSBR process.[70] PARP1 has also been implicated in the repair of DNA DSBs by nonhomologous end-joining and alternative end-joining. PARP inhibitors are often used to interfere with DNA repair and induce tumor cell death in homologous recombination–deficient cancers, such as those caused by *BRCA1/2* or other genes in the homologous recombination pathway.[71,72] PARP inhibitors (PARPis) prevent the release of PARP1 from DNA.[73] This PARP trapping prevents the repair machinery from accessing DNA. Thus, PARP trapping suppressed DNA repair and induced cell death.

PARPis are selectively lethal to cells lacking DNA repair components. In *BRCA1/2*-deficient cells, PARPis increase the number of DNA SSBs, which are converted into irreversible DNA DSBs during replication.[74] DNA DSBs trigger cell death through apoptosis when the quantity of DNA damage is too high for repair.[74] It has been suggested that ARID1A-deficient tumors could be vulnerable to PARPis, as *ARID1A* mutations can impair the DNA damage response.[56] PARPi may be useful in treating cancers with *ARID1A* mutations, including breast cancer and cholangiocarcinoma.[75,76] A case report detailed the favorable response to olaparib therapy for almost 13 months in a patient with pancreatic ductal adenocarcinoma who had a detrimental *ARID1A* mutation.[77] Park et al[78] discovered that ARID1A-deficient cells are more vulnerable to PARPi because ionizing radiation–induced DSBs make them rely on PARP-dependent repair pathways. Preclinical studies have shown promising results supporting this hypothesis, but its clinical relevance has not been confirmed yet.[79,80] Ongoing clinical trials are investigating the efficacy of PARPis in ARID1A-deficient tumors, but further research is needed to establish this association.[81,82]

However, *ARID1A* alterations have been linked to a paradoxical clinical scenario in ovarian cancer. Despite being correlated with PARPI sensitivity in preclinical contexts, *ARID1A* mutations appear remarkably to induce resistance to platinum-based chemotherapeutic agents in ovarian cancer.[83–87] To investigate this paradox, one research group examined the complex mechanisms of platinum resistance associated with these mutations.[88] They discovered that the absence of ARID1A protein resulted in a remarkable transcriptional upregulation of multidrug resistance-associated protein 2 (MRP2).[88] MRP2, an efflux pump that facilitates the ATP-dependent active transport of platinum compounds across the cellular membrane, may play a crucial role in promoting platinum resistance.[88,89] Thus, the observed transcriptional shift induced by ARID1A loss may provide a mechanistic

explanation for the platinum resistance observed in patients with ovarian cancer.

EZH2 inhibitors

ARID1A interacts with EZH2 at its carboxyl terminus and suppresses the interferon response mediated by EZH2. Gene expression patterns indicated that EZH2 and ARID1A directly targeted PI3K-interacting protein 1 (*PIK3IP1*), a negative regulator of PI3K-Akt signaling.[56] ARID1A activates *PIK3IP1* expression, whereas EZH2 suppresses *PIK3IP1* expression. The ARID1A protein appears to inhibit EZH2 activity. The loss of ARID1A function consequently results in the suppression of PIK3IP1, which normally inhibits the PI3K pathway. By inhibiting unrestrained EZH2 activity, the PI3K pathway could be rendered ineffective. Tazemetostat, an oral EZH2 inhibitor, demonstrated significant clinical activity in a phase 2 study, with a 69% objective response rate, a median response duration of 10.9 months, and a median progression-free survival (mPFS) of 13.8 months in patients with *EZH2*-mutant relapsed or refractory follicular lymphoma.[90] Tazemetostat showed a respectable safety profile.[90] Bitler et al[56] demonstrated that inhibiting EZH2 decreased cell proliferation and increased cell death in cancer cells with *ARID1A* mutations. Nonetheless, the phase 2 clinical trial (ClinicalTrials.gov identifier: NCT03348631) of Tazemetostat for patients with recurrent ovarian or endometrial cancer is still ongoing.

PI3K/AKT pathway inhibitors

Targeting EZH2 in *ARID1A*-mutated tumors has been associated with the suppression of PI3K/AKT signaling, and studies have shown a linkage between the ARID1A and PI3K pathways in clear cell ovarian cancer.[56,91] Class I PI3K is the most abundant of the four classes of PI3K. It plays a central role in cell survival, growth, proliferation, autophagy, differentiation, and metabolism by converting phospho-inositide 4,5-bisphosphate to phospho-inositide 3,4,5-triphosphate in various cellular membranes.[92–96] Class I PI3K enzymes have a catalytic and regulatory subunit.[97–99] The binding of regulatory subunits to catalytic subunits stabilizes the catalytic subunit proteins and permits the precise regulation of their enzymatic activity.[95] Five regulatory subunit proteins are expressed from the following three genes: *PIK3R1*/p85/p55/p50, *PIK3R2*/p85, and *PIK3R3*/p55.[97–99] Two catalytic subunit proteins are expressed from two genes, *PIK3CA*/p110 and *PIK3CB*/p110.[97–99] Phosphatase and tensin homolog mutations or deletions are frequently observed in various malignancies, activating the PI3K/AKT pathway and facilitating the growth and progression of tumors.[100–102]

Abnormal activation of this pathway, which serves as a downstream signal transducer for several cell surface receptors, is often associated with the development of cancer, such as somatic changes that activate the PI3K/AKT/mTOR pathway are seen in about 30% of patients with bladder cancer.[103] In bladder cancer, the absence of ARID1A activates the PI3K signaling pathway, promoting cell proliferation and survival.[104] Inhibitors of EZH2 and PI3K have proven to be particularly effective against ARID1A-deficient bladder cancer cells, both in vitro and in vivo.[104] Additionally, breast cancer and gastric cancer cells with ARID1A deficiency exhibited enhanced sensitivity to therapy using small molecule inhibitors targeting the PI3K/AKT signaling pathway.[59,105] When the PI3K/AKT pathway was inhibited, pancreatic cancer cells deficient in ARID1A were more sensitive to radiation in vitro due to increased apoptosis and a weakened DNA damage response.[106] In addition, Yang et al[107] discovered that a combination of PARP and PI3K inhibitors may be used to treat gastric cancer. Based on these findings, therapy of ARID1A-deficient cancers with inhibitors of the PI3K signaling pathway shows promise.

Glutathione inhibitors

Gamma-glutamate cysteine ligase (GCL) is a rate-limiting enzyme synthesizing the antioxidant glutathione (GSH).[108] ARID1A collaborates with the BAF complex, BRG1, the catalytic subunit of the SWI/SNF chromatin remodeling complex, RNA polymerase II, and the antioxidant transcription factor NRF2 to create a complex that binds to the transcription start site of SLC7A11.[62] SLC7A11 encodes a subunit of the transporter XCT that imports cystine into the cell in exchange for glutamate.[62,109] Thioredoxin reductase then converts the imported cystine to cysteine to produce thioredoxin.[62] GCL uses both cysteine and glutamate to produce reduced GSH.[62] Thioredoxin and GSH collaborate to control reactive oxygen species (ROS) levels and avert cell death. In ARID1A-deficient cells, however, SLC7A11 is weakly expressed, and XCT levels are low, resulting in a decrease in intracellular cystine, cysteine, and GSH [62] These cells are susceptible to inhibition of thioredoxin reductase and GSH by compounds such as auranofin, APR-246, and buthionine sulphoximine (BSO), which further depletes the antioxidant capacity of ARID1A-deficient cells.[62] Consequently, ROS levels increase indiscriminately, causing cell mortality. ROS can damage cells and induce cell death At high concentrations, whereas cancer cells rely on the antioxidant GSH to combat excessive ROS, making GSH a prospective cancer treatment target.[109–111] Under such conditions, inhibition of GGLC (glutamate-cysteine ligase synthetase catalytic subunit)results in apoptotic cell death in ARID1A-deficient gastric cancer cells.[62,112] Similarly, the GSH inhibitor APR-246 and GGLC inhibitor buthionine sulfoximine (BSO) are effective against ARID1A-deficient ovarian clear cell carcinomas (OCCC) cells.[113] BSO works by depleting cells of cysteine, a key component in GSH synthesis, which can lead to decreased levels of intracellular GSH.[114] This depletion of GSH can sensitize cells to oxidative stress and induce cell death.[115] In preclinical studies, BSO has been shown to have antitumor effects, particularly in combination with other chemotherapeutic agents.[116] Therefore, inhibition of GSH by

synthetic lethal targeting of GCL is a promising therapeutic approach for malignancies lacking ARID1A.

HDAC inhibitors

In preclinical mouse models, *ARID1A* mutations rendered OCCCs sensitive to treatment with pan–histone deacetylase (HDAC) inhibitors, such as suberoylanilide hydroxamic acid.[91] This sensitivity is attributed to the recruitment of HDAC2 to ARID1A/EZH2 target genes such as *PIK3IP1* in *ARID1A*-altered cells, not in *ARID1A* WT cells. As HDAC2, a co-repressor of EZH2, suppresses *PIK3IP1* expression in an *ARID1A* status-dependent manner, inhibition of HDAC2 restores *PIK3IP1* expression in ARID1A-deficient cells. As such, suberoylanilide hydroxamine (or vorinostat), a pan-HDAC inhibitor, suppressed the growth of oncogenic *ARID1A*-mutated OCCCs in orthotopic and genetic mouse models.[91] Similarly, inhibition of HDAC6 with ACY1215 was associated with a reduction in the growth of *ARID1A*-mutated but not WT tumors, indicating that HDAC6 inhibitors selectively promoted apoptosis of *ARID1A*-mutated cells. The above findings provide the rationale for evaluating HDAC6 inhibitors in treating patients with ARID1A-deficient OCCC.

Bromodomain and extra terminal domain inhibitors

In 2018, Berns et al[117] reported an in-depth study investigating the sensitivity of OCCC with *ARID1A* mutations to bromodomain and extra terminal domain (BET) inhibitors. The study identified BRD2, a member of the BET (bromodomain and extra terminal domain) family, as a crucial factor in *ARID1A* mutant cell line sensitivity to BET inhibition.[117] Analyses of numerous OCCC cell lines suggest that cell lines containing *ARID1A* mutations, particularly JQ1 and iBET-762, are more sensitive to BET inhibitors.[117] To validate these in vitro drug sensitivity findings, the researchers used both OCCC cell line xenografts and patient-derived xenograft models derived from OCCC patients.[117] The results of these in vivo models corroborated the in vitro findings, highlighting the therapeutic potential of BET inhibitors for patients with *ARID1A*-mutated malignancies.[117] Swisher et al[118] also investigated the efficacy of the oral BET inhibitor PLX2853 as a monotherapy for *ARID1A*-mutated gynecologic malignancies and in combination with carboplatin for platinum-resistant ovarian cancer in a recent Phase 1b/2a clinical trial. Initial results from the study indicate that both PLX2853 monotherapy and its combination with carboplatin exhibit encouraging antitumor activity and tolerable toxicity profiles.[118] These results emphasize the potential of BET inhibitors, such as PLX2853, as a novel therapeutic strategy for patients with *ARID1A*-mutated gynecologic malignancies and provide evidence for future clinical studies in this patient population.

AURKA inhibitor

ARID1A represses transcription of *AURKA* by occupying the AURKA promoter.[65] Therefore, ARID1A deficiency enhances AURKA transcription, which activates the nuclear localization of cell division cycle 25C to promote the G2/M transition and mitotic entry.[119] Thus, AURKA inhibition in ARID1A-deficient cells induces G2/M arrest and apoptosis.[65] As ARID1A has a synthetic lethal interaction with AURKA in colorectal cancer cells,[65] ARID1A-deficient cells are vulnerable to the action of AURKA inhibitors, warranting further clinical evaluation.

Proto-oncogene tyrosine-protein kinase, Abelson murine leukemia viral oncogene homolog 1, and KIT proto-oncogene receptor tyrosine kinase inhibitors

In preclinical OCCC models, ARID1A deficiency rendered cells sensitive to dasatinib, a proto-oncogene tyrosine-protein kinase, Abelson murine leukemia viral oncogene homolog 1, and KIT proto-oncogene receptor tyrosine kinase inhibitor.[79] Dasatinib showed the highest specific inhibitory effect on *ARID1A*-mutant OCCC cells compared with the *ARID1A* WT cell lines.[79] The sensitivity of *ARID1A*-mutant OCCC cells to dasatinib is attributed to G1–S cell cycle arrest and addiction of *ARID1A*-mutant OCCC cells to YES1, a dasatinib target that is highly expressed in OCCCs.[79] Although these findings are promising for using dasatinib in treating OCCC, limited activity has been observed in clinical trials.[120,121] However, it should be noted that the sample size was limited, and the study did not assess the ARID1A status in these patients.

IMMUNE CHECKPOINT INHIBITORS

ARID1A deficiency is associated with increased PD-L1 expression, mismatch repair (MMR) deficiency, microsatellite instability (MSI), a high mutation load, DDR, tumor microenvironment, and tumor-infiltrating lymphocytes.[122] As all the above factors are considered predictors of response to the immune checkpoint blockade, it has been hypothesized that ARID1A deficiency may serve as a biomarker of response to immune checkpoint inhibitors (ICIs)[14,123,124]

Increased PD-L1 Expression

Increased PD-L1 expression has been observed in ARID1A-deficient ovarian and gastric cancers.[122,125] Increased PD-L1 expression in ARID1A deficiency is attributed to upregulation of the PI3K pathway and DSBs induced by impaired ATR activation in ARID1A-deficient cells.[34,44,126–128] In mouse models, mice bearing ARID1A-deficient ovarian tumors treated with the PD-L1 antibody had reduced tumor burden and significantly prolonged survival compared with the control group.[122] Focusing on the prevalence and impact of *ARID1A*, *ARID1B*, and *ARID2* mutations, Zhu et al[129] analyzed genomic and clinical data of a cohort of patients with NSCLC from The Cancer Genome Atlas and five cohorts of patients from the Memorial Sloan Kettering Cancer Center who underwent ICB treatment. Among patients with an available PD-L1 score, higher PD-L1 scores were reported in patients with an *ARIDA1B* mutation, while

lower PD-L1 scores were reported in patients with *SMARCA4* mutation. In patients with low PD-L1 scores (< 50), the mPFS was significantly longer in patients with any SWI/SNF complex mutation (8.3 months) compared with WT patients (3.7 months; $p = 0.001$). They found that these mutations were associated with a higher mutational burden in the tumor and a better response to ICB therapy.[129] In addition, patients with *ARID1A*, *ARID1B*, or *ARID2* mutations exhibited superior progression-free survival and overall survival compared with patients without such mutations.[129] In 2020, Okamura et al[130] demonstrated the clinical significance of *ARID1A* alterations as a biomarker for predicting positive outcomes in anti-PD-1/PD-L immunotherapy patients. The researchers conducted a comprehensive investigation on a cohort of patients with cancer, including those with gastric, colorectal, and pancreatic cancers.[130] Patients with *ARID1A* mutations (as determined by comprehensive genomic profiling) exhibited substantially prolonged progression-free survival after treatment withICIs targeting the PD-1/PD-L axis.[130] *ARID1A*-inactivating mutations can result in considerable increases in PD-L1 expression, which makes tumors with *ARID1A* deficiency more sensitive to PD-L1 antibodies. Although these findings are compelling, additional research with suitable controls is required to determine the prognostic versus predictive role of *ARID1A* mutations in immune checkpoint blockade.

MMR Deficiency and MSI

MMR is a DNA repair process that primarily corrects mismatched bases to preserve genomic stability.[131] ARID1A activates MMR by enlisting MSH2.[122] Thus, *ARID1A* deletion can lead to MMR deficiency and MSI in several types of cancer, including endometrioid carcinoma of the uterus, gastric cancer, and colorectal cancer.[132–135] It is unclear if ARID1A loss results in a functional deficiency of ssDNA repair by MSH2 or if alterations in ARID1A result from MSI. To this end, a study was conducted in patients with sporadic MSI endometrial cancer (tumors MLH1 expression because of promoter hypermethylation of the *MLH1* gene) and those with germline tumors (Lynch syndrome).[127] Loss of ARID1A expression was reported in 75% of patients with sporadic MSI tumors as against 14% of those with germline tumors, suggesting that ARID1A could be a causal gene rather than a target gene of MSI. Given that MSI can lead to the accumulation of mutations, producing neoantigens, ARID1A-deficient tumors may be sensitive to immune checkpoint blockade.[136,137]

Tumor Mutation Burden and DNA Damage Response

High tumor mutation burden (TMB) is more typical in cancers with mutated *ARID1A* than tumors with WT *ARID1A*.[138] DDR gene alterations are emerging as promising predictive biomarkers for immunotherapy response.[139,140] Patients with high TMB had better immunotherapy responses than those than those who had low TMB, suggesting a potential predictive role for TMB in immunotherapy outcomes.[130,141] Given the correlation between elevated TMB and enhanced immunotherapy response, it is plausible that *ARID1A*-mutated tumors would also exhibit enhanced immunotherapy responses. However, additional research is required to validate this hypothesis and establish a direct link between *ARID1A* mutations, TMB, and immunotherapy outcomes.

Tumor Microenvironment and Tumor-Infiltrating Lymphocytes

ARID1A expression is significantly decreased in tumors with increased levels of tumor-infiltrating lymphocytes (TILs), and biliary tract tumors can be divided into immunologically "hot" and "cold" subgroups.[142] According to accumulating evidence *ARID1A* alterations may serve as prospective biomarkers for predicting an immunotherapy response. After anti–PD-1/PD-L1 immunotherapy, patients with *ARID1A* mutations experienced prolonged progression-free survival, and this association has been observed across several cancer types.[5,130] In addition, *ARID1A* mutations have been linked to elevated immune activity in gastrointestinal cancer.[143] These results suggest a link between ARID1A and the immune response in the tumor microenvironment, which could have significant implications for cancer treatment strategies. Additional research is required to elucidate the precise function of *ARID1A* alterations in shaping the immune response and predicting immunotherapy outcomes in various types of cancer. By comprehending these predictors, researchers and clinicians can better customize immunotherapy approaches for patients with ARID1A-deficiency malignancies, thereby improving treatment outcomes.

OTHER SWITCH/SUCROSE NONFERMENTING (SWI/SNF) MEMBERS

In addition to *ARID1A*, mutations in other SWI/SNF components, such as *ARID1B*, *SMARCA4*, and *SMARCB1*, have been found in several human cancers.[144–148] Genes for components of the SWI/SNF chromatin-remodeling complex, *ARID1A* and its homolog *ARID1B*, have similar functions.[149] However, they are mutually exclusive and differ in kinetics.[150] Their expression profiles during the cell cycle were significantly different. While ARID1A accumulates during the G0 cell cycle phase, its levels continue to decline throughout the remaining phases of the cell cycle; however, ARID1B levels continue to rise even during mitosis.[55,151] Although mutations in *ARID1A* or *ARID1B* in NSCLC are both associated with higher TMB, increased PD-L1 expression, and improved response to ICB, loss of ARID1B destabilizes the SWI/SNF complex and inhibits cell proliferation in *ARID1A*-mutant tumor cell lines.[128,152] *ARID1B* is a

potentially attractive therapeutic target for synthetic lethality in tumors with *ARID1A* mutations.

The frequent co-occurrence of *ARID1A* and *BRG1* mutations in various cancers presents a potential therapeutic opportunity.[153] When ARID1A function is lost, cancer cells may rely more on other SWI/SNF complex functional components, such as BRG1.[149] Inhibiting BRG1 can induce synthetic lethality in ARID1A-deficient cancer cells, selectively eliminating them while sparing normal cells with functional ARID1A.[56,150,154] Developing targeted therapies, like small-molecule inhibitors, to selectively inhibit BRG1 in *ARID1A*-deficient tumors could offer a promising treatment approach for patients with these cancers.[155]

SMARCB1 is another component of SWI/SNF chromatin remodeling complex that promotes stability of ARID1A through enhancer formation and function.[144] Loss of expression of SMARCB1, the hallmark feature of renal medullary carcinomas and rhabdoid tumors, contributes to poor differentiation and aggressive behavior of tumors.[156,157] Re-expression of SMARCB1 significantly increases protein levels for numerous SWI/SNF subunits, particularly the tumor suppressor subunits ARID1A and ARID1B, represses the oncogenic and ferroptosis resistance programs, and promotes epithelial programs.

SUMMARY

ARID1A mutations observed across tumor types result in the loss of ARID1A expression. Loss of function ARID1A alterations negatively impact cellular differentiation, cell cycle, and DNA damage repair. The crosstalk between ARID1A and other signaling pathways allows for the synthetic lethal targeting of ARID1A-deficient cells with inhibitors of the PI3K pathway, PARP, EZH2, and HDACs. Furthermore, the association between ARID1A deficiency and MSI, high TMB, increased PD-L1 expression, and tumor-infiltrating lymphocytes renders them vulnerable to ICI blockade. Large-scale clinical trials are needed to evaluate the agents that target ARID1A.

References

1. Versteege I, Sévenet N, Lange J, et al. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature*. 1998;394:203–206.
2. Helming KC, Wang X, Roberts CWM. Vulnerabilities of mutant SWI/SNF complexes in cancer. *Cancer Cell*. 2014;26:309–317.
3. Kadoch C, Hargreaves DC, Hodges C, et al. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet*. 2013;45:592–601.
4. Shain AH, Pollack JR. The spectrum of SWI/SNF mutations, ubiquitous in human cancers. *PLoS One*. 2013;8: e55119.
5. Jiang T, Chen X, Su C, et al. Pan-cancer analysis of ARID1A alterations as biomarkers for immunotherapy outcomes. *J Cancer*. 2020;11:776–780.
6. Bagchi A, Mills AA. The quest for the 1p36 tumor suppressor. *Cancer Res*. 2008;68:2551.
7. Bailey MH, Tokheim C, Porta-Pardo E, et al. Comprehensive characterization of cancer driver genes and mutations. *Cell*. 2018;173:371–385.e18.
8. Ross JS, Wang K, Gay L, et al. Comprehensive genomic profiling of carcinoma of unknown primary site: new routes to targeted therapies. *JAMA Oncol*. 2015;1:40–49.
9. Zhang X, Sun Q, Shan M, et al. Promoter hypermethylation of ARID1A gene is responsible for its low mRNA expression in many invasive breast cancers. *PLoS One*. 2013;8.
10. Hung YP, Redig A, Hornick JL, Sholl LM. ARID1A mutations and expression loss in non-small cell lung carcinomas: clinicopathologic and molecular analysis. *Mod Pathol*. 2020;33:2256–2268.
11. Gibson WJ, Hoivik EA, Halle MK, et al. The genomic landscape and evolution of endometrial carcinoma progression and abdominopelvic metastasis. *Nat Genet*. 2016;48:848–855.
12. Li H, Wang J, Mor G, Sklar J. A neoplastic gene fusion mimics trans-splicing of RNAs in normal human cells. *Science*. 2008;321:1357–1361.
13. Li M, Zhao H, Zhang X, et al. Inactivating mutations of the chromatin remodeling gene ARID2 in hepatocellular carcinoma. *Nat Genet*. 2011;43:828–829.
14. Yang L, Wei S, Zhao R, et al. Loss of ARID1A expression predicts poor survival prognosis in gastric cancer: a systematic meta-analysis from 14 studies. *Sci Rep*. 2016;6:1–8.
15. Fitzmaurice C, Dicker D, Pain A, et al. The global burden of cancer 2013. *JAMA Oncol*. 2015;1:505–527.
16. Pan QX, Su ZJ, Zhang JH, et al. A comparison of the prognostic value of preoperative inflammation-based scores and TNM stage in patients with gastric cancer. *Onco Targets Ther*. 2015;8:1375–1385.
17. Wang W, Friedland SC, Guo B, et al. ARID1A, a SWI/SNF subunit, is critical to acinar cell homeostasis and regeneration and is a barrier to transformation and epithelial-mesenchymal transition in the pancreas. *Gut*. 2019;68:1245.
18. Cho HD, Lee JE, Jung HY, et al. Loss of tumor suppressor ARID1A protein expression correlates with poor prognosis in patients with primary breast cancer. *J Breast Cancer*. 2015;18:339–346.
19. Mamo A, Cavallone L, Tuzmen S, et al. An integrated genomic approach identifies ARID1A as a candidate tumor-suppressor gene in breast cancer. *Oncogene*. 2012;31:2090–2100.
20. Zhao J, Liu C, Zhao Z. ARID1A: a potential prognostic factor for breast cancer. *Tumor Biol*. 2014;35:4813–4819.
21. ARID1A: a potential prognostic factor for breast cancer. EBSCOhost. Accessed Apr 14, 2023. web.p.ebscohost.com/ehost/pdfviewer/pdfviewer?vid=1&sid=6ac0326a-e02a-4fea-bb43-a4d0725137df%40redis
22. Takao C, Morikawa A, Ohkubo H, et al. Downregulation of ARID1A, a component of the SWI/SNF chromatin remodeling complex, in breast cancer. *J Cancer*. 2017;8:1–8.
23. Wang C, Liu X, Qiu Q, et al. TCRP1 promotes NIH/3T3 cell transformation by over-activating PDK1 and AKT1. *Oncogenesis* 2017;6:e323.
24. Somsuan K, Peerapen P, Boonmark W, et al. ARID1A knockdown triggers epithelial-mesenchymal transition

and carcinogenesis features of renal cells: role in renal cell carcinoma. *FASEB J*. 2019;33:12226–12239.
25. Lichner Z, Scorilas A, White NMA, et al. The chromatin remodeling gene ARID1A is a new prognostic marker in clear cell renal cell carcinoma. *Am J Pathol*. 2013;182:1163–1170.
26. Thielmann CM, Matull J, Roth S, et al. Genetic and clinical characteristics of ARID1A mutated melanoma reveal high tumor mutational load without implications on patient survival. *Cancers (Basel)*. 2022;14.
27. Lee LH, Sadot E, Ivelja S, et al. ARID1A expression in early stage colorectal adenocarcinoma: an exploration of its prognostic significance. *Hum Pathol*. 2016;53:97–104.
28. Erfani M, Hosseini SV, Mokhtari M, et al. Altered ARID1A expression in colorectal cancer. *BMC Cancer*. 2020;20.
29. Wei XL, Wang DS, et al. Clinicopathologic and prognostic relevance of ARID1A protein loss in colorectal cancer. *World J Gastroenterol*. 2014;20:18404–18412.
30. Jang SH, Lee JH, Lee HJ, et al. Loss of ARID1A expression is associated with poor prognosis in non-small cell lung cancer. *Pathol Res Pract*. 2020;216:153156.
31. Kelley R, Ideker T. Systematic interpretation of genetic interactions using protein networks. *Nat Biotechnol*. 2005;23:561–566.
32. Setton J, Zinda M, Riaz N, et al. Synthetic lethality in cancer therapeutics: the next generation. *Cancer Discov*. 2021;11:1626–1635.
33. Li J, Wang W, Zhang Y, et al. Epigenetic driver mutations in ARID1A shape cancer immune phenotype and immunotherapy. *J Clin Invest*. 2020;130:2712–2726.
34. Shen J, Peng Y, Wei L, et al. ARID1A deficiency impairs the DNA damage checkpoint and sensitizes cells to PARP inhibitors. *Cancer Discov*. 2015;5:752–767.
35. Tsai S, Fournier LA, Chang EYC, et al. ARID1A regulates R-loop associated DNA replication stress. *PLoS Genet*. 2021;17:e1009238.
36. Wilson BG, Roberts CWM. SWI/SNF nucleosome remodellers and cancer. *Nat Rev Cancer*. 2011;11:481–492.
37. Nie Z, Xue Y, Yang D, et al. A specificity and targeting subunit of a human SWI/SNF family-related chromatin-remodeling complex. *Mol Cell Biol*. 2000;20:8879–8888.
38. Dechassa ML, Zhang B, Horowitz-Scherer R, et al. Architecture of the SWI/SNF-nucleosome complex. *Mol Cell Biol*. 2008;28:6010–6021.
39. Wu JN, Roberts CWM. ARID1A mutations in cancer: another epigenetic tumor suppressor? *Cancer Discov*. 2013;3:35–43.
40. Pavlidou EN, Balis V. Diagnostic significance and prognostic role of the ARID1A gene in cancer outcomes (review). *World Acad Sci J*. 2020;2:49-64.
41. Chang L, Azzolin L, Di Biagio D, et al. The SWI/SNF complex is a mechanoregulated inhibitor of YAP and TAZ. *Nature*. 2018;563:265–269.
42. Sykes SM, Mellert HS, Holbert MA, et al. Acetylation of the p53 DNA-binding domain regulates apoptosis induction. *Mol Cell*. 2006;24:841–851.
43. Bitler BG, Wu S, Park PH, et al. ARID1A-mutated ovarian cancers depend on HDAC6 activity. *Nat Cell Biol*. 2017;19:962–973.
44. Zang ZJ, Cutcutache I, Poon SL, et al. Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes. *Nat Genet*. 2012;44:570–574.
45. Hohmann AF, Vakoc CR. A rationale to target the SWI/SNF complex for cancer therapy. *Trends Genet*. 2014;30:356–363.
46. Sun X, Wang SC, Wei Y, et al. Arid1a has context-dependent oncogenic and tumor suppressor functions in liver cancer. *Cancer Cell*. 2017;32:574–589.e6.
47. Zhao J, Chen J, Lin H, et al. The clinicopathologic significance of BAF250a (ARID1A) expression in hepatocellular carcinoma. *Pathol Oncol Res*. 2016;22:453–459.
48. Uhlen M, Zhang C, Lee S, et al. A pathology atlas of the human cancer transcriptome. *Science*. 2017;357.
49. Zhai Y, Kuick R, Tipton C, et al. Arid1a inactivation in an APC- and PTEN-defective mouse ovarian cancer model enhances epithelial differentiation and prolongs survival. *J Pathol*. 2016;238:21–30.
50. Hartwell LH, Szankasi P, Roberts CJ, et al. Integrating genetic approaches into the discovery of anticancer drugs. *Science (1979)*. 1997;278:1064–1068.
51. Kaelin WG. Choosing anticancer drug targets in the postgenomic era. *J Clin Invest*. 1999;104:1503–1506.
52. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly (ADP-ribose) polymerase. *Nature*. 2005;434:913–917.
53. Farmer H, McCabe H, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005;434:917–921.
54. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361:123–134.
55. Flores-Alcantar A, Gonzalez-Sandoval A, Escalante-Alcalde D, Lomelí H. Dynamics of expression of ARID1A and ARID1B subunits in mouse embryos and in cells during the cell cycle. *Cell Tissue Res*. 2011;345:137–148.
56. Bitler BG, Aird KM, Garipov A, et al. Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers. *Nat Med*. 2015;21:231–238.
57. Bitler BG, Fatkhutdinov N, Zhang R. Potential therapeutic targets in ARID1A-mutated cancers. *Expert Opin Ther Targets*. 2015;19:1419-–1422.
58. Williamson CT, Miller R, Pemberton HN, et al. ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. *Nat Commun*. 2016;7.
59. Samartzis EP, Gutsche K, Dedes KJ, et al. Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition. *Oncotarget*. 2014;5:5295–5303.
60. Gupta S, Albertson DJ, Parnell TJ, et al. Histone deacetylase inhibition has targeted clinical benefit in ARID1A-mutated advanced urothelial carcinoma. *Mol Cancer Ther*. 2019;18:185–195.
61. Fukumoto T, Fatkhutdinov N, Zundell JA, et al. HDAC6 inhibition synergizes with anti-PD-L1 therapy in arid1a-inactivated ovarian cancer. *Cancer Res*. 2019;79:5482–5489.
62. Ogiwara H, Takahashi K, Sasaki M, et al. Targeting the vulnerability of glutathione metabolism in ARID1A-deficient cancers. *Cancer Cell*. 2019;35:177–190.e8.
63. Hosoya N, Miyagawa K. Targeting DNA damage response in cancer therapy. *Cancer Sci*. 2014;105:370–388.
64. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009;461:1071–1078.

65. Wu C, Lyu J, Yang EJ, et al. Targeting AURKA-CDC25C axis to induce synthetic lethality in ARID1A-deficient colorectal cancer cells. *Nat Commun*. 2018;9:3212.
66. Aasland D, Gotzinger L, Hauck L, et al. Temozolomide induces senescence and repression of DNA repair pathways in glioblastoma cells via activation of ATR-CHK1, p21, and NF-κB. *Cancer Res*. 2019;79:99–113.
67. Wang L, Yang L, Wang C, et al. Inhibition of the ATM/Chk2 axis promotes cGAS/STING signaling in ARID1A-deficient tumors. *J Clin Invest*. 2020;130:5951–5966.
68. Williamson CT, Miller R, Pemberton HN, et al. ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. *Nat Commun*. 2016;7:1–13.
69. Curtin NJ, Szabo C. Poly(ADP-ribose) polymerase inhibition: past, present and future. *Nat Rev Drug Discov*. 2020;19:711–736.
70. Caldecott KW. Protein ADP-ribosylation and the cellular response to DNA strand breaks. *DNA Repair (Amst)*. 2014;19:108–113.
71. Mateo J, Lord CJ, Serra V, et al. A decade of clinical development of PARP inhibitors in perspective. *Ann Oncol*. 2019;30:1437–1447.
72. Slade D. PARP and PARG inhibitors in cancer treatment. *Genes Dev*. 2020;34:360–394.
73. Murai J, Huang SYN, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res*. 2012;72:5588–5599.
74. Chen CC, Feng W, Lim PX, et al. Homology-directed repair and the role of BRCA1, BRCA2, and related proteins in genome integrity and cancer. *Annu Rev Cancer Biol*. 2018;2:313–336.
75. Huang CC, Tsai YF, Liu CY, et al. Prevalence of tumor genomic alterations in homologous recombination repair genes among Taiwanese breast cancers. *Ann Surg Oncol*. 2022;29:3578–3590.
76. Bezrookove V, Patino JM, Nosrati M, et al. Niraparib suppresses cholangiocarcinoma tumor growth by inducing oxidative and replication stress. *Cancers (Basel)*. 2021;13.
77. Zhao XS, Zhou J, Dong L, et al. Durable response to olaparib in pancreatic duct adenocarcinoma with deleterious ARID1A mutation. *Chin Med J (Engl)*. 2019;132:3012–3014.
78. Park YR, Park Y, Park Y, et al. Loss of ARID1A in tumor cells renders selective vulnerability to combined ionizing radiation and PARP inhibitor therapy. *Clin Cancer Res*. 2019;25:5584–5594.
79. Miller RE, Brough R, Bajrami I, et al. Synthetic lethal targeting of ARID1A-mutant ovarian clear cell tumors with dasatinib. *Mol Cancer Ther*. 2016;15:1472–1484.
80. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med*. 2010;363:1532–1543.
81. Mateo J, Lord CJ, Serra V, et al. A decade of clinical development of PARP inhibitors in perspective. *Ann Oncol*. 2019;30:1437–1447.
82. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. *Cancer Discov*. 2015;5:1137–1154.
83. Hu HM, Zhao X, Kaushik S, et al. A quantitative chemotherapy genetic interaction map reveals factors associated with PARP inhibitor resistance. *Cell Rep*. 2018;23:918–929.
84. Luo Q, Wu X, Zhang Y, et al. ARID1A ablation leads to multiple drug resistance in ovarian cancer via transcriptional activation of MRP2. *Cancer Lett*. 2018;427:9–17.
85. Katagiri A, Nakayama K, Rahman MT, et al. Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma. *Mod Pathol*. 2012;25:282–288.
86. Shen J, Peng Y, Wei L, et al. ARID1A deficiency impairs the DNA damage checkpoint and sensitizes cells to PARP inhibitors. *Cancer Discov*. 2015;5:752–767.
87. Park Y, Chui MH, Rahmanto YS, et al. Loss of ARID1A in tumor cells renders selective vulnerability to combined ionizing radiation and PARP inhibitor therapy. *Clin Cancer Res*. 2019;25:5584–5593.
88. Luo Q, Wu X, Zhang Y, et al. ARID1A ablation leads to multiple drug resistance in ovarian cancer via transcriptional activation of MRP2. *Cancer Lett*. 2018;427:9–17.
89. Myint K, Li Y, Paxton J, McKeage M. Multidrug resistance-associated protein 2 (MRP2) Mediated transport of oxaliplatin-derived platinum in membrane vesicles. *PLoS One*. 2015;10:e0130727.
90. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2020;21:1433–1442.
91. Fukumoto T, Park PH, Wu S, et al. Repurposing pan-HDAC inhibitors for ARID1A-mutated ovarian cancer. *Cell Rep*. 2018;22:3393–3400.
92. Balla T. Phosphoinositides: tiny lipids with giant impact on cell regulation. *Physiol Rev*. 2013;93:1019–1137.
93. Brachmann SM, Yballe CM, Innocenti M, et al. Role of phosphoinositide 3-kinase regulatory isoforms in development and actin rearrangement. *Mol Cell Biol*. 2005;25:2593–2606.
94. Burke JE. Structural basis for regulation of phosphoinositide kinases and their involvement in human disease. *Mol Cell*. 2018;71:653–673.
95. Ito Y, Hart JR, Vogt PK. Isoform-specific activities of the regulatory subunits of phosphatidylinositol 3-kinases - potentially novel therapeutic targets. *Expert Opin Ther Targets*. 2018;22:869–877.
96. Raghu P, Joseph A, Krishnan H, et al. Phosphoinositides: regulators of nervous system function in health and disease. *Front Mol Neurosci*. 2019;12. DOI: 10.3389/fnmol.2019.00208.
97. Fruman DA, Chiu H, Hopkins BD, et al. The PI3K pathway in human disease. *Cell*. 2017;170:605–635.
98. Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, Bilanges B. The emerging mechanisms of isoform-specific PI3K signalling. *Nat Rev Mol Cell Biol*. 2010;11:329–341.
99. Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-kinase, growth disorders, and cancer. *N Engl J Med*. 2018;379:2052–2062.
100. Flinn IW, O'Brien S, Kahl B, et al. Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. *Blood*. 2018;131:877–887.
101. Krop IE, Mayer IA, Ganju V, et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2016;17:811–821.

102. Dolly SO, Wagner AJ, Bendell JC, et al. Phase I study of apitolisib (GDC-0980), dual phosphatidylinositol-3-kinase and mammalian target of rapamycin kinase inhibitor, in patients with advanced solid tumors. *Clin Cancer Res*. 2016;22:2874–2884.
103. Zhu S, Ma AH, Zhu Z, et al. Synergistic antitumor activity of pan-PI3K inhibition and immune checkpoint blockade in bladder cancer. *J Immunother Cancer*. 2021;9: e002917.
104. Rehman H, Chandrashekar DS, Balabhadrapatruni C, et al. ARID1A-deficient bladder cancer is dependent on PI3K signaling and sensitive to EZH2 and PI3K inhibitors. *JCI Insight*. 2022;7:e155899.
105. Lee D, Yu EJ, Ham IH, et al. AKT inhibition is an effective treatment strategy in ARID1A-deficient gastric cancer cells. *Onco Targets Ther*. 2017;10:4153–4159.
106. Yang L, Yang G, Ding Y, et al. Inhibition of PI3K/AKT signaling pathway radiosensitizes pancreatic cancer cells with ARID1A deficiency in vitro. *J Cancer*. 2018;9:890–900.
107. Yang L, Yang G, Ding Y, et al. Combined treatment with PI3K inhibitor BKM120 and PARP inhibitor olaparib is effective in inhibiting the gastric cancer cells with ARID1A deficiency. *Oncol Rep*. 2018;40:479–487.
108. Lu SC. Glutathione synthesis. *Biochim Biophys Acta*. 2013;1830:3143–3153.
109. Harris IS, Treloar AE, Inoue S, et al. Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. *Cancer Cell*. 2015;27:211–222.
110. Liu T, Sun L, Zhang Y, et al. Imbalanced GSH/ROS and sequential cell death. *J Biochem Mol Toxicol*. 2022;36.
111. Niu B, Liao K, Zhou Y, et al. Application of glutathione depletion in cancer therapy: enhanced ROS-based therapy, ferroptosis, and chemotherapy. *Biomaterials*. 2021;277.
112. Sasaki M, Chiwaki F, Kuroda T, et al. Efficacy of glutathione inhibitors for the treatment of ARID1A-deficient diffuse-type gastric cancers. *Biochem Biophys Res Commun*. 2020;522:342–347.
113. Kuroda T, Kohno T. Precision medicine for ovarian clear cell carcinoma based on gene alterations. *Int J Clin Oncol*. 2020;25:419–424.
114. Meister A. Glutathione biosynthesis and its inhibition. *Methods Enzymol*. 1995;252:26–30.
115. Franco R, Cidlowski JA. Apoptosis and glutathione: beyond an antioxidant. *Cell Death Differ*. 2009;16:1303–1314.
116. Bailey HH. L-S,R-buthionine sulfoximine: historical development and clinical issues. *Chem Biol Interact*. 1998;111-112:239–254.
117. Berns K, Caumanns JJ, Hijmans EM, et al. ARID1A mutation sensitizes most ovarian clear cell carcinomas to BET inhibitors. *Oncogene*. 2018;37:4611–4625.
118. Swisher EM, Duska LR, Hamilton EP, et al. Abstract CT160: Phase 1b/2a clinical trial of the oral BET inhibitor PLX2853 as monotherapy for ARID1A mutated gynecologic cancers and in combination with carboplatin for platinum resistant ovarian cance. *Cancer Res*. 2023;83(8_Supplement):CT160–CT160.
119. Toyoshima-Morimoto F, Taniguchi E, Nishida E. Plk1 promotes nuclear translocation of human Cdc25C during prophase. *EMBO Rep*. 2002;3:341–348.
120. Secord AA, Teoh DK, Barry WT, et al. A phase I trial of dasatinib, an SRC-family kinase inhibitor, in combination with paclitaxel and carboplatin in patients with advanced or recurrent ovarian cancer. *Clin Cancer Res*. 2012;18:5489–5498.
121. Schilder RJ, Brady WE, Lankes HA, et al. Phase II evaluation of dasatinib in the treatment of recurrent or persistent epithelial ovarian or primary peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;127:70–74.
122. Shen J, Ju Z, Zhao W, et al. ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. *Nat Med*. 2018;24:556–562.
123. Hu G, Tu W, Yang L, et al. ARID1A deficiency and immune checkpoint blockade therapy: From mechanisms to clinical application. *Cancer Lett*. 2020;473:148–155.
124. Luchini C, Veronese N, Solmi M, et al. Prognostic role and implications of mutation status of tumor suppressor gene ARID1A in cancer: a systematic review and meta-analysis. *Oncotarget*. 2015;6:39088–39097.
125. Kim YB, Ahn JM, Bae WJ, Sung CO, Lee D. Functional loss of ARID1A is tightly associated with high PD-L1 expression in gastric cancer. *Int J Cancer*. 2019;145:916–926.
126. Liang H, Cheung LWT, Li J, et al. Whole-exome sequencing combined with functional genomics reveals novel candidate driver cancer genes in endometrial cancer. *Genome Res*. 2012;22:2120–2129.
127. Bosse T, Ter Haar NT, Seeber LM, et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer. *Mod Pathol*. 2013;26:1525–1535.
128. Yamamoto S, Tsuda H, Takano M, et al. PIK3CA mutations and loss of ARID1A protein expression are early events in the development of cystic ovarian clear cell adenocarcinoma. *Virchows Arch*. 2012;460:77–87.
129. Zhu G, Shi R, Li Y, et al. ARID1A, ARID1B, and ARID2 mutations serve as potential biomarkers for immune checkpoint blockade in patients with non-small cell lung cancer. *Front Immunol*. 2021;12.
130. Okamura R, Kato S, Lee S, et al. ARID1A alterations function as a biomarker for longer progression-free survival after anti-PD-1/PD-L1 immunotherapy. *J Immunother Cancer*. 2020;8:e000438.
131. De'angelis GL, Bottarelli L, Azzoni C, et al. Microsatellite instability in colorectal cancer. *Acta Biomed*. 2018;89:97–101.
132. Wang K, Kan J, Yuen ST, et al. Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. *Nat Genet*. 2011;43:1219–1223.
133. Abe H, Maeda D, Hino R, et al. ARID1A expression loss in gastric cancer: pathway-dependent roles with and without Epstein-Barr virus infection and microsatellite instability. *Virchows Arch*. 2012;461:367–377.
134. Allo G, Bernardini MQ, Wu RC, et al. ARID1A loss correlates with mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas. *Mod Pathol*. 2014;27:255–261.
135. Muzny DM, Bainbridge MN, Chang K, et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;487:330–337.

136. Ganesh K, Stadler ZK, Cercek A, et al. Immunotherapy in colorectal cancer: rationale, challenges and potential. *Nat Rev Gastroenterol Hepatol*. 2019;16:361–375.
137. Chang L, Chang M, Chang HM, Chang F. Microsatellite instability: a predictive biomarker for cancer immunotherapy. *Appl Immunohistochem Mol Morphol*. 2018;26: e15–e21.
138. Li L, Rao X, Wen Z, et al. Implications of driver genes associated with a high tumor mutation burden identified using next-generation sequencing on immunotherapy in hepatocellular carcinoma. *Oncol Lett*. 2020;19:2739–2748.
139. Brown JS, O'Carrigan B, Jackson SP, Yap TA. Targeting DNA repair in cancer: beyond PARP inhibitors. *Cancer Discov*. 2017;7:20–37.
140. Yap TA, Plummer R, Azad NS, Helleday T. The DNA damaging revolution: PARP inhibitors and beyond. *Am Soc Clin Oncol Educ Book*. 2019;39:18–195.
141. Rizzo A, Ricci AD, Brandi G. PD-L1, TMB, MSI, and other predictors of response to immune checkpoint inhibitors in biliary tract cancer. *Cancers (Basel)*. 2021;13:1–11.
142. Wang L, Qu J, Zhou N, et al. Effect and biomarker of immune checkpoint blockade therapy for ARID1A deficiency cancers. *Biomed Pharmacother*. 2020;130:110626.
143. Li L, Li M, Jiang Z, Wang X. ARID1A mutations are associated with increased immune activity in gastrointestinal cancer. *Cells*. 2019;8:678.
144. Wang X, Lee RS, Alver BH, et al. SMARCB1-mediated SWI/SNF complex function is essential for enhancer regulation. *Nat Genet*. 2017;49:289–295.
145. Kohashi K, Oda Y. Oncogenic roles of SMARCB1/INI1 and its deficient tumors. *Cancer Sci*. 2017;108:547–552.
146. Xia W, Nagase S, Montia AG, et al. BAF180 is a critical regulator of p21 induction and a tumor suppressor mutated in breast cancer. *Cancer Res*. 2008;68:1667–1674.
147. Pan D, Kobayashi A, Jiang P, et al. A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing. *Science*. 2018;359:770–775.
148. Yu X, Zheng L, Shen J. BRD7: a novel tumor suppressor gene in different cancers. *AM J Transl Res*. 2016;8:742–748.
149. Helming KC, Wang X, Wilson BG, et al. ARID1B is a specific vulnerability in ARID1A-mutant cancers. *Nat Med*. 2014;20:251–254.
150. Wilson BG, Roberts CWM. SWI/SNF nucleosome remodellers and cancer. *Nat Rev Cancer*. 2011;11:481–492.
151. Nagl NG, Patsialou A, Haines DS, et al. The p270 (ARID1A/SMARCF1) subunit of mammalian SWI/SNF-related complexes is essential for normal cell cycle arrest. *Cancer Res*. 2005;65:9236–9244.
152. Sun D, Tian L, Zhu Y, et al. Subunits of ARID1 serve as novel biomarkers for the sensitivity to immune checkpoint inhibitors and prognosis of advanced non-small cell lung cancer. *Mol Med*. 2020;26:78.
153. Jones S, Wang TL, Shih IM, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. *Science*. 2010;330:228.
154. Oike T, Ogiwara H, Nakano T, Yokota J, Kohno T. Inactivating mutations in SWI/SNF chromatin remodeling genes in human cancer. *Jpn J Clin Oncol*. 2013;43:849–855.
155. Kim KH, Roberts CWM. Targeting EZH2 in cancer. *Nat Med*. 2016;22:128–134.
156. Elliott A, Bruner E. Renal medullary carcinoma. *Arch Pathol Lab Med*. 2019;143:1556–1561.
157. Vokshi BH, Davidson G, Tawanaie Pour Sedehi N, et al. SMARCB1 regulates a TFCP2L1-MYC transcriptional switch promoting renal medullary carcinoma transformation and ferroptosis resistance. *Nat Commun*. 2023;14:3034.