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Review Article

Targeting the alterations of ARID1A in pancreatic cancer: tumorigenesis, prediction of treatment, and prognostic value

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Abstract: The chromatin remodeling gene AT-rich interactive domain 1A (*ARID1A*), encoding a subunit of the switch/sucrose non-fermentable (SWI/SNF) complex, is one of the most frequently mutated chromatin regulators across a broad spectrum of cancers. Most of the *ARID1A* alterations are inactivating, leading to the loss or reduced expression of the protein. Recently, *ARID1A* has been demonstrated as a tumor suppressor gene in pancreatic ductal adenocarcinoma (PDAC), as its inactive alterations attribute to carcinogenesis. Importantly, *ARID1A* alterations are revealed as predictive biomarkers for the selection of targeted therapy and immune checkpoint blockade (ICB) therapy. In PDAC, the application of *ARID1A* alterations in stratifying patients for precise treatment has also been widely explored in preclinical and early clinic studies with encouraging preliminary results. Furthermore, the prognostic value of *ARID1A* mutations in PDAC has been suggested by various studies. In this review, we focus on the functions of *ARID1A* alterations in PDAC, particularly their functions during carcinogenesis and their predictive value in treatment selection and prognosis, to provide a comprehensive overview on our current understanding of *ARID1A* alterations in PDAC.

Keywords: AT-rich interactive domain 1A (ARID1A), pancreatic cancer, tumorigenesis, biomarker, prognosis

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a type of cancer with one of the highest mortality rates. It ranks sixth as the leading cause of cancer-related death in China, fourth in the United States, and is may be as high as second by 2030 [1-3]. Approximately 80% of patients diagnosed with PDAC are not suitable for surgical resection due to local invasion and distal metastasis. Unfortunately, PDAC responds poorly to chemotherapy and radiotherapy. Thus, only about 8% of PDAC patients survive over 5 years, which has been barely improved over the past five decades despite vigorous efforts in the field [3].

Due to the advanced stage upon diagnosis, many PDAC patients are not eligible for surgical resection or local radiotherapy. Currently, the standard first-line treatment for PDAC is chemotherapy with FOLFIRONOX (a combination of 5FU, leucovorin, irinotecan, and oxaliplatin) or gemcitabine plus albumin-bound (nab) paciltaxel [4]. Since the clinical outcome is still poor, current studies are focusing on uncovering personalized targeted therapy and improving the efficacy of immunotherapy for patients with PDAC.

For targeted therapy, erlotinib, a potent inhibitor of the tyrosine kinase activity of human epidermal growth factor receptor (EGFR), is the first targeted drug approved to treat PDAC. However, it is rarely used in clinics due to the limited benefit in progression-free survival (PFS) by only two weeks [5]. In 2019, the POLO (Pancreas Cancer Olaparib Ongoing) study demonstrated

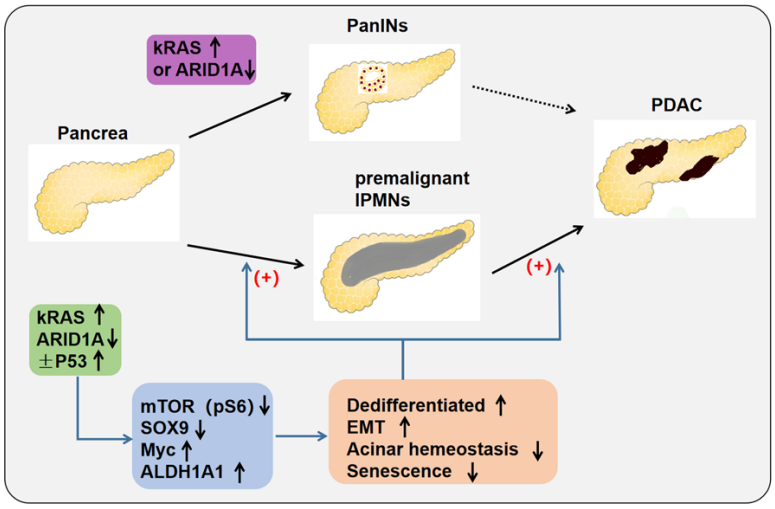

Figure 1. The inactive alterations of *ARID1A* attribute to the carcinogenesis of PDAC. PanINs, pancreatic intraepithelial neoplasias; IPMNs, intraductal papillary mucinous neoplasms; PDAC, pancreatic ductal adenocarcinoma; EMT, epithelial-mesenchymal transition.

that olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, significantly improved PFS by 3.6 months compared with placebo among PDAC patients harboring *BRCA1/2* variants [6], which led to its prompt approval by the FDA. Nevertheless, no significant differences in overall survival (OS), second PFS, or the objective response rate (ORR) were observed between the olaparib-treated and placebo groups. Moreover, gene profiling has indicated that only ~7% of PDAC patients harbor germline *BRCA* mutations, suggesting that only a small subgroup of patients could benefit from PARP inhibitors.

During the past decades, immune checkpoint inhibitors (ICIs), including anti-programmed death receptor-1/programmed death receptor-ligand 1 (PD-1/PD-L1) agents and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agents, have been approved to treat a variety of cancers, which have reshaped the landscape of cancer treatment [7]. However, clinical trials demonstrate that most PDAC patients do not respond to ICIs [8].

Through large-scale next generation sequencing (NGS), the chromatin remodeling gene AT-rich interactive domain containing protein 1A (*ARID1A*) was discovered as one of the most frequently mutated epigenetic regulators in many types of human cancers [9], including ovarian clear cell carcinoma (varying from 40% to 57%) [10], liver cancer (varying from 10% to 17%) [11], gastric cancer (varying from 18% to 27%) [12] and pancreatic cancer (varying from 6% to 10%) [13]. *ARID1A* encodes an essential noncatalytic subunit of the switch/sucrose nonfermentable (SWI/SNF) complex, an ATP-dependent chromatin remodeling complex that controls nucleosome topology and DNA access and ultimately regulates DNA replication, transcription, and DNA damage repair [14, 15].

The majority of *ARID1A* alterations, including nonsense and frameshift mutations, are inactivating and usually lead to the loss or reduced expression of the protein [10, 16, 17]. Recent reports have revealed the pivotal roles of *ARID1A* alterations during the carcinogenesis and progression of PDAC [18-20]. Moreover, in PDAC, the predictive value of ARID1A in precise cancer treatment, such as targeted therapy and immune checkpoint blockade (ICB) therapy, and in prognosis have also been investigated.

Herein, we comprehensively review the roles of *ARID1A* alterations in PDAC, particularly, their functions during tumorigenesis and their predictive values in treatment selection and prognosis, from mechanisms to potential clinical applications. Better understanding the roles of ARID1A in PDAC might help improve the outcome of patients with PDAC, which is a critical unmet medical need.

ARID1A alterations attribute to the carcinogenesis of pancreatic cancer

ARID1A is postulated as a tumor suppressor gene in human pancreatic cancer, owing to its recurrent loss-of-function mutations. The direct evidence for the tumor suppression function of ARID1A were demonstrated by several recent studies (**Figure 1**).

One study was performed using genetically engineered mouse (GEM) models with pancreatic expression of activated *KRAS* and/or disruption of *ARID1A* [18]. Mice with pancreatic

expression of activated *KRAS* only developed pancreatic intraepithelial neoplasias (PanINs), whereas mice with activated *KRAS* cooperated with disrupted *ARID1A* developed premalignant intraductal papillary mucinous neoplasms (IPMNs) and PDAC through reducing the activity of the mTOR pathway, suggesting the involvement of ARID1A in carcinogenesis. In addition, tissues from patients with IPMNs and PDAC exhibited lower expression of *ARID1A* [18]. The study concluded that, ARID1A was able to inhibit the formation of PDAC from IPMNs in the presence of activated *KRAS*.

A similar study also reported that *ARID1A* restrained oncogenic *KRAS*-driven formation of IPMNs [19]. Mechanically, *ARID1A* played a key role in pancreatic acinar homeostasis, the response to injury, and inhibition of epithelial-mesenchymal transition (EMT). Furthermore, *ARID1A* loss in the context of mutant *KRAS* and *P53* led to shorter tumor latency, forming poorly differentiated tumors with more mesenchymal features, and conferring high migratory/invasive and stem-like properties [19].

Consistently, Wang *et al.* demonstrated that *ARID1A* loss concurrent with *KRAS* activation accelerated the development of cysts and PDAC formation [20]. Pancreas-specific *ARID1A* loss in mice was sufficient to induce inflammation, PanIN and mucinous cysts. RNA sequencing showed that *ARID1A* knockdown increased MYC activity and protein translation, which appeared to be associated with the function of *ARID1A* in suppressing pancreatic neoplasia.

Furthermore, attenuating *KRAS*-induced senescence is another driving mechanism of *ARID1A* deficiency in promoting PDAC [21]. *ARID1A* loss activates the expression of aldehyde dehydrogenase 1 family member A1 (*ALDH1A1*), which, in turn, attenuates *KRAS*-induced senescence and promotes the development of PDAC [22].

Paradoxically, a recent study demonstrated that the expression of *ARID1A* was critical during the early stages of pancreatic tumorigenesis in mouse models, which was evidenced by lower proliferation and higher apoptosis staining detected in "KAC" (Ptf1a-Cre; $Kras^{G12D}$; $Arid1a^{f/f}$) mice than in "KC" (Ptf1a-Cre; $Kras^{G12D}$) mice. A possible explanation of this observation is that a multitude of "escaper" mechanisms drive tumor progression in PDAC, which arises in the setting of *ARID1A* loss [22]. Nevertheless, thorough studies are needed to validate this hypothesis.

Collectively, the alterations of *ARID1A* promote the carcinogenesis of PDAC through multiple molecular mechanisms. Furthermore, the functions of *ARID1A* in carcinogenesis vary during different stages of tumor formation, progression, and vary in different contexts of combined gene alterations as well.

ARID1A alterations predict the sensitivity of pancreatic cancer to precise treatment

Targeted therapy

Although *ARID1A* is among the most frequently mutated genes in cancers, there are no approved therapies targeting the alterations of *ARID1A*. As the majority of *ARID1A* mutations are inactive and lead to low or loss of expression of the protein, it is difficult to directly recover the function of *ARID1A*, which makes it a poor therapeutic target [23]. In this situation, the strategy of synthetic lethality is usually applied, based on the concept that concurrent inhibition of two genes that have collaborative biological functions can lead to a lethal effect. Synthetic lethality has been demonstrated as a useful strategy to selectively target tumor cells with specific intrinsic deficiency, for example, the application of PARP inhibitors in tumors with *BRCA1/2* mutations [24].

Until now, several targets have been reported to have synthetic lethality with *ARID1A* deficiency in tumors, including PARP [25], EZH2 [26], PI3K/Akt/mTOR, ATR, and HDAC6 (**Figure 2**) [9, 27]. Some of them have already been tested in PDAC (**Table 1**).

PARP inhibitors

The strategy of synthetic lethality has been applied successfully using olaparib in PDAC harboring *BRCA* mutations in the phase III POLO trial [6]. Due to the low incidence of *BRCA* mutations, the concept of "BRCAness" was introduced to identify phenotypic changes besides *BRCA* mutations that may also cause PARP inhibitor susceptibility [28].

Initially, Shen *et al.* demonstrated that ARID1A functioned in the repair of DNA double-strand breaks (DSBs) and sensitized cancer cells to PARP inhibitors. Mutations in *ARID1A* usually

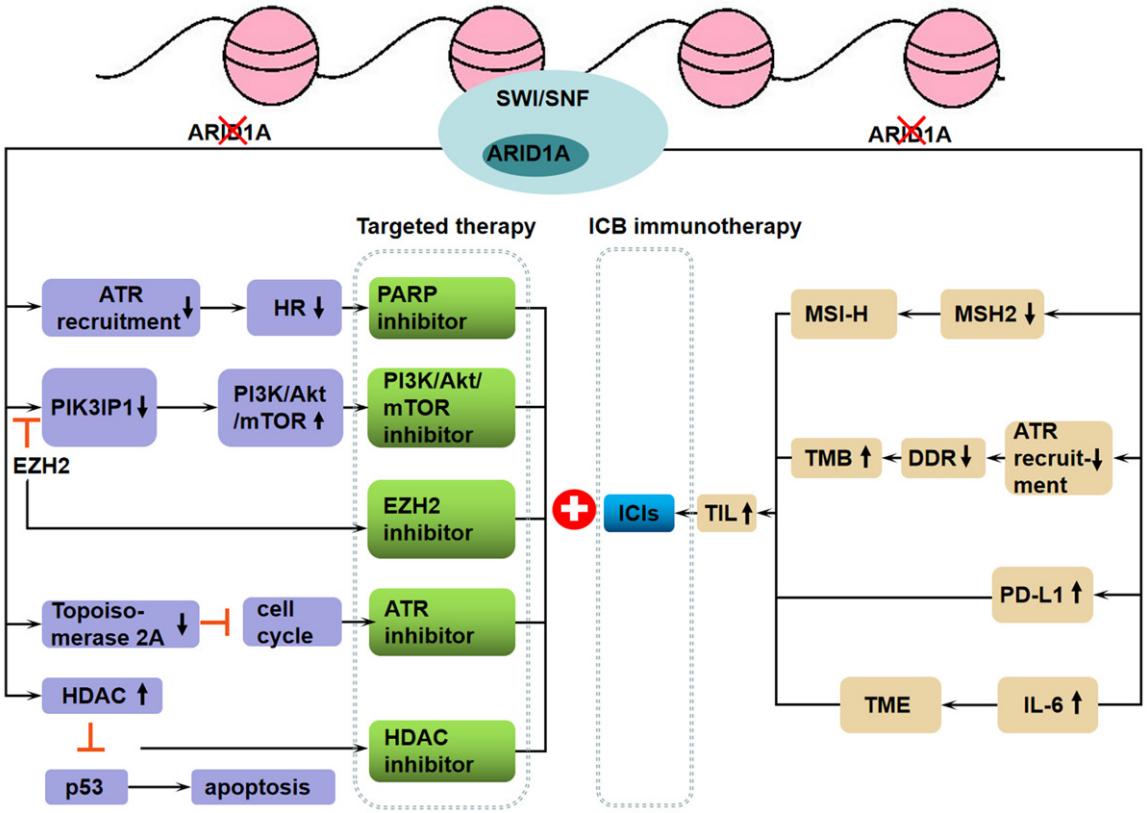

Figure 2. Mechanisms of *ARID1A* alterations contributing to sensitivity of pancreatic cancer to targeted agents, ICB immunotherapy, and the combinations. HR, homologous recombination; DDR, DNA damage Repair; MSI-H, microsatellite instability-high; PARP, poly ADP-ribose polymerase; ICB, immune checkpoint blockade; TMB, tumor mutation burden; TME, tumor microenvironment; ICIs, immune checkpoint inhibitors.

cause homologous recombination (HR) deficiency, which mimics the phenotypic changes of *BRCA* mutations and is associated with the response to PARP inhibitors. Currently, a clinical trial (NCT04042831) is ongoing to evaluate the efficacy of olaparib in treating patients with metastatic biliary tract cancer harboring aberrant DNA damage repair (DDR) gene mutations, including *ARID1A* mutation.

However, it is still unclear whether synthetic lethality between *ARID1A* mutations and PARP inhibitors exists in PDAC. Recently, a study explored the effect of PARP inhibitor olaparib in treating PDAC patients harboring mutations of DDR genes other than germline *BRCA* alterations [29]. From two phase 2 clinical trials, a total of 46 pretreated patients with advanced PDAC who received olaparib were analyzed. Among them, 24 patients had the DDR genetic alterations, including *ATM* (n = 14), *ARID1A* (n = 3), *PALB2* (n = 2), *FANCB* (n = 2), *PTEN* (n = 1), *RAD51* (n = 1), *CCNE* (n = 1), and *BRCA* somatic (n = 1). The results revealed that olaparib increased the median PFS more significantly in PDAC patients with DDR genetic alterations than in the others (5.7 months *vs.* 3.7 months, p = .008), and the estimated median OS was also improved (13.6 months *vs.* 9.9 months). These data indicate that olaparib is therapeutically effective and safe for PDAC patients with specific DDR genetic mutations other than germline *BRCA* alterations. Since *ARID1A* is included in the DDR genes in this study, *ARID1A* mutations may also confer vulnerability to PARP inhibitors in PDAC.

Interestingly, a recent case report described a patient with PDAC harboring mutation of *ARID1A* (c.3979C>T, p.Q1327*) who achieved an objective response to therapies including olaparib, which lasted for more than 13.0 months [30]. Further randomized clinical trials are warranted to evaluate the therapeutic effect of PARP inhibitors in PDAC patients harboring ARID1A deficiency.

Table 1. Studies for the treatment of pancreatic cancer (or solid tumors including PDAC) with *ARID1A*-alterations

Study types	Cancer types	Molecular characteristics	Intervention	Results
Clinical trial (Javle et al. 2021)	PDAC	DDR genetic alterations, including *ARID1A, ATM*, and etc. other than germline *BRCA* variants	Olaparib (PARP inhibitor)	PFS↑ OS↑
Case report (Zhao et al. 2019)	PDAC	Deleterious ARID1A mutation (c.3979C>T, p.Q1327*)	olaparib-based therapy	PFS > 13M OS↑
A study *in vitro* (Yang et al. 2018)	PDAC cells	ARID1A deficiency	PI3K/Akt inhibition combined with IR	Cell death↑
Clinical trial Phase 2 (NCT05023655)	Solid tumors (including PDAC)	ARID1A deficiency	Tazemetostat (EZH2 inhibitor)	Not available now
Clinical trial (Okamura R et al. 2020)	Solid tumors (including PDAC)	*ARID1A* alteration	ICB	PFS↑ (11M *vs.* 4M) OS↑ (31M *vs.* 20M)
Clinical trial (NCT02478931) (Botta et al. 2021)	PDAC	SWI/SNF alterations (*ARID1A* 77%)	ICB	ORR 89% PFS 9M OS 15M
Clinical trial (NCT03842228)	Solid tumors (including PDAC)	25 gene alterations (including *ARID1A*)	Olaparib Copanlisib (PI3K inhibitor) Durvalumab (An anti-PD-L1 antibody)	Not available now

PDAC, pancreatic ductal adenocarcinoma; DDR, DNA damage repair; PFS, progression-free survival; OS, overall survival; IR, iron radiation; ICB, immune checkpoint blockade; M, month.

Furthermore, in ARID1A-deficient cancer cells, ionizing radiation (IR), which caused exogenous DNA damage, attributed to the additional sensitivity to PARP inhibitors [31]. Low-dose IR combined with olaparib significantly improved the antitumor efficacy in mice bearing ARID1A-deficient tumors and resulted in long-term remission [31]. Nevertheless, these results need to be validated in PDAC.

Inhibition of the PI3K/Akt/mTOR pathway

Activation of the PI3K/Akt/mTOR pathway is common across cancer types and has long been considered as an oncogenic pathway [32, 33]. The concurrence of *ARID1A* inactivation and *PIK3CA* activation has been reported in ovarian clear cell carcinoma (OCCC) [34, 35], nasopharyngeal carcinoma, and gastric cancer [36, 37]. One underlying mechanism of this concurrence is that ARID1A binds to the PI3K-interacting protein 1 (*PIK3IP1*) promoter to activate the expression of *PIK3IP1*, so that *ARID1A* inactivation downregulates *PIK3IP1* expression, thereby leading to the activation of the PI3K/Akt/mTOR pathway [26]. Therefore, inhibitors of the PI3K/Akt pathway are potentially effective against ARID1A-deficient cancers [38].

A recent study suggested that targeting the mTOR pathway could be a new strategy for gastric adenocarcinoma with deficient ARID1A [39]. Mechanically, alterations of *ARID1A* activate the pS6 and SOX9 axis and promote the progression of gastric cancer, which can be inhibited by mTOR inhibitors.

In PDAC, our team reported that knockdown of *ARID1A* activated the PI3K/Akt signaling pathway and led to aggravated resistance to IR [40]. Accordingly, inhibitors of PI3K or Akt improved the sensitivity of ARID1A-deficient pancreatic cancer cells to IR *in vitro.* These results suggest that the PI3K/Akt pathway may be a valuable target to sensitize ARID1A-deficienct PDAC to radiotherapy, which needs to be further validated *in vivo* and in clinical trials.

ATR inhibitors

Ataxia-telangiectasia and rad3-related protein kinase (ATR) is an apical kinase involved in intra-S-phase DNA damage response, especially in the process of HR, to protect cells from replication stress [41, 42]. It has been reported that cancer cells with deficient ARID1A are sensitive to ATR inhibitors [43]. ARID1A deficiency results in the defects of topoisomerase 2A and cell cycle, leading to a high dependency on the function of ATR. Inhibition of ATR promotes premature mitotic entry and aggravates genomic instability, which induces the death of *ARID1A*-deficient cancer cells. Hence, inhibition of ATR represents synthetic lethality in cancer cells with *ARID1A* mutations. Currently, a clinical trial, ATARI trial (NCT04065269), is ongoing to explore the effect of AZD6738, an ATR inhibitor, in combination with olaparib in gynecological cancers with ARID1A loss.

In PDAC, the combination treatment of AZD6738 with gemcitabine was investigated *in vitro* and *in vivo*, and a synergistic growth inhibition of cancer cells was observed [44]. However, the anti-tumor effect of ATR inhibitors in PDAC with *ARID1A* deficiency requires further evaluation.

EZH2 inhibitors

In OCCC, inhibition of the enhancer of zeste homolog 2 methyltransferase (EZH2) has been reported to be selective against ARID1A depletion [26]. ARID1A and EZH2 antagonistically regulate *PIK3IP1* expression. When ARID1A is depleted, EZH2 silences *PIK3IP1* and activates the downstream PI3K/Akt pathway. Therefore, suppression of EZH2 up-regulates the expression of *PIK3IP1,* which inhibits the PI3K/Akt pathway induced by ARID1A deficiency, suggesting that inhibition of EZH2 has a synthetic lethal role on ARID1A-mutated cancers.

However, it is unclear whether this strategy could be applied broadly in various tumors. For example, although the synthetic lethal strategy was effective to OCCC, it failed to achieve objective efficacy in patients with high-grade bladder cancers [45]. Thus, exploration on this issue in PDAC is warranted. Currently, a phase II study (NCT05023655) is ongoing to evaluate the antitumor effect of tazemetostat, an EZH2 inhibitor, in solid tumors harboring an *ARID1A* mutation.

Pan-HDAC inhibitors

The growth of *ARID1A*-mutated ovarian cancers was initially found to be dependent on

HDAC6 activity as *ARID1A* mutation inactivated the apoptosis-promoting function of p53 by upregulating HDAC6 [9]. In preclinical models, pan-HDAC inhibitors was demonstrated to be specifically effective in ovarian cancers with *ARID1A* mutations [46]. Notably, in a clinical study of the urothelial carcinoma, patients that responded to HDAC inhibition were characterized by harboring *ARID1A* mutations, identifying *ARID1A* loss as a basis for the clinical response to pan-HDAC inhibition [47]. In PDAC, no similar studies have been reported, and the antitumor effect of HDAC inhibitors is being tested in PDAC in clinical trials [48].

Immune checkpoint blockade

Although ICB has revolutionized the treatment strategy of multiple malignancies, it fails to demonstrate efficacy in PDAC [49]. The highly immunosuppressive tumor microenvironment in PDAC, which is incapable of spurring an immune response to checkpoint inhibition, is postulated to be the main cause of the failure [49].

Notably, clinical trials have discovered a subgroup of cancer patients who are sensitive to ICB immunotherapy. Thus, biomarkers are required to guide the treatment selection more efficiently [50]. Indeed, several biomarkers have been identified to predict the response to ICIs, including microsatellite instability high (MSI-H), tumor mutation burden (TMB), and the expression of PD-L1 [51-53]. Moreover, MSI-H and TMB have been approved as indicators for the use of pembrolizumab, an anti-PD-1 antibody, regardless of the origin of cancers [54]. In the phase II clinical trial KEYNOTE-158, subgroup analysis discovered that the ORR of pancreatic cancer patients with MSI-H was 18.2% (95% CI 5.2-40.3%) using pembrolizumab [55]. Since only approximately 1% of PDAC patients exhibit MSI-H, identification of other biomarkers for ICIs in PDAC is crucial.

Recently, inactivating alterations of *ARID1A* have emerged as a possible biomarker for the vulnerability to ICIs in a variety of cancers [23, 56, 57]. An initial study revealed that *ARID1A* interacted with the mismatch repair (MMR) protein MSH2 and promoted MMR in multiple human cancer types. Therefore, *ARID1A* inactivation compromised MMR, elevated TMB, and increased tumor-infiltrating lymphocytes (TILs) and the expression of PD-L1. Notably, an anti-PD-L1 antibody showed anti-tumor effect and prolonged the survival of mice bearing ovarian tumors with *ARID1A*-deficient-type but not with *ARID1A*-wild-type. This study suggested that *ARID1A* deficiency led to impaired MMR and attributed to the mutator phenotypes in cancers, which could be used in combination with ICB [23]. Consistently, other studies also demonstrated the association of *ARID1A* deficiency with the MSI-H phenotype and the increased TMB and PD-L1 expression (**Figure 2**) [58, 59].

A recent study explored the association between *ARID1A* alterations and clinical outcomes after anti-PD-1/PD-L1 immunotherapy across histologies of cancers (**Table 1**) [56]. A total of 3,403 cancer patients who had tumor tissue NGS data were examined, and in nine cancer subtypes harboring > 5% prevalence of *ARID1A* mutations, including PDAC, MSI and TMB, they were significantly higher in tumors with *ARID1A*-mutation than in *ARID1A* wild-type. The patients with *ARID1A*-altered tumors achieved significantly longer median PFS from ICB therapy than those with *ARID1A* wild-type tumors (11 months *vs.* 4 months, $p = 0.006$). Additionally, multivariate analysis revealed that alterations of *ARID1A* were associated with longer PFS via ICB therapy, which was independent of the status of MSI or TMB. Although the difference of median OS did not reach statistical significance, it showed the trend of longer OS in patients with *ARID1A*-altered tumors than in wild-type tumors (31 months *vs.* 20 months). These findings indicate that *ARID1A* mutations may serve as a valuable biomarker for ICIs across cancer types. Currently, a clinical trial (NCT04953104) is undergoing to evaluate the antitumor effect of nivolumab, an anti-PD-1 antibody, for patients with metastatic urothelial cancer with *ARID1A* mutations.

Till now, there are few clinical trials that directly explore whether a subpopulation of PDAC with *ARID1A* deficiency will show better response to ICB immunotherapy. Most recently, a study was conducted to evaluate the predictive value of SWI/SNF complex abnormalities for ICIs in pancreatic cancer (NCT02478931) (**Table 1**) [60]. In this study, 6,831 cancer patients with NGS profiles were included. Among them, fifteen patients with pancreatic cancer harboring alterations of SWI/SNF complex were further strati-

fied from the entire 123 PDAC patients. Nine out of the fifteen patients received ICIs. Among the nine patients, seven had *ARID1A* alterations, two had *ARID1B* alterations, three had *SMARCA4* alterations, one had *SMARCB1* alterations, and one had *PBRM1* alterations. Only three tumors were of the MSI-H phenotype. The clinical outcome showed that eight of the nine patients achieved objective response, with one patient achieving complete remission (CR). The longest duration of response was ongoing for over 36 months. Surprisingly, tumors with intact MMR, low TMB, and/or low expression of PD-L1 also showed responses to ICB immunotherapy. The median PFS and OS of the nine patients were 9 and 15 months, respectively. Interestingly, in the other four patients with MMR proficiency but no alterations of SWI/SNF, immunotherapy failed to induce objective responses. This study indicates that a small subset of PDAC patients harboring alterations of SWI/SNF complex, including *ARID1A*, appear to be responsive to ICIs, which needs to be verified in prospective, large-scale clinical trials. Furthermore, since *ARID1A* inactivation is the most frequent gene alteration of the SWI/SNF complex in PDAC (77% in this study), clinical trials especially in PDAC patients with *ARID1A* deficiency, should be carried out in the future.

As ARID1A deficiency correlates with the MSI-H phenotype, whether the predictive role of ARID1A for ICB immunotherapy depends on MSI-H phenotype is evaluated. In fact, in addition to MMR, ARID1A deficiency increases TMB, elevates the expression of PD-L1, and modulates the tumor immune microenvironment through its function in DNA damage repair and chromatin remodeling to regulate gene transcription [49]. The increased TMB and frameshift mutations resulting from *ARID1A*-mutantions elevated the level of neoantigens and enhanced the tumor immunogenicity and sensitivity to ICB immunotherapy. Results from a clinical study also demonstrated that *ARID1A* mutations should be recognized as a unique immunologically active subgroup independent of MIS-H phenotype [57]. In this study, the characteristics of patients with microsatellite stable (MSS) colorectal cancer were analyzed, and the results showed that in this subtype, *ARID1A* alterations were enriched and were strongly correlated with higher interferon-gamma (IFNγ) expression and infiltration of T cells, suggesting that tumors harboring *ARID1A* mutations may be more susceptible to ICB immunotherapy even in the MSS subgroup.

On the other hand, T cell exhaustion remains a major challenge in immunotherapy, which limits antitumor immunity. A recent study reported that *ARID1A* depletion could decrease the acquisition of exhaustion-associated chromatin accessibility and inhibit T cell exhaustion, which ultimately led to enhanced antitumor immunity [61]. Given that ARID1A can promote lymphocyte function and limit T cell exhaustion, it is proposed that ARID1A alterations may also influence the therapeutic effect of adoptive transfusion therapy such as CAR-T [61]. However, few reports are available on this subject now.

Targeted therapy combined with ICB immunotherapy

Because of the low response rate to ICB immunotherapy, various combinational therapeutic strategies have been explored to improve the clinical outcome [58]. Among them, targeted therapy combined with ICB immunotherapy is a promising approach due to its more precise nature compared with chemotherapy or radiotherapy and its relatively better tolerance (**Figure 2**).

In *ARID1A*-depleted tumors, our team used cell-based and animal models and found that the inhibition of ATM/Chk2 checkpoint axis potentiated the efficacy of ICIs. Mechanically, the inhibition of ATM/Chk2 pathway induced replication stress and increased cytosolic DNA, thereby activating the STING pathway, which, in turn, enhanced innate immune response in tumors with ARID1A variants, but not with wild-type [62].

In *ARID1A*-inactivated OCCC, the combination of HDAC6 inhibition with ICIs represents a promising treatment strategy [63]. The HDAC6 inhibitor ACY1215 combined with anti-PD-L1 antibodies reduced the tumor burden and improved the survival in $ARID1A^{flox/flox}$/$PIK3CA^{H1047R}$ OCCC mice due to the activation and increased presence of IFNγ positive $CD8^+$ T cells [63].

Some combinations of targeted therapy with ICB have been evaluated in clinical trials. In a

phase 1 clinical trial (NCT03842228), the combination of olaparib, copanlisib (PI3K inhibitor) and durvalumab was used to treat patients with solid tumors selected by 25 genes mutation-assay, including *ARID1A, ATM, ATRX, BARD1, BRCA1,* and *BRCA2* (**Table 1**) [58]. Another clinical trial (NCT04284202) was designed to explore the combination of toripalimub (an anti-PD1 antibody) and dasatinib (a multi-kinase inhibitor) as third-line treatment for advanced non-small cell lung cancer with *ARID1A* Mutations. These two trials are ongoing, and the results are not available now.

Currently, two clinical trials (NCT03851614, NCT02660034) are being performed to investigate the effect of PARP inhibitors combined with ICIs in solid tumors, including PDAC; however, these two clinical trials did not select patients by molecular biomarkers, such as *ARID1A* mutations.

Other targeting agents, such as the inhibitors of EZH2 and ATR, combined with ICIs have also been explored in clinical trials (NCT03854474, NCT03334617, and NCT02264678) with promising preliminary results. As these targets show "synthetic lethality" with *ARID1A* alterations, further studies in *ARID1A*-mutation-selective cancers, including PDAC, should be considered.

Other treatments

A recent study identified ARID1A deficiency as a valuable biomarker for increased sensitivity to proteotoxic agents in PDAC. Loss of ARID1A promoted an EMT phenotype, which sensitized PDAC cells to an inhibitor of HSP90, NVP-AUY922, *in vitro* and *in vivo* [64].

ARID1A alterations predict the prognosis of pancreatic cancer

ARID1A alterations have been reported as a prognostic factor in gastric cancer [65, 66], breast cancer [67], and endometrium-related gynecological cancer [68]; however, regarding the prognostic function of ARID1A in PDAC, controversy still exists.

In an initial study enrolling 109 microdissected PDAC cases, demonstrated that altered *ARID1A* was found to be associated with significantly shorter disease-free survival (DFS) and OS, suggesting that mutations in *ARID1A* predicted poor survival [13]. Consistently, in a study with 22 PDAC patients who received neoadjuvant chemoradiation therapy, univariate analysis revealed worse survival in patients with *ARID1A* alterations, although multivariate analysis suggested that the difference was insignificant, possibly due to the small sample size and confounding factors in this study [69].

In contrast, Sausen M *et al.* reported that patients with *ARID1A* mutations had better survival in PDAC; however, the short follow-up time in this study was debatable [70]. Additionally, some other studies suggested that *ARID1A* was not a prognostic factor in PDAC [60, 71, 72].

Interestingly, in a recent study with a cohort of 90 Chinese patients with pancreatic cancer, targeted sequencing and survival analyses revealed that altered *ARID1A* was associated with significantly shorter DFS and OS [73]. The median DFS and OS were 12 and 16 months, respectively, in patients with alternated *ARID1A,* while 24 months in those with wild-type. This study also analyzed the data from the TCGA pancreatic cancer patient cohort and surprisingly found that there was no significant difference in DFS and OS between mutant *ARID1A* and wild-type *ARID1A* subgroups. These results suggested that race and genetic background might influence the prognostic value of *ARID1A* alterations in PDAC. Further clinical investigation is needed to clarify this notion.

Conclusion and perspective

In summary, the chromatin remodeling gene *ARID1A* plays important roles in PDAC, particularly participating carcinogenesis, predicting response to precise therapeutic strategies, including targeted therapy and ICB immunotherapy, and predicting prognosis. The promising preliminary results from accumulated preclinical and early clinic studies suggest that the functions of *ARID1A* alterations in PDAC deserve to be further exploited.

As most of the current clinical results are from retrospective analysis with small sample size, selection bias and confounding factors may influence the conclusion. Prospective, multicenter, large-scale clinical trials are warranted to provide definitive conclusions on the predic-

tive and prognostic value of *ARID1A* alterations in PDAC. Hopefully, based on this research, the subgroup of PDAC patients harboring *ARID1A* alterations will achieve better clinical outcomes in the future.

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Disclosure of conflict of interest

None.

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