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Review

ARID1A mutant ovarian clear cell carcinoma: A clear target for synthetic lethal strategies

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A B S T R A C T

SWI/SNF chromatin remodeling complexes play an important role in the epigenetic regulation of chromatin structure and gene transcription. Mutual exclusive subunits in the SWI/SNF complex include the DNA targeting members ARID1A and ARID1B as well as the ATPases SMARCA2 and SMARCA4. SWI/SNF complexes are mutated across many cancer types. The highest mutation incidence is found in *ARID1A*, primarily consisting of deleterious mutations. Current advances have reported synthetic lethal interactions with the loss of ARID1A in several cancer types. In this review, we discuss targets that are only important for tumor growth in an *ARID1A* mutant context. We focus on synthetic lethal strategies with ARID1A loss in ovarian clear cell carcinoma, a cancer with the highest *ARID1A* mutation incidence (46–57%). ARID1A directed lethal strategies that can be exploited clinically include targeting of the DNA repair proteins PARP and ATR, and the epigenetic factors EZH2, HDAC2, HDAC6 and BRD2.

1. Introduction

ATP dependent chromatin remodeling is an epigenetic process regulating gene transcription in which chromatin structure can be co-ordinated through mobilization of nucleosomes. The evolutionary conserved ATP dependent chromatin remodelers consist of four sub-classes. These are Imitation SWI (ISWI), INO80, nucleosome remodeling and histone deacetylase Mi2/CHD (NURD/Mi2/CHD) and switch su-crose non-fermenting (SWI/SNF) and are involved in diverse cellular processes such as tissue differentiation, proliferation and DNA repair [1]. While all chromatin remodelers contain ATPase domains, additional subunits differ per subclass and are important for modulation of ATPase activity and chromatin complex recruitment onto tissue-specific genomic loci. SWI/SNF chromatin remodeling complexes are implicated in many stages of pluripotency and tissue differentiation along mammalian development. Compared to the SWI/SNF subclass, the role of ISWI, INO80 and Mi2/CHD chromatin remodeling complexes in these processes is limited but supplementary to SWI/SNF (for a review see Hota et al. [2]). BAF SWI/SNF chromatin remodeling complexes contain multiple subunits with mutual exclusive characteristics, which include the DNA targeting subunits ARID1A and ARID1B, and the AT-Pase subunits SMARCA2 and SMARCA4 (Fig. 1). These mutual

exclusive members discriminate BAF SWI/SNF complexes from coun-terpart PBAF SWI/SNF complexes that contain SMARCA4 but not the other three proteins. BAF and PBAF SWI/SNF complexes have distinct regulatory roles in lineage development. For instance, BAF specific SMARCA2 plays a key role in smooth muscle formation, while the PBAF specific subunit ARID2 is important for coronary morphogenesis. More SWI/SNF subunits have been shown to coordinate specific develop-mental processes [2]. Therefore, it is conceivable that a specific subunit mutation causes changes in SWI/SNF chromatin binding at typical transcriptional enhancer sites, which ultimately results in loss of dif-ferentiation potential and drives cells into a proliferative state [3]. Over 20% of cancers contain a mutation in at least one of the members of the 15-subunit BAF SWI/SNF complex (hereinafter referred to as SWI/SNF) [4]. Especially *ARID1A* and *ARID1B* and *SMARCA2* and *SMARCA4* have high mutation frequencies and are suggested to be driver mutations in multiple cancers [5, 6]. The mutation incidence in SWI/SNF subunits varies per tumor type, indicative for distinct roles of SWI/SNF com-plexes in human tissues. For instance, ARID1A deficient mice are re-sistant to hepatocellular carcinoma initiating agents while mice with established hepatocellular carcinoma showed enhanced metastasis upon ARID1A loss [7]. Conversely, *ARID1A* mutations promote color-ectal tumor formation, indicating the context dependent effect of
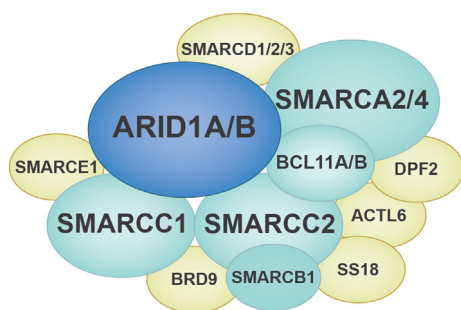

Fig. 1. SWI/SNF complex members. ARID1A and ARID1B are mutual exclusive core components in the mammalian BAF SWI/SNF chromatin remodeling complex. Other core members are shown in turquoise and exchangeable components in yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ARID1A loss [8]. *ARID1A* is the most frequently mutated SWI/SNF complex member. The highest alteration incidence, 46–57%, is found in ovarian clear cell carcinoma (OCCC) [9–11]. Other tumor types harboring *ARID1A* mutations comprise uterine endometrioid carcinoma (47–60%), ovarian endometrioid carcinoma (30%), gastric cancer (29%), colorectal cancer (5–10%) and pancreatic cancer (3–5%) [6, 12–14]. Tumors with mutations in *ARID1B* include OCCC (18%), colorectal cancer and gastric cancer (5–10%) (Fig. 2). Mutations in *SMARCA2* are found in colorectal cancer, lung cancer (3–5%) and OCCC (2%). Mutations in *SMARCA4* are found in melanoma, lung cancer (5–10%) and OCCC (5%) [6, 15] (Fig. 3).

In this review, we discuss recent developments in strategies that take advantage of cellular dependencies specific for *ARID1A* mutant cancers. This concept, named synthetic lethality, describes a relation between two genes in which cells remain viable after loss of either gene alone but loss of both genes will result in a lethal phenotype [16]. Synthetic lethal targets, including proteins involved in DNA repair and epigenetic regulation are reviewed, focusing on targets recently identified in *ARID1A* mutant OCCC.

2. Role of *ARID1A* in ovarian clear cell carcinoma

Mutations in *ARID1A* are often heterozygous nonsense or frameshifts that are not enriched in hotspot sites [9, 10]. *ARID1A* mutations, homo- or heterozygous, coincides with loss of ARID1A protein expression in OCCC. This suggests haploinsufficiency or the occurrence of other mechanisms that are responsible for complete loss of protein expression, such as epigenetic silencing, mutations in non-coding regions or post transcriptional mechanisms [9, 17–20]. Additionally, two studies described loss of ARID1A protein expression in precursor lesions of OCCC, i.e. ovarian endometriosis, indicating that ARID1A loss is an early event in progression to OCCC [21, 22]. Two studies described a worse progression-free survival in ARID1A deficient OCCC patients. However, literature consistently showed that overall survival in OCCC is not predicted by ARID1A status [11, 23–25].

$ARID1A^{-/-}$ or $ARID1A^{+/-}$ knockout causes lethality in early embryonic mouse development [26]. In contrast, depletion of *ARID1A* expression induced proliferation in ovarian surface epithelium cells. Another study showed that knockdown of *ARID1A* provided phenotypic changes associated with neoplastic transformation in an immortalized endometriosis cell line [27]. Upon *ARID1A* knockdown the expression of 99 genes was up or downregulated. Many of these genes are also dysregulated in OCCC tumors [28]. Still, ARID1A loss itself is not sufficient to induce tumorigenesis in the ovaries of conditional Cre-Lox mouse models. Only mice with combined ARID1A and PTEN loss developed ovarian hyperplasia, which progressed to tumors in 59% [29]. Another study showed that additional $ARID1A^{-/-}$ or $ARID1A^{+/-}$ knockout in *APC* and *PTEN* null mice actually delayed ovarian tumor formation but promoted epithelial differentiation and metastasis [30]. Moreover, Chandler et al. demonstrated that ovarian tumor formation only occurred in mice with concurrent homozygous knockout of *ARID1A* and $PIK3CA^{H1047R}$ missense mutation. These tumors manifested an OCCC like histopathology and gene expression signature. Furthermore, a mechanistic link was identified between ARID1A loss and PIK3CA activation with the induction of cytokine expression, including IL-6, via NF-ƙB signaling [31]. In vitro and in vivo suppression of IL-6 reduced the tumor cell proliferation, presenting IL-6 blocking as potential synthetic lethal strategy in an *ARID1A* and *PIK3CA* mutant
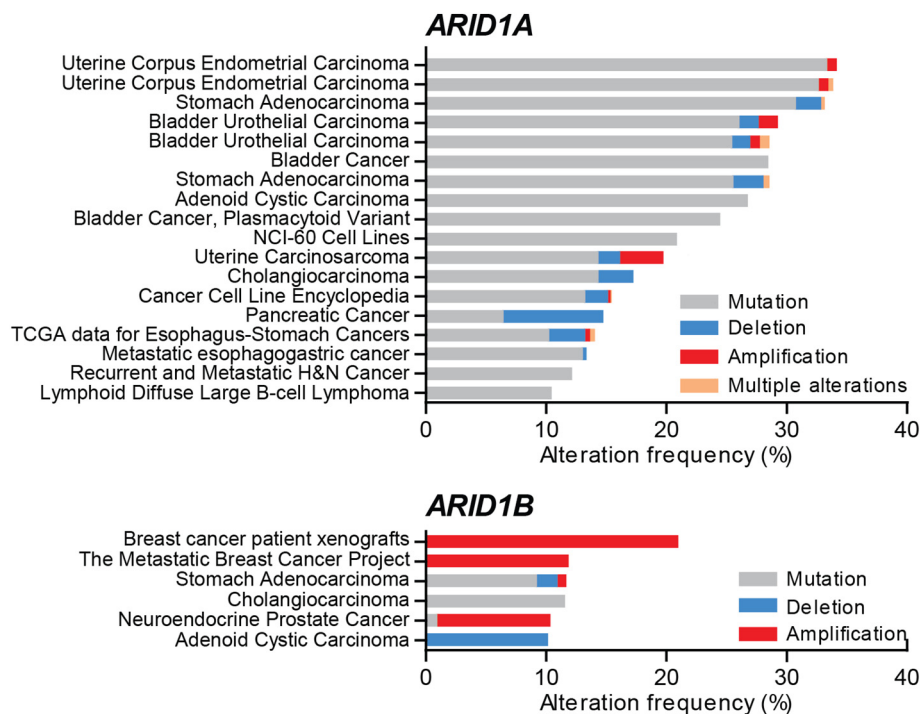

Fig. 2. *ARID1A* and *ARID1B* alterations in cancer. Alteration frequencies of *ARID1A* and *ARID1B* in published and provisional datasets incorporated in cBioPortal are depicted with a 10% cutoff (http://cbioportal.org downloaded 3-10-2017). Of note, *ARID1A* and *ARID1B* mutations are commonly found in several cancer types, but not always displayed due to the cutoff.
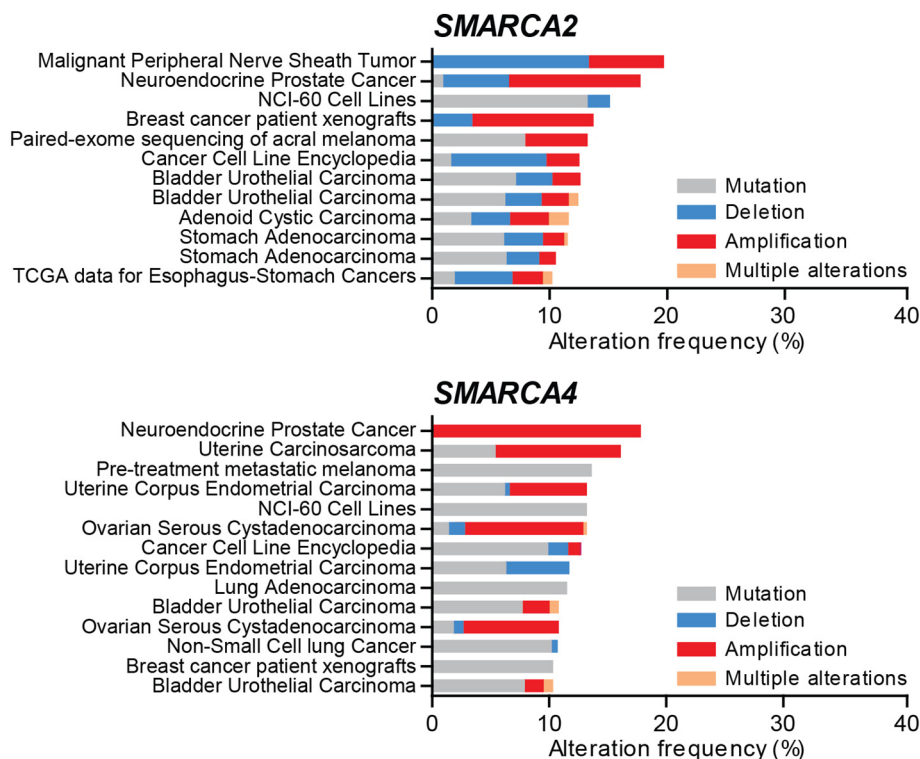
Fig. 3. *SMARCA2* and *SMARCA4* alterations in cancer. Alteration frequencies of *SMARCA2* and *SMARCA4* in published and provisional datasets incorporated in cBioPortal are depicted with a 10% cutoff (http://cbioportal.org downloaded 3-10-2017). Of note, *SMARCA2* and *SMARCA4* mutations are commonly found in several cancer types, but not always displayed due to the cutoff.

OCCC background [32].

3. Mutual exclusive roles for ARID1A and ARID1B

The SWI/SNF subunits encoding genes *ARID1A* and *ARID1B* share 60% sequence identity but are thought to have disparate roles in cell cycle regulation [33]. *ARID1B* mutations are less prevalent in cancer with fewer deleterious mutations as compared to *ARID1A* (Fig. 2). In 2007, Nagl et al. reported opposing roles for ARID1A and ARID1B in regulating proliferation in osteoblasts. They found that ARID1B had a more proliferation inducing role via MYC and Cyclin E activation as compared with ARID1A [34]. ARID1A loss modifies chromatin accessibility in colorectal cancer cells and this accessibility is further modified by loss of ARID1B. In the presence of wild-type ARID1A, ARID1B loss did not have an effect on chromatin accessibility, indicating a dominant effect of ARID1A. It was reported that ARID1B in the absence of ARID1A facilitates expression of proliferative genes involved in PI3K/AKT/mTOR and ERBB receptor tyrosine kinase signaling in colorectal carcinoma and OCCC cells [35]. These findings hypothesize that redundant incorporation of ARID1B in residual SWI/SNF complexes in *ARID1A* deficient cells could stimulate proliferation. The consecutive discovery that *ARID1A* mutant tumors are specifically vulnerable to ARID1B loss was based on the Achilles project, a loss of function genetic screen database, which includes over 200 cancer cell lines [36]. Subsequently, Helming et al. demonstrated a reduced proliferation in two *ARID1A* mutant OCCC cell lines after shRNA induced ARID1B loss. They found a destabilization of full size SWI/SNF complexes after loss of both proteins, suggesting that depletion of intact SWI/SNF complexes is responsible for the observed synthetic lethality. Co-mutations in *ARID1A* and *ARID1B* do occur but never biallelic in both genes, indicating some ARID1 function is essential for cell survival of both cancer and normal cells [36].

4. *ARID1A*-directed synthetic lethality

Several studies have shown that *ARID1A*-directed synthetic lethality can be attained through diverse molecular mechanisms. These synthetic lethal interactions with *ARID1A* mutations go beyond direct targeting of ARID1B.

4.1. Lethal relationship between ARID1A loss and inhibition of the DNA damage response

Besides ARID1A's regulatory role in SWI/SNF complex binding to DNA, it is also involved in DNA double-strand break (DSB) repair. Initially, the SWI/SNF ATPase subunits SMARCA2 and SMARCA4 were described to interact with the DSB localizing protein γ-H2AX upon DSB formation, suggesting a role for SWI/SNF in the DNA damage response (DDR) [37]. Recently, ARID1A and ARID1B were found to localize to DSBs and facilitate non-homologous end joining (NHEJ) and ARID1A was assigned a role in homologous recombination (HR) [38, 39]. NHEJ is the more error prone DSBs repair mechanism compared to HR. ARID1A and ARID1B recruit the NHEJ proteins KU70 and KU80 to the site of DNA damage and are thus involved in this type of DSB repair at an early stage. Downregulation of ARID1A or ARID1B sensitized osteosarcoma cells and immortalized pancreatic ductal epithelial cells to DSB inducing treatments such as oxaliplatin and cisplatin [38, 40]. Two studies have investigated synthetic lethality approaches based on targeting of DDR proteins in *ARID1A* mutant cancers. Shen et al. identified a role for ARID1A in DSB repair as binding partner of ATR, a DDR central regulator involved in DSB and single strand DNA breaks [39]. With chromatin immunoprecipitation assays they found ARID1A to be enriched at chromatin regions close to DSBs, a recruitment that was lost upon ATR inhibition. Phenotypically, *ARID1A* stopcodon introduction in HCT116 colorectal carcinoma cells resulted in impaired G2/M checkpoint control upon irradiation-induced DSBs. Cells lacking ARID1A more frequently re-entered the cell cycle after irradiation as compared with control cells. The phosphorylation of ATR and CHK1, another DDR protein important in G2/M checkpoint control, was reduced in *ARID1A* mutant cells, indicating that ARID1A is involved in G2/M progression. Furthermore, ARID1A loss reduced localization of the DDR adaptor proteins γ-H2AX and 53BP1 at the site of DSBs. Collectively, they reveal an important role for ARID1A to conduct ATR-mediated DDR signaling required for HR (Fig. 4). It is unclear if ARID1A
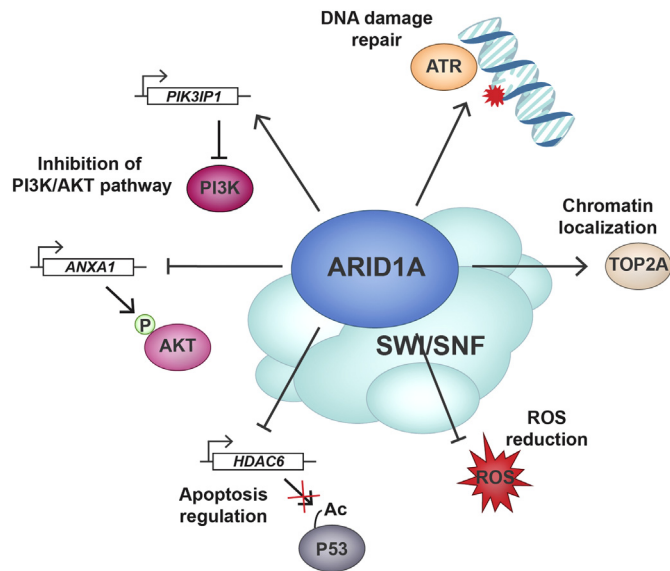
Fig. 4. ARID1A implicated mechanisms with synthetic lethal opportunities after ARID1A loss. ARID1A itself or incorporated in the SWI/SNF chromatin remodeling complex is involved in multiple oncogenic suppressive processes. Therapeutic targeting of these indicated mechanisms were found to be lethal in an *ARID1A* mutant background.

4.2. Epigenetic targeting and ARID1A synthetic lethality

Synthetic lethality between ARID1A loss and inhibition of multiple distinct epigenetic proteins was recently found in OCCC. The lethal interaction between *ARID1A* mutation and inhibition of polycomb repressive complex 2 (PRC2) catalytic subunit EZH2 resulted in the first therapeutically druggable target for *ARID1A* mutant cancers [43]. In contrast to SWI/SNF complexes that generate a more open chromatin structure, PRC2 closes chromatin by methylation of histone 3 lysine 27 (H3K27me3), which is associated with gene repression [44]. Disruption of epigenetic chromatin remodeling is suggested to drive oncogenesis in tumors that lack genomic instability [1]. Therefore, Bitler et al. presumed *ARID1A* mutant OCCC depend on epigenetic mechanisms, since genomic instability is lower compared with *ARID1A* wild-type OCCC. A panel of HDAC and EZH2 inhibitors was tested on RMG1 OCCC cells with *ARID1A* knockdown in 3D matrigel cultures. The highest tumor sphere reduction was achieved by GSK126, an inhibitor of EZH2 H3K27Me3 methyltransferase activity. Treated tumor spheres showed loss of the proliferation marker Ki67 and increased apoptosis. Similar results were found in xenografts. Approximately two-fold increase in GSK126 sensitivity was observed in *ARID1A* mutant ($n = 4$) versus *ARID1A* wild-type ($n = 3$) OCCC 3D cell line models. Gene expression profiling of *ARID1A* mutant cells treated with GSK126 identified *PIK3IP1*, a negative regulator of PI3K/AKT/mTOR signaling, as a mechanistic link for the synthetic lethality between ARID1A loss and EZH2 inhibition [45]. PIK3IP1 was found to be downregulated upon ARID1A loss. After ARID1A loss EZH2 methyltransferase induced H3K27Me3 methylation of the *PIK3IP1* gene thus preventing expression of PIK3IP1, which is then followed by induction of PI3K/AKT/mTOR signaling and proliferation (Fig. 4). GSK126-induced loss of the *PIK3IP1* promoter H3K27Me3 mark resulted in PIK3IP1 expression and lethality, demonstrating the addiction of *ARID1A* mutant ovarian cancer cells to low PIK3IP1 levels [43]. Consecutive work indicated that *ARID1A* mutant OCCC is selectively susceptible to inhibition of HDAC2, a known binding partner of the EZH2-containing PRC2 complex [46]. As it turns out, HDAC2 only interacts with this complex in the absence of ARID1A. In line with the observations on EZH2 inhibition, knockdown of *HDAC2* or chemical inhibition of HDAC2, using the non-specific HDAC inhibitor vorinostat, caused re-expression of PIK3IP1 in *ARID1A* mutant OCCC cells, which resulted in reduced proliferation and increased apoptosis. Vorinostat IC_{50} was 10-fold lower in *ARID1A* mutant ($n = 4$) versus *ARID1A* wild-type ($n = 4$) ovarian cancer cell lines. Similar results were observed with two primary cultures.

For clinical applicability it will be important to know if the synthetic lethal interaction between *ARID1A* loss and HDAC2 or EZH2 inhibition holds true in a larger set of OCCC models and in other tumor lineages.

To this end, EZH2 inhibition was found to be lethal in lung, adrenal gland and renal carcinoma cell lines with mutations in the SWI/SNF components *ARID1A, PBRM1* and *SMARCA4* [47]. Kim et al. propose that SWI/SNF mutant tumors could generally depend on EZH2 activity. Their data suggests that EZH2 inhibition is only lethal when the EZH2-PRC2 complex interaction is destabilized, an effect which GSK126 did not achieve in all cell lines. Based on the Achilles project they additionally showed *RAS* mutations to predict resistance to EZH2 inhibition in SWI/SNF mutant cancer cell lines. Future inhibitors of EZH2 with the ability to disrupt EZH2-PRC2 complex interaction can presumably be applied in *ARID1A, PBRM1* and *SMARCA4* mutant cancers with wild-type *RAS*.

In other work by Bitler et al. shRNA interference of 11 histone deacetylases (HDACs) in *ARID1A* mutant OCCC led to the discovery of a lethal relationship between ARID1A loss and inhibition of HDAC6, an epigenetic protein known to deacetylate numerous substrates [48]. Chemical inhibition of HDAC6 with ACY1215 was only effective in an *ARID1A* mutant background in a panel of four *ARID1A* mutant versus four *ARID1A* wild-type OCCC cell lines (10-fold lower IC_{50}) and in orthotopically transplanted *ARID1A* mutant xenografts. They further

alone or in complex with other SWI/SNF members localizes to DSBs and activates ATR and subsequent DDR. The involvement of ARID1A in DSB repair led Shen et al. to test for synthetic lethality of PARP inhibitors in *ARID1A* mutant cells as these inhibitors are known to be lethal in cells with DSB repair deficiencies, such as *BRCA1/2* mutations. Multiple inhibitors of PARP provided toxicity in (*BRCA* wild-type) isogenic pairs of ARID1A-depleted non-transformed breast epithelial, breast epithelial carcinoma and colorectal carcinoma cells and a panel of ovarian carcinoma cell lines, showing more than three-fold reduced colony formation in *ARID1A*-depleted cell lines. Additionally, PARP treatment efficacy was detected in (*BRCA* wild-type) ARID1A-depleted xenograft models of breast and colorectal cancer [39].

In another study by Williamson et al., RNAi screening libraries identified ARID1A loss as a genetic determinant of sensitivity to ATR inhibition in the triple negative (ER, PR and ERBB2 negative) breast cancer cell line HCC1143 and immortalized normal mammary epithelial cell line MCF12A [41]. ARID1A loss in combination with ATR inhibition by VX-970 was confirmed to be over three-fold more effective in multiple cancer lineages, including several OCCC cell lines and an isogenic ARID1A-deficient pair of the colorectal cancer cell line HCT116. Sensitivity to ATR inhibition was observed in xenograft models of the isogenic HCT116 cancer cell line pair and to a lesser extent in the xenograft model of *ARID1A* mutant TOV21G OCCC cells. In this study, it was also demonstrated that ARID1A loss in HCT116 cells resulted in accumulation of cells in G2/M. In line with this result, *ARID1A* mutant HCT116 xenografts showed reduced tumor growth. In the presence of ATR inhibitors, they found reduced accumulation of *ARID1A* mutant HCT116 cells in G2/M and multiple indications of chromosomal instability and apoptosis induction in these cells [41].

Previously, it was reported that SMARCA4 deprived mouse embryonic stem cells have decreased DNA localization of DNA topoisomerase 2-alpha (TOP2A), an enzyme important in DNA transcription and translation [42]. Elaborating on this study, Williamson et al. found *ARID1A* mutant HCT116 cells to have decreased TOP2A DNA localization as well, indicating that SWI/SNF complexes are important for stable function of TOP2A [41]. Since ARID1A status did not determine TOP2A expression, more likely, SWI/SNF complexes directly bind to TOP2A via ARID1A, which is important for the localization of TOP2A to at least 12.000 genomic loci, as demonstrated earlier (Fig. 4) [42].

identified ARID1A as direct transcriptional repressor of HDAC6. ARID1A loss led to re-expression of HDAC6, which specifically deacetylate p53-lysine120, a residue known to regulate p53-mediated apoptosis (Fig. 4). Knockdown of *TP53* reverted ACY1215 mediated apoptosis induction and proliferation inhibition in *ARID1A* mutant cells, illustrating that *ARID1A* mutant OCCC specific ACY1215 sensitivity is p53 dependent. Additional data demonstrated that acetylated p53-lysine120 localizes to mitochondria and destabilizes mitochondrial membrane potential, presenting a mechanism for the lethal relationship between ARID1A loss and HDAC6 inhibition.

Recently, a fourth epigenetic determinant of *ARID1A* mutation dependent synthetic lethality was identified by shRNA mediated screening against all human kinases. In a panel of nine *ARID1A* mutant versus five *ARID1A* wild-type OCCC cell lines, knockdown of the BET bromodomain member *BRD2* established specific lethality in *ARID1A* mutant lines [49]. BET bromodomains bind acetylated lysine histone tails and are involved in transcriptional regulation, but have also been reported to act as kinases [50, 51]. As a result of high homology between the BET members BRD2/3/4 and BRDT, only inhibitors that target all four proteins are available to date. The BET inhibitors JQ1 and iBET762 demonstrated specific sensitivity in *ARID1A* mutant OCCC cells, which was verified in two *ARID1A* deficient isogenic OCCC cell line pairs, in *ARID1A* mutant OCCC xenografts and patient-derived xenograft models. Explicitly, *ARID1A* mutant cells had over two-fold stronger growth reduction after JQ1 treatment, as observed in the panel of nine *ARID1A* mutant versus five *ARID1A* wild-type OCCC cell lines. JQ1 or shRNA mediated inhibition of *BRD2* reduced the expression of *ARID1B*. Chromatin immunoprecipitation assays indicated direct transcriptional regulation of ARID1B expression by BRD2 at the *ARID1B* promoter. Therefore, the previously described mutual exclusive relation between ARID1A and ARID1B can at least partially explain the lethal interaction between BET inhibitor mediated BRD2 inhibition and ARID1A loss [36]. In addition to ARID1B reduction, more SWI/SNF members were downregulated at the mRNA level, potentially augmenting to the lethal phenotype by further reducing the SWI/SNF function. This study provides a first opportunity to chemically inhibit ARID1B expression and utilize the ARID1A and ARID1B mutual exclusive properties in *ARID1A* mutant OCCC.

4.3. Synthetic lethality of ROS induction with ARID1A

Previous observations indicated that SWI/SNF function is required for oxidative stress resistance in the model organisms *Saccharomyces cerevisiae* and *Caenorhabditis elegans* [52, 53]. A comparison of about 140 drug sensitivities in *ARID1A* mutant versus wild-type human cancer cell lines in the "genomics of drug sensitivity in cancer" database (cancerrxgene.org), encompassing over 700 cancer cell lines, revealed the HSP90 inhibitor and reactive oxygen species (ROS) inducing agent elesclomol as the most differential sensitive drug [54]. Only cell lines with *ARID1A* frameshift or nonsense mutations were retained in the analysis, potentially generating a bias considering the proportion of cancer patients with this type of *ARID1A* mutations [9]. Subsequently, Kwan et al. proved elesclomol sensitivity to be higher in *ARID1A* mutants in a panel of 11 ovarian cancer cell lines, including four OCCC cell lines, and three endometrial cancer cell lines [54]. Elesclomol was five to six-fold more effective in *ARID1A* mutant cells compared with *ARID1A* wild-type cells and increased ROS levels and apoptosis. Re-expression of ARID1A induced resistance to elesclomol. Importantly, knockdown of the SWI/SNF subunits *SMARCA4* and *SNF5* induced elesclomol sensitivity in *ARID1A* wild-type OCCC cells, suggesting that loss of other SWI/SNF components can predict elesclomol sensitivity as well. *ARID1A* knockdown induced intracellular ROS levels in two ovarian cancer cell lines. A similar observation was made in OCCC tumor samples where low ARID1A expression was associated with high expression of 8-hydroxyguanosine, as a marker of oxidative stress [54]. The synthetic lethal finding by Kwan et al. is not supported by in vivo

data and the mechanisms underlying ROS induction after ARID1A loss are inconclusive (Fig. 4).

4.4. ARID1A synthetic lethality approaches using dasatinib

In another drug screening study, 68 clinically approved or late-stage clinically developed inhibitors were screened on three *ARID1A* wild-type and eight *ARID1A* mutant OCCC cell lines [55]. The SRC, ABL and C-KIT inhibitor dasatinib gave the most specific inhibitory effect in *ARID1A* mutant OCCC cells, demonstrating a more than two-fold increased sensitivity compared to *ARID1A* wild-type OCCC cells. Dasatinib synthetic lethality was consistently found after *ARID1A* knockdown in two OCCC cell lines, one breast cancer cell line and *ARID1A* knockout in the cell line HCT116. Using mass spectrometry analysis of active kinases, five targets of dasatinib were shown to be upregulated in *ARID1A* mutant OCCC cells. The dasatinib target and SRC family protein YES1 was most selective for ARID1A deficient OCCC cell lines. Dasatinib treatment increased G1 cell cycle arrest and caspase activity in *ARID1A* mutant lines, indicating a cell-cycle arrest/apoptotic phenotype. Using siRNA screening, Miller et al. identified expression of p21 (CIP1/WAF1) and its downstream target RB1 as determinants of dasatinib sensitivity. Dasatinib treatment was previously shown to induce p21 expression [56]. *ARID1A* mutant xenograft growth of TOV21G was reduced after dasatinib treatment, demonstrating therapeutic efficacy in vivo. Results from this study are consistent with previous research describing p21 to be regulated via ARID1A [57]. However, Miller et al. did not indicate a mechanism through which dasatinib could result in p21 and RB1 induction. Regulation of these two proteins could be mediated by YES1 or other dasatinib targets.

4.5. Targeting of PI3K/AKT signaling in ARID1A mutant cancers

Results from the Achilles project demonstrated *PIK3CA* to be the second best hit for synthetic lethality with ARID1A loss [36]. Accordingly, another analysis from the drug sensitivity in cancer database from Kwan et al. showed AZD8055, an mTORC1/2 inhibitor that targets PI3K/AKT signaling downstream, as second best hit in *ARID1A* mutant cells in their screen [54]. Both studies suggest a link between ARID1A loss and PI3K/AKT/mTOR activation. The co-existence of *ARID1A* mutations and activation of PI3K/AKT/mTOR signaling has been described in multiple cancer types. Significant enrichment of *PIK3CA* activating mutations and PTEN loss were detected in *ARID1A* mutant endometrial cancer. Moreover, knockdown of *ARID1A* induced phosphorylation of the PI3K downstream target AKT [58]. PI3K/AKT pathway activation occurred after ARID1A depletion in MCF7 breast cancer cells. These cells gained AKT phosphorylation, and enhanced sensitivity to AKT and PI3K inhibitors upon *ARID1A* knockdown. [59]. In OCCC, concurrent *PIK3CA* activating mutations and PTEN loss were significantly associated with *ARID1A* mutations, but *ARID1A* knockdown did not induce AKT phosphorylation in OCCC cell lines [60, 61]. One study described *ARID1A* mutant OCCC lines to have lower IC_{50} for AKT inhibitors. However, no induction of PI3K/AKT pathway activity was found in these cells after *ARID1A* knockdown [59]. Moreover, *ARID1A* status could not discriminate between IC_{50} for PI3K and mTOR inhibitors in a large panel of OCCC cell lines and PDX models [11].

Some mechanistic links between ARID1A loss and PI3K/AKT pathway activation have been established. As stated earlier, ARID1A was found to inhibit PI3K/AKT activity by regulating expression of the PI3K suppressor PIK3IP1 in ovarian cancer [43]. In breast cancer ARID1A was identified as negative transcriptional regulator of *ANXA1*, a membrane bound protein and activator of AKT (Fig. 4) [62]. These two studies suggest that ARID1A loss may indirectly activate PI3K in some cancer types. Given that PI3K and mTOR inhibitor sensitivity is not only dependent on *ARID1A* mutational status in OCCC, targeting the PI3K/AKT pathway should not be regarded as a synthetic lethal strategy for *ARID1A* mutant OCCC.

Table 1
Clinical development of agents with ARID1A mutation specific lethality and their industry names, from ClinicalTrials.gov (http://clinicaltrials.gov).

Molecular target	Most advanced clinical phase	Compounds in clinical development, most advanced are depicted in bold
EZH2	Phase II	**EPZ-6438**, CPI-1205
HDAC6	Phase II	**ACY-125**, KA2507
BRD2 (BET)	Phase II	**I-BET-762**, GSK2820151, RO6870810, CPI-0610, GS-5829, INCB054329, INCB057643, ABVV-075, BMS-986158, FT-1101, PLX-51107, SF1126, CC90010, ZEN003694, BI894999, *N*-methyl pyrrolidone, ODM-207
YES1	Phase IV	**BMS-354825**, AZD0530, **SKI-606**
ATR	Phase II	**VX-970**, BAY1895344, **AZD6738**
PARP1/2	Phase IV	**AZD2281**, ABT-888, BMN673, AG-014699, MK-4827, SHR3162, SC10914, SOMCL-9112, BGB-290
HSP90	Phase II	**AT13387**, TAS-116, SNX-2112, XL888, **PEN-866**
PI3Kα/β/δ	Phase III	**BKM120**, RP6530, BYL719, PKI-587, AZD8186, **BAY80-6946**, **TGR-1202**, GSK2636771, SF1126, KA2237, **GDC0032**, **INK1197**, GDC-0077, **GDZ173**, **GS-1101**

5. Clinical development of agents with *ARID1A* specific lethality

Multiple agents showing synthetic lethality in an *ARID1A* mutant context are in clinical development (Table 1). From the epigenetic targets with *ARID1A* mutation specific lethality in OCCC, the first generation EZH2 inhibitors (DZNep) gave toxicity in vivo. Two novel EZH2 inhibitors are now in clinical trials [63]. An alternative for EZH2 targeting agents is HDAC2 inhibition using the clinically applicable broad HDAC inhibitor vorinostat. The HDAC6 inhibitor ACY1215 proved to be well tolerated in myeloma patients, supporting clinical applicability of HDAC6 inhibition for treating ARID1A deficient OCCC patients in the future [64]. BET bromodomain inhibition has attracted great interest for the treatment of cancer. Many BET-inhibitors are under clinical investigation, and several BET-inhibitors, such as iBET-762, are currently evaluated in phase II trials. ARID1A status might be a biomarker to enrich for sensitivity in OCCC and possible other cancer types as well. Dasatinib is approved for the treatment of leukemia's and is under investigation in multiple solid tumors. Dasatinib efficacy in recurrent ovarian cancer patients was limited [65]. However, no selection based on *ARID1A* status was made. PI3K, PARP and ATR inhibitors are being tested in clinical trials for diverse genetic backgrounds in cancer, utmost in phase III, IV and II respectively. Considering the advanced clinical development of PI3K and PARP targeting compounds, including trials in ovarian cancer patients, these agents may provide direct therapeutic opportunities for *ARID1A* mutant cancer patients including *ARID1A* mutant OCCC. Though efficacy against *ARID1A* wild-type OCCC should not be excluded.

6. SMARCA2 and SMARCA4-directed synthetic lethal strategies

Aside from synthetic lethal targeting strategies in the context of *ARID1A* mutations, the SWI/SNF complex members SMARCA2 and SMARCA4 have been exploited for this purpose as well. Having *SMARCA2* and *SMARCA4* mutations in approximately 2% and 5% of the tumors, OCCC could benefit from such strategies [15]. In 2013, Oike et al. described susceptibility for SMARCA2 inhibition in SMARCA4 deficient non-small cell lung cancer. Treatment with *SMARCA2* siRNA induced markers of senescence in *SMARCA4* mutant cell lines [66]. An epigenome directed shRNA screen further supported the finding that SMARCA4 deficient cancers depend on SMARCA2. SMARCA4/SMARCA2 synthetic lethality was later demonstrated in multiple other cancer types [67]. SMARCA4 loss resulted in enhanced integration of SMARCA2 in the residual SWI/SNF complexes, which in turn may drive oncogenesis [68]. *SMARCA2* and *SMARCA4* alterations have a similar incidence in cancer, with the exception of small cell carcinoma of the ovary hypercalcaemic type (SCCOHT) in which *SMARCA4* mutations are present in 90% of the tumors (Fig. 3). A recent

study reported the absence of SMARCA2 expression in SMARCA4 deficient SCCOHT, indicating that SMARCA2/SMARCA4 mutual exclusivity is not synthetic lethal in all cancer types. Somehow these cancers have overcome dependency on either one of the SWI/SNF ATPases. Moreover, restoration of SMARCA2 or SMARCA4 inhibited proliferation [69]. These results suggest that dependency on SWI/SNF ATPases is lost in SCCOHT. In line with these observations, another study identified several *SMARCA4* mutant cancers cell lines with absent or low expression of SMARCA2. Inhibition of the PRC2 subunit EZH2 re-expressed SMARCA2 only in the EZH2 sensitive *SMARCA4* mutant subset of cell lines. EZH2 inhibition specifically induced apoptosis in one (the ovarian endometrioid cancer cell line TOV-112D) of the four EZH2 sensitive *SMARCA4* mutant lines [70]. It is unknown whether the SWI/SNF function is retained after loss of SMARCA2 and SMARCA4 or that these tumors are more dependent on other chromatin remodelers. Chemical inhibitors of SMARCA2 and SMARCA4 are currently under development. The first SMARCA2/SMARCA4 specific inhibitor PFI-3 did not show anti-proliferative effects in lung cancer cells, possibly because of insufficient inhibition of SMARCA2 binding to DNA [71]. To utilize the SMARCA2/SMARCA4 dependency in a clinical setting, development of inhibitors that target either SMARCA2 or SMARCA4 might be beneficial to achieve tumor selective lethality.

7. Conclusion and future considerations

The abundance of *ARID1A* loss of function mutations across cancer types designates mutant *ARID1A* as an attractive target for synthetic lethal approaches. Mechanistic insight into inhibitor induced synthetic lethality with ARID1A loss is at least partially revealed (Fig. 4). EZH2, HDAC2, HDAC6, BRD2 and YES1 inhibition were found to be specifically lethal in *ARID1A* mutant OCCC. Additional lethal targets that have been verified across multiple other *ARID1A* mutant cancer lineages, included PARP, ATR and HSP90 (Fig. 5).

Inhibition of the synthetic lethal targets HDAC2 and HDAC6 demonstrated a large difference in sensitivity between *ARID1A* mutant and wild-type OCCC cell lines. Since both targets were tested in a limited number of cell lines evaluation in a larger cell line panel of would be required to verify the robustness of HDAC2 and HDAC6 inhibition. Synthetic lethality of drugs targeting EZH2 and BRD2 in *ARID1A* mutant OCCC was less pronounced. Though, the advantage of these last two studies was the use of 3D in vitro models for the assessment of sensitivity to EZH2 inhibition and the use of patient-derived xenotransplants in addition to a large panel of OCCC cell lines to determine sensitivity to BRD2 inhibition. The distinct function of SWI/SNF complexes among tissues indicates that molecular dependencies in *ARID1A* mutant cancers are lineage specific, thus requiring testing of ATR and HSP90 inhibitors in the context of OCCC. For example, PARP
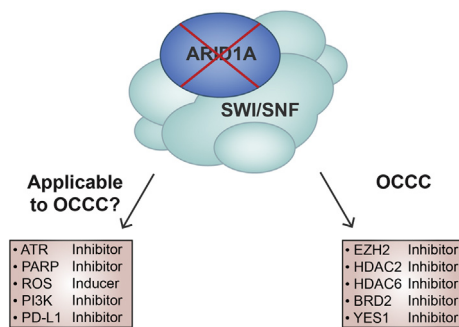
Fig. 5. Synthetic lethal therapies identified in *ARID1A* mutant OCCC and other tumor types. Inhibition of EZH2, HDAC2, HDAC6, BRD2 and YES1 were found to be synthetic lethal in ARID1A deficient OCCC. *ARID1A* mutation dependent (driven) synthetic lethality was observed in other tumor types with ROS induction (via HSP90 inhibition) and inhibition of ATR, PARP, PI3K and PD-L1. Whether these synthetic lethal therapies can be applied to OCCC remains to be proven.

inhibitor potency has been evaluated in OCCC cell lines but did not seem to provide selective sensitivity in *ARID1A* mutant OCCC cells [11, 72]. We found no enrichment for alterations in DNA repair genes in *ARID1A* mutant versus wild-type OCCC tumors and cell lines, which may provide an explanation for this observation [11]. However, genetic evidence using isogenic OCCC models still needs to be provided.

Besides, ARID1A was recently assigned an important role in mismatch repair as it recruits the mismatch repair gene MSH2 to chromatin during DNA replication. ARID1A loss correlated with mismatch repair deficiency, high mutational load and increased numbers of tumor-infiltrating lymphocytes across many human cancer types [73]. These data propose that ARID1A loss induces microsatellite instability, which subsequently provides a vulnerability to immunotherapy. In *ARID1A* mutant syngeneic mouse ovarian and colorectal cancer models high susceptibility to immune checkpoint blockade of PD-L1 compared to isogenic *ARID1A* wild-type models was already shown [73]. A small study in OCCC patients found high PD-L1 expression and more tumor infiltrating lymphocytes in microsatellite instable cancers, but the *ARID1A* mutation status was not determined [74]. However, the frequency of microsatellite instability in OCCC is relatively low (10–14%), implying that the percentage of OCCC tumors with microsatellite instable and *ARID1A* loss will be even lower [74, 75]. Taken together, these results support exploring immunotherapeutic approaches in the context of *ARID1A* mutant OCCC and could be relevant for a small subset of OCCC patients (Fig. 5).

The question remains whether direct targeting of ARID1B in an *ARID1A* mutant context in OCCC is feasible. It will be challenging to chemically inhibit ARID1B, since both ARID1A and ARID1B lack actionable ATPase or catalytic domains. Moreover, in several OCCC tumors mutations in both *ARID1A* and *ARID1B* were observed, suggesting that in these cells some expression of ARID1A or ARID1B was retained, the SWI/SNF complex is no longer active or compensatory proteins have taken over the DNA binding function of ARID1A and ARID1B within the SWI/SNF complex [15]. Synthetic lethality in *SMARCA2* or *SMARCA4* mutant OCCC may be an alternative strategy. However, limited results indicate context dependency of loss of SMARCA2 and SMARCA4 as well, but this has not been investigated in the context of OCCC. Important questions are whether inhibitors selective for either SMARCA2 or SMARCA4 can be developed and which other targets can be used for synthetic lethality approaches in the context of SMARCA2 or SMARCA4 loss in OCCC.

ARID1A mutation directed lethal strategies using agents in clinical development are becoming feasible in *ARID1A* mutant OCCC. Ultimately, simultaneous inhibition of multiple synthetic lethal targets in *ARID1A* mutant OCCC should be assessed to overcome the onset of resistance toward single target synthetic lethality.

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