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Potential Therapeutic Targets in *ARID1A*-Mutated Cancer

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Abstract

ARID1A is a subunit of the Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin-remodeling complex that regulates gene expression by controlling gene accessibility. *ARID1A* shows one of the highest mutation rates across different human cancer types. For example, *ARID1A* is mutated in ~50% of ovarian clear cell carcinoma (OCCC). There is considerable interest in developing cancer therapeutics that correlate with *ARID1A* mutational status. A recent study demonstrated a synthetic lethality by targeting EZH2 histone methyltransferase activity in *ARID1A*-mutated OCCC using a clinically applicable small molecule inhibitor. The observed synthetic lethality correlated with inhibition of PI3K/AKT signaling. In addition, there is evidence indicating that *ARID1A*-mutated cancer may also be subjected to therapeutic intervention by targeting residual SWI/SNF activity, the PI3K/AKT pathway, the DNA damage response, the tumor immunological microenvironment and stabilizing wild-type p53. In summary, we propose EZH2 inhibitor-based combinatorial strategies for targeting *ARID1A*-mutated cancers.

1. Introduction

The Switch/Sucrose Non-Fermentable (SWI/SNF) complex regulates gene transcription through its ATP-dependent chromatin-remodeling activity. Consistent with its role in gene transcription, the SWI/SNF complex is involved in essential cellular processes such as transformation, development, DNA damage repair and cell cycle regulation. The SWI/SNF complex has garnered substantial attention because subunits of the complex are collectively mutated in >20% of human cancers [1]. Among the SWI/SNF subunits, *ARID1A* has highest mutation rate in human cancers. *ARID1A* is mutated in ~50% of ovarian clear cell carcinoma (OCCC) [2, 3]. *ARID1A* mutations are typically nonsense or frame-shift, which cause loss of ARID1A protein expression. Further highlighting the importance of the SWI/SNF complex in human cancer, several studies have found correlations between the mutational and/or expressional status of SWI/SNF complex subunits and tumor progression, prognosis and

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Declaration of Interest.

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response to chemotherapy. These findings have raised considerable interest in developing targeted therapies that take advantage of *ARID1A* mutations.

Here we will highlight advances in identifying therapeutic targets for *ARID1A*-mutated cancers and discuss additional therapeutic targets based on newly gained mechanistic insights into ARID1A's role in cancer.

2. Epigenetic synthetic lethality by targeting EZH2 in *ARID1A*-mutated cancers

A recent study examined epigenetic inhibitors that selectively suppress the growth of ARID1A-deficient compared with proficient OCCC cells. The authors identified an inhibitor of EZH2, a histone methyltransferase, which selectively promotes apoptosis in *ARID1A*-mutated OCCC cells [4]. EZH2, a subunit of the polycomb complex, represses gene transcription. Mechanistically, the observed synthetic lethality is due to the antagonistic roles played by ARID1A and EZH2 in regulate the expression of ARID1A/EZH2 target genes. Similar epigenetic antagonism exists between EZH2 and SNF5, a core subunit of the SWI/SNF complex that is often deleted in childhood rhabdoid tumors [5]. Consistently, inhibition of EZH2 causes regression of SNF5-deleted rhabdoid tumors [5]. In addition, mutations of *SMARCA4*, the gene encoding the ATPase SWI/SNF subunit BRG1, in non-small lung cancer increases sensitivity to a combinatorial EZH2 and topoisomerase inhibition [6].

EZH2 inhibitors are in clinical development for hematopoietic malignancies such as diffuse large B cell lymphoma. These recent findings indicate that targeting EZH2 using a clinically applicable EZH2 inhibitor represents a strategy for cancers with mutations in subunits of the SWI/SNF complex. Further studies are warranted to determine whether EZH2 inhibition displays a similar selectivity in cancers with genetic inactivation of other SWI/SNF subunits and whether the selectivity of EZH2 inhibition in *ARID1A*-mutated cancer cells is tissue- and/or genetic context-dependent.

3. Targeting residual SWI/SNF complex as a specific vulnerability in *ARID1A*-mutated cancers

The observation that knockdown of SWI/SNF's catalytic subunit, BRG1, inhibits the growth of SNF5-deficient rhabdoid tumors suggests that the survival of SNF5-deficient tumors depends upon residual SWI/SNF complex activity [7]. Residual SWI/SNF complex dependence was further validated by examining mutually exclusive SWI/SNF subunits. Specifically, ARID1A and ARID1B are mutually exclusive in their association with the SWI/SNF complex. The survival of *ARID1A*-mutated cancer cells depends upon the presence of ARID1B in the residual SWI/SNF complex [8]. Likewise, BRG1 and BRM1 (encoded by the *SMARCA2* gene) are mutually exclusive subunits of the SWI/SNF complex and survival of *SMARCA2*-mutated cells depends upon the residual BRG1-containing complex [9]. Conversely, knockdown of BRM1 selectively suppresses the growth of BRG1-deficient cells. Collectively, these findings raise the possibility of targeting residual SWI/SNF complex based on mutual exclusivity of different subunits. The challenge of this

potential approach lies in the development of a subunit-specific inhibitor given the structure and functional similarities.

4. Targeting mutual exclusivity between *TP53* and *ARID1A* mutation

Genetic profiling of *ARID1A*-mutated ovarian cancer reveals enrichment of wild-type *TP53* in these tumors [10]. Functional characterization reveals that ARID1A and p53 function in the same pathway to regulate the expression of p53 target genes [10]. It is therefore possible that stabilization of wild-type p53 might be sufficient to overcome the effects of ARID1A loss and reactivate p53 target tumor suppressor genes. Notably, Nutlin 3, a p53 stabilizer, suppresses the growth of *ARID1A*-mutated A2780 ovarian cancer cells [11]. Clinically applicable p53-stabilizers have been developed [12]. Although it is unlikely that a p53-stabilizer itself will have substantial clinical activity, it provides a target for combinational therapies.

5. Targeting PI3K/AKT Signaling in *ARID1A*-mutated cancers

ARID1A mutation often co-exists with genetic alterations that lead to activation of the PI3K/AKT pathway. These include gain-of-function mutations in the *PIK3CA* oncogene in OCCC or inactivation of the tumor suppressor PTEN in ovarian endometrioid carcinoma (OEC). In an immunohistochemical analysis of OCCC tumors, loss of nuclear ARID1A expression correlated to an increase in AKT phosphorylation [13]. Combination of conditional inactivation of *ARID1A* with activation of *PIK3CA* or inactivation of *PTEN* drives the development of OCCC and OEC, respectively [14]. PIK3IP1, an inhibitor of PI3K/AKT, plays a major role in the observed synthetic lethality between *ARID1A* mutation and EZH2 inhibition [4]. *ARID1A*-mutated cells are more sensitive to PI3K/AKT inhibitors compared with *ARID1A* wild-type cells [4, 15].. Notably, inhibitors of mTOR, the downstream effector activated by PI3K/AKT signaling, such as temsirolimus and everolimus, are now in clinical trials for OCCC. The single-agent inhibition of PI3K/AKT is likely not sufficient to eradicate the disease. Consistently, in an ARID1A/PIK3CA mouse model of OCCC, an inhibitor of PI3K only increased survival by 3.5 weeks [14].

6. Targeting the SWI/SNF-dependent DNA damage response in *ARID1A*-mutated cancers

In addition to modulating signaling through gene regulation, the SWI/SNF complex is implicated in DNA damage repair. SWI/SNF complexes often localize to sites of DNA double-strand breaks (DSB) and facilitate phosphorylation of histone H2AX via ATM/ATR [16]. Thus, SWI/SNF mutated cancers could be sensitive to DNA damage-inducing chemotherapeutics. Counter intuitively, *ARID1A*-mutated OCCC typically lacks genomic instability, and OCCC tumors are less responsive to DNA damage inducing platinum-based chemotherapy. This suggests that the role of the SWI/SNF complex in DNA damage might be subunit- and/or tissue dependent.

7. Targeting tumor microenvironment in *ARID1A*-mutated cancers

The link between chronic inflammation and carcinogenesis is well-characterized and is a hallmark of cancer. Chronic inflammation and expression of pro-inflammatory cytokines (e.g. IL6) are important for escape from anti-tumor immune responses. Recent evidence suggests that ARID1A protects against inflammation-driven tumorigenesis [14]. In a mouse model, *ARID1A* loss and *PIK3CA* mutation cooperate to promote OCCC through sustained IL6 production. Subsequently, IL6 knockdown resulted in significantly smaller tumors, indicating the potential for anti-IL6 therapies in *ARID1A*-mutated cancers. Given the recent success in targeting immune checkpoints, it will be interesting to evaluate the impact of *ARID1A* mutation on anti-tumor immunity and whether *ARID1A*-mutated cancers are sensitive to reactivation of anti-tumor immunity.

8. Conclusion

Recent genome-wide sequencing studies have revealed frequent *ARID1A* mutations in a variety of cancer types. Clinical and pathological studies suggest a great need to develop precision therapy that correlates with *ARID1A* mutational status. In this review, we discussed literature on therapeutic targets with the potential of specifically and selectively targeting *ARID1A*-mutated cancers (Figure 1A). They include EZH2, residual SWI/SNF activity, the PI3K/AKT pathway, the DNA damage response, the tumor immunological microenvironment and stabilizing wild-type p53. The synthetic lethality between EZH2 inhibition and *ARID1A* mutation presents a unique opportunity for developing novel combination therapeutic strategies that correlate with *ARID1A* mutation, the very definition of precision medicine.

9. Expert Opinion

EZH2 inhibition is synthetic lethal with *ARID1A* mutation and causes the regression of established *ARID1A*-mutated OCCC *in vivo*. These findings indicate that the newly discovered synthetic lethality between *ARID1A* mutation and EZH2 inhibition could be developed as an urgently needed therapeutic for *ARID1A*-mutated OCCC. It will be important to investigate whether this approach can be extended into other cancers with *ARID1A* mutation. Since EZH2 inhibition has also been shown to inhibit the growth of SNF5-deficient rhabdoid tumors, it will be interesting to determine whether EZH2 inhibition-based synthetic lethality extends to mutations in other SWI/SNF complex subunits.

Despite the well-described advantages of selectivity and limited toxicity of targeted cancer therapy, clinical trials have extensively demonstrated that targeted therapy, including synthetic lethality-based therapy, often leads to the development of resistance and is not sufficient to eradiate cancer. Combinational therapeutic strategies offer a solution for this major clinical challenge. Clinically applicable drugs that target EZH2, stabilize wild-type p53 or inhibit PI3K/AKT signaling have already been developed. Based on the genetic makeup of *ARID1A*-mutated cancers such as OCCC, an EZH2 inhibitor in combination with a PI3K/AKT signaling inhibitor or wild-type p53 stabilizer may represent a therapeutic strategy that conveys a sustained clinical response (Figure 1B). Further studies are warranted

to investigate potential side effects and pharmacodynamics of these proposed combinatorial approaches. In the long-term, given the recent evidence that ARID1A suppresses tumor-promoting inflammation, it will be interesting to explore EZH2 inhibition in combination with reagents that target the tumor immunological microenvironment.

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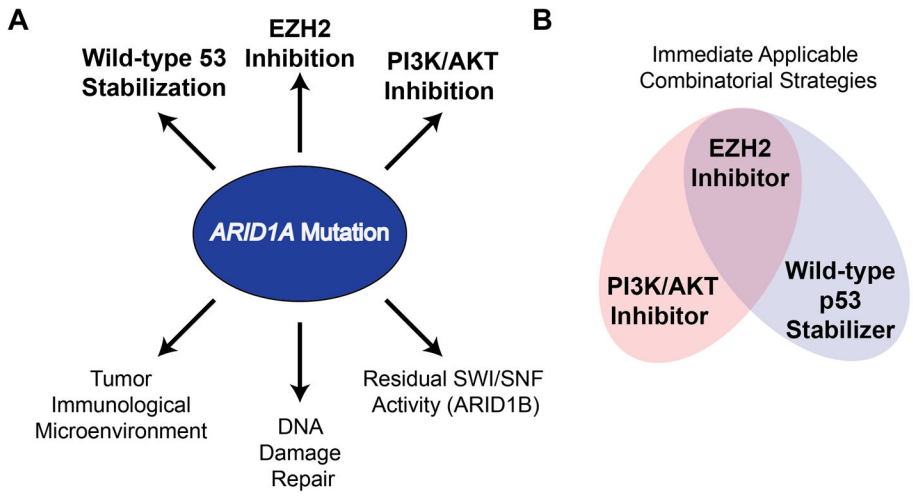

Figure 1. Potential Therapeutic Targets in *ARID1A*-Mutated Cancer

ARID1A-containing SWI/SNF chromatin remodeling-complex regulates multiple biological processes related to tumor suppression. **A)** *ARID1A* mutation and/or loss of expression leads to atypical signaling and cellular functions. In *ARID1A*-mutated cancers, the indicated pathways are potential targets that are selective against *ARID1A* mutation. **B)** To achieve a sustained clinical response, combinatorial therapies will be necessary. An EZH2 inhibitor-based approach presents a unique opportunity for combinatorial strategies.