

Tumor Suppressor Gene ARID1A in Cancer: Recent Advances and Future Perspective

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Received date: January 20, 2016; Accepted date: February 25, 2016; Published date: February 29, 2016

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Keywords: Tumor suppressor gene; ARID1A; Human malignancies; Prognostic genes

Introduction

Tumor suppressor gene AT-rich interactive domain 1A (ARID1A) is a subunit of the Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin-remodeling complex; it regulates gene expression by controlling gene accessibility [1,2]. Genes involved in epigenetic mechanisms establishing chromatin structure are very often mutated in different cancer types; among these, gynecological and gastrointestinal malignancies play a very important role [3-9]. Particularly, ARID1A shows one of the highest mutation rates among human malignancies [10]. Therefore, there is considerable interest in developing cancer therapeutics that can negatively interact with ARID1A mutational status. A recent report showed a synthetic lethality by targeting EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) histone methyltransferase activity in ARID1A-mutated clear cell ovarian cancer, thanks to a small-molecule inhibitor, available and clinically applicable [11]. Its synthetic lethality is associated with inhibition of PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) / AKT (v-akt murine thymoma viral oncogene homolog 1) signaling. Furthermore, there is evidence suggesting that ARID1A-mutated cancer may also be treated by targeting residual SWI/SNF activity, the PI3K/AKT pathway, the tumor immunological microenvironment, stabilizing wild-type p53 and by targeting the DNA damage response [10,12]. About the DNA damage response, a recently developed class of drugs, the poly(ADP-ribose) polymerase-inhibitors (PARPi), are currently being developed in clinical trials as a targeted treatment, acting on the pathway of DNA repair [13]. PARP-1 is a well-characterized protein in the PARP family: through the base excision repair pathway, it is critical to the repair of single-strand DNA breaks [13-15]. The inhibition of PARP conducts to the accumulation of single-strand breaks, resulting in double-strand breaks. In cells with defective HR (homologous recombination) gene, like the BRCA (Breast Cancer gene)-mutations carriers, PARP inhibition can lead to chromosomal instability, cell cycle arrest and subsequent apoptosis [14]. Recently, similarly to BRCA, also ARID1A mutations have been associated with defects in DNA repair, indicating tumors with such mutations as another possible target of PARPi [15]. Since ARID1A mutations are prognostic significant [12,16-19], further studies and clinical trials are needed to define the possible effects of PARPi on ovarian tumors, not only with BRCA1 (Breast Cancer 1) and BRCA2 (Breast Cancer 2) genes, but also with ARID1A mutations.

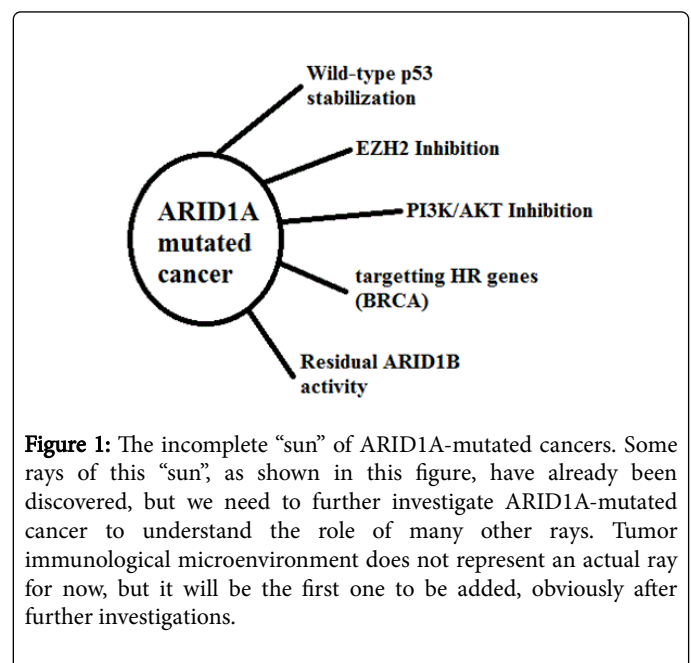


Figure 1: The incomplete “sun” of ARID1A-mutated cancers. Some rays of this “sun”, as shown in this figure, have already been discovered, but we need to further investigate ARID1A-mutated cancer to understand the role of many other rays. Tumor immunological microenvironment does not represent an actual ray for now, but it will be the first one to be added, obviously after further investigations.

Noticeably, a recent meta-analysis indicate that loss of ARID1A shortened time to cancer-specific mortality as well as to recurrence of disease, when adjusting for potential confounders, highlighting the importance of the the search of new therapeutic strategies against tumors with its mutation. A very important aim for surgical pathologist and oncologist, towards personalized medicine, is to investigate and to document on the final pathology report all the morphological aspects with a prognostic impact (e.g.: presence of nodal metastasis, extra-nodal extension of nodal metastasis, presence of vascular embolization) [20-24] and all the molecular features (e.g. BRCA mutations, ARID1A mutations) [12,25] that can indicate the prognosis and may address the therapies. To this aim, the most important prognostic genes, as ARID1A, have to be studied in depth.

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