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Review: Immune Gene Regulation via cGAS-STING in ARID1A-deficient cancers and their response to therapeutic stress

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Abstract

ARID1A, a subunit of the SWI/SNF chromatin remodeling complex, plays a crucial role in maintaining genomic stability by facilitating DNA double-strand break (DSB) repair through chromatin loop formation and transcriptional regulation. Its deficiency is frequently observed in various cancers and is associated with impaired DNA repair mechanisms and increased accumulation of cytosolic DNA. This triggers the activation of the CGAS-STING pathway, a cytosolic DNA-sensing mechanism that induces type I interferon (IFN-I) responses and expression of interferon-stimulated genes (ISGs) such as IFIT1, ISG15, CXCL9, CXCL10, and CCL5. These immune modulators enhance antitumor immunity by promoting immune cell infiltration into the tumor microenvironment. Experimental studies using ARID1A-deficient cancer cell lines—including MDA-MB-231 and AID-Diva—demonstrated increased expression of IFN-α, IL-6, and chemokines upon DNA damage, confirming CGAS-STING pathway activation. Clinically, these downstream genes serve as potential biomarkers for predicting response to DNA-damaging agents and immune checkpoint inhibitors. The findings support the potential of targeting DNA damage-induced innate immune signaling to enhance therapeutic efficacy in ARID1A-deficient tumors.

Keywords: Arid1a; C Gas-Sting; Interferon; DNA Damage; Immunotherapy

1. Introduction

AT-rich interaction domain protein 1A (ARID1A), also known as BAF250a, is the largest subunit of the SWI/SNF (CBAF) chromatin remodeling complex and contains a DNA-binding domain [1]. Chromatin remodeling factors such as the SWI/SNF complex mediate histone modifications and nucleosome displacement, leading to chromatin relaxation that facilitates DNA repair. This complex possesses helicase and ATPase activities that help unwind or relax condensed chromatin structures [2]. As a component of the SWI/SNF complex, ARID1A plays a role in modulating chromatin structure around double-strand break (DSB) sites, thereby influencing the accessibility and activity of DNA repair proteins. ARID1A has been implicated in the regulation of various DNA damage repair pathways, particularly non-homologous end joining (NHEJ) and homologous recombination (HR). However, direct evidence detailing how ARID1A affects specific protein dynamics within these pathways remains limited, underscoring the need for further research to elucidate its precise regulatory roles [3].

ARID1A acts as a regulator of DNA repair by facilitating the formation of chromatin loops necessary for the efficient establishment of γH2AX foci at double-strand break (DSB) sites. γH2AX serves as an early marker of DNA damage that is crucial for recruiting other DNA repair factors. By promoting chromatin loop formation, ARID1A enhances accessibility to DNA damage sites, thereby supporting the repair process. In addition, ARID1A is involved in regulating transcriptional repression at DSB sites located within actively transcribed genomic regions. This transcriptional

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silencing is essential to prevent conflicts between DNA repair processes and ongoing transcription, which could otherwise lead to further damage or exacerbate genomic instability. Therefore, ARID1A's role as an epigenetic regulator is vital for maintaining the balance between chromatin structure, DNA repair, and transcriptional control, thereby ensuring genomic stability [3] [4].

The CGAS-STING-IFN-I axis represents a pivotal component of the innate immune response, functioning as a cytosolic DNA sensing mechanism that activates downstream immune signaling [5]. Cyclic GMP-AMP synthase (CGAS) detects aberrant cytoplasmic double-stranded DNA (dsDNA), which may arise from viral infection or DNA damage within tumor cells [6] [7]. Upon recognition, CGAS catalyzes the synthesis of -cyclic GMP-AMP (cGAMP), a second messenger that binds and activates Stimulator of Interferon Genes (STING). Activated STING translocated from the endoplasmic reticulum to the Golgi apparatus, where it recruits TBK1 and promotes phosphorylation of IRF3, leading to transcriptional induction of type I interferons (IFNs) and interferon-stimulated genes (ISGs) such as IFIT1, ISG15, and CCL5 [8] [9].

In ARID1A-deficient cancer cells, such as bladder cancer, this pathway gains relevance. ARID1A is a key subunit of the SWI/SNF chromatin remodeling complex and functions as a tumor suppressor. Its deficiency impairs DNA damage repair mechanisms like mismatch repair (MMR), thereby increasing genomic instability and the accumulation of cytosolic DNA—an activator of the CGAS-STING axis (Wang et al., 2020). Studies show that ARID1A-deficient tumors express higher levels of neoantigens, which enhance both innate and adaptive anti-tumor immunity. Importantly, the activation of the CGAS-STING pathway in these cells leads to an upregulation of inflammatory chemokines such as CXCL9, CXCL10, and CCL5, which recruit cytotoxic T cells and NK cells into the tumor microenvironment, thereby potentiating immune surveillance [10] [3].

Furthermore, treatment with DNA-damaging agents, commonly used in cancer cell line, exacerbates cytosolic DNA accumulation, further amplifying CGAS-STING signaling. While this may enhance immune-mediated tumor clearance, resistance mechanisms such as expansion of myeloid-derived suppressor cells (MDSCs) and epigenetic repression of chemokines can impair immune infiltration despite pathway activation. Therefore, understanding the regulation and modulation of the CGAS-STING-IFN-I axis in ARID1A-deficient contexts is critical for developing effective immunotherapy combinations and overcoming resistance [11].

2. Clinical implication and biomarker potential

The CGAS-STING pathway and its downstream genes, including type I interferons (e.g., IFNB1) and chemokines such as CXCL9, CXCL10, and CCL5, have emerged as promising biomarkers of innate immune activation and potential predictors of therapeutic response in ARID1A-deficient cancers. A study by Wang et al. (2020) demonstrated that ARID1A-deficient ovarian and colorectal cancer cells exhibit heightened activation of the CGAS-STING-IFN-I axis in response to DNA damage and checkpoint inhibition. Treatment with ATM and Chk2 inhibitors, which increase replication stress and cytosolic DNA accumulation, selectively triggered STING-TBK1 pathway activation in ARID1A-deficient cells, leading to the upregulation of immune genes such as CCL5 and CXCL10. These genes function not only as markers of immune activation but also as effectors that recruit cytotoxic T cells and natural killer (NK) cells into the tumor microenvironment [12].

Clinically, this activation translated into enhanced immune checkpoint blockade (ICB) efficacy when ARID1A-deficient tumors were treated with a combination of ATM inhibitors and anti–PD-L1 antibodies, resulting in increased infiltration of CD8+ T cells, reduced tumor burden, and prolonged survival in syngeneic mouse models. This underscores the utility of CCL5, CXCL10, and IFNB1 as predictive biomarkers of therapeutic responsiveness and highlights the potential of targeting cancer-intrinsic DNA damage responses to modulate tumor immunogenicity. Importantly, these findings support a precision medicine approach in which the ARID1A mutational status and expression of STING-related biomarkers may guide the use of DNA damage response inhibitors and immunotherapies for optimal treatment outcomes [12].

The research done in 2024, conduct research with various cancer cell lines including MDA-MB-231, a human breast cancer cell line, and AID-Diva cells, which are U2OS-derived and engineered to generate site-specific double-strand breaks (DSBs) upon induction. To investigate the role of ARID1A, the authors utilized CRISPR-Cas9 to generate ARID1A-knockout (ARID1A-KO) models, followed by assays such as RNA-seq, qtr.-PCR, immunofluorescence staining, and Western blotting to examine gene expression and signaling activity [3]. The study found that ARID1A deficiency led to the accumulation of unrepaired DNA, formation of micronuclei, and activation of the CGAS-STING pathway, a cytosolic DNA-sensing mechanism that stimulates innate immune responses. Upon DNA damage (e.g., ionizing radiation), ARID1A-deficient cells exhibited increased phosphorylation of IRF3, a downstream effector of STING activation, and

significantly elevated expression of type I interferon IFN-α, pro-inflammatory cytokine IL-6, and chemokines CXCL9 and CXCL10. These molecules are known for recruiting immune cells such as T cells and macrophages to the tumor microenvironment [3]. Thus, loss of ARID1A amplifies the expression of IFN-α, IL-6, CXCL9, and CXCL10 by enhancing cytosolic DNA sensing via CGAS-STING, linking DNA repair defects to a pro-inflammatory and potentially anti-tumor immune response. These findings position ARID1A as a crucial epigenetic regulator not only in DNA damage repair but also in modulating the immune landscape of tumors [3].

3. Conclusion

In conclusion, ARID1A deficiency not only impairs DNA repair but also enhances innate immune activation through the CGAS-STING-IFN-I axis. This leads to the upregulation of pro-inflammatory cytokines and chemokines such as IFN-α, IL-6, CXCL9, and CXCL10, which attract cytotoxic immune cells to the tumor microenvironment. These immune responses highlight the dual role of ARID1A as both a genomic stabilizer and a modulator of tumor immunogenicity. The expression of downstream genes like IFNB1, CXCL10, and CCL5 may serve as valuable biomarkers for patient stratification and for guiding combination therapies involving DNA damage response inhibitors and immunotherapies. Future research should focus on overcoming resistance mechanisms, such as immune suppression by MDSCs or epigenetic silencing, to fully harness the immunotherapeutic potential of ARID1A-deficient tumors.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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