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REVIEW ARTICLE

The emerging role of Arid5a in cancer: A new target for tumors

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Abstract AT-rich interactive domain 5a (Arid5a) is a member of the arid family of proteins, which contain a helix-turn-helix domain and an ability to bind to nucleic acids. Current evidence suggests that Arid5a performs dual functions as a transcription factor and an RNA-binding protein in immune, nonimmune, and/ or tumor cells depending on its cellular localization. The contribution of Arid5a to the development of inflammation, autoimmunity, and obesity through its transcriptional and posttranscriptional regulatory functions has broadly been reviewed. Recent studies have indeed revealed an association of Arid5a with cancers, including breast, pancreatic, colorectal, and lung cancers and glioma. Notably, Arid5a affects various aspects of cellular homeostasis, including invasion, metastasis, epithelial-to-mesenchymal transition, immune evasion, adipogenesis and M1-like tumor-associated macrophage (TAM)-to-M2-like TAM transition. This review aims to summarize current knowledge of Arid5a from a cancer perspective and highlights recent advances in Arid5a-related cancer research. This review may improve the understanding of Arid5a-mediated molecular mechanisms and their relevance to cancers.

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Introduction

The AT-rich interactive domain (Arid) is a nucleic acid-binding domain that is evolutionarily conserved in higher eukaryotes. Arids consist of a consensus sequence of ~100 amino acids and a helix-turn-helix motif.[1–3] The arid family comprises 15 members and has been shown to have importance in cell development, differentiation, proliferation, and tissue-specific gene expression.[4–6] The association of some arid family members with cancers has already been established, and their function in the initiation and progression of human cancers is well understood. However, studies on the role of Arid5a in cancer have just begun.

Arid5a, one of the arid family proteins, is translocated to the cytoplasm from the nucleus under inflammatory conditions.[7] It shows different functions in the regulation of mRNAs or genes depending on its subcellular (nuclear or cytoplasmic) localization. Moreover, nuclear and cytoplasmic Arid5a perform dual roles associated with transcriptional and posttranscriptional regulation. Arid5a mediates the transcriptional regulation of genes in the nucleus; however, recent advances in Arid5a research have established it as an RNA-binding protein (RBP), unveiling its important function in the posttranscriptional regulation of inflammatory mRNA transcripts.[8–11]

Arid5a is expressed abundantly in human cardiovascular tissue and acts as an estrogen receptor (ER)-interacting repressor of gene expression[12] by binding to the N-terminus and C-terminus of *ER-*α in the nucleus. In addition, Arid5a is also expressed in cartilage and induces chondrocyte differentiation as a transcriptional partner of *sex-determining region Y box transcription factor 9 (Sox9)*, which regulates chondrocyte differentiation through activation of *Col2a1*, a chondrocyte-specific gene.[13] In the nucleus, Arid5a has been shown to negatively regulate the transcription of the *Mie* gene of human cytomegalovirus (HCMV) in human Tera-2 cells, a human embryonal carcinoma cell line, by binding to multiple sites on the modulator located upstream of the *Mie* gene enhancer of HCMV.[14] Our group showed that *Arid5a* is expressed and resides primarily in the nucleus of fibroblasts, where it is involved in the transcriptional repression of *Ppar-*γ, a master regulator of adipogenesis; in this way, Arid5a inhibits adipogenesis and obesity in mice.[15] More recently, Arid5a was found to be involved in the transcriptional regulation of long noncoding RNA (lncRNA)-*AU021063*, which induces invasion and metastasis of breast cancer cells.[16]

On the other hand, posttranscriptional control of mRNA usually occurs in the cytoplasm. As mentioned, many studies have reported another function of Arid5a in the stabilization of mRNA transcripts of a set of inflammatory genes,[8–11] which suggests the presence of Arid5a in the cytoplasm and its ability to participate in post-transcriptional regulatory mechanisms as an RBP.[7]

RBPs are key players in posttranscriptional events. The combination of the versatility of their RNA-binding domains with structural flexibility enables RBPs to control the metabolism of a large array of transcripts.[17] Given the central role of RBPs in the regulation of gene expression, it comes as no surprise that RBP malfunctions, or mutations in the RNA elements they recognize, can lead to diseases, including cancer. Moreover, perturbations in RBP-RNA network activity have been causally associated with cancer development. Increasing evidence suggests that post-transcriptional regulation also controls several important cellular mechanisms, including proliferation, differentiation, invasion, metastases, apoptosis and angiogenesis, that could lead to a cancer phenotype.[18] It is likely that transcripts of nearly all known oncogenes and tumor suppressors may be controlled by various mechanisms that define mRNA stability and, ultimately, competency for translation. Arid5a has been identified to have a novel function in the stabilization of mRNAs, including Interleukin-6 (IL-6), *T-bet*, Signal Transducer and Activator of Transcription 3 (Stat3), and *Ox40*,[8–11] and to be associated with inflammation and autoimmunity. Furthermore, Arid5a was shown to inhibit the destabilizing effect of Regnase-1, an RBP, on *IL-6* mRNA by binding to the 3' UTR of *IL-6* mRNA, thereby interfering with Regnase-1-mediated destabilization of *IL-6* (Fig. 1).[8] Interestingly, *Arid5a* deficiency inhibited the elevation of IL-6 and interferon-gamma (IFNγ) serum levels in lipopolysaccharide (LPS)-treated mice; as a result, the mice became resistant to septic shock (Fig. 2).[10] Additionally, decreased IL-6 levels during *Arid5a* deficiency suppressed the development of Th17 cells in an experimental autoimmune encephalomyelitis (EAE) model by controlling the stability of *Stat3* mRNA (Fig. 2).[9] Although Arid5a plays a crucial role in the development of numerous human diseases through transcriptional and post-transcriptional regulation of many transcripts, the function of Arid5a in cancer remains unclear. Recent studies have reported significant functions of Arid5a in numerous types of cancer, including pancreatic, colorectal, breast, and lung cancers and glioma, which broadens the potential utility of Arid5a in cancer research.[19–22] Here, we highlight recent advances in Arid5a research, especially the association of Arid5a with the tumor microenvironment (TME) and cellular homeostasis. It is expected that an increased understanding of the function of Arid5a in cancer cells will aid the development of prognostic and response biomarkers and potentially improve strategies for the design of therapeutics.

The effects of Arid5a on RNA stability, inflammation and autoimmunity

When it was initially discovered, Arid5a was observed to be associated with mRNA stability in a study that investigated the mechanism by which chlorpromazine (CPZ), an antihistaminic and antipsychotic drug, mediated inhibition of IL-6 in macrophages.[23] CPZ specifically inhibits LPS-induced IL-6 production in macrophages, while other inflammatory cytokines are not affected.[8,23] Arid5a is also inhibited by CPZ, and an *IL-6* 3' UTR RNA-protein binding assay coupled with mass spectrometry revealed a novel function of Arid5a as an *IL-6* 3′ UTR RBP. Furthermore, *Arid5a*$^{-/-}$ mice show reduced IL-6 concentrations in serum following LPS treatment[10] and are unable to develop EAE.[8] Experimentally, the reduction in IL-17-producing CD4^{+} T cells in *Arid5a*-

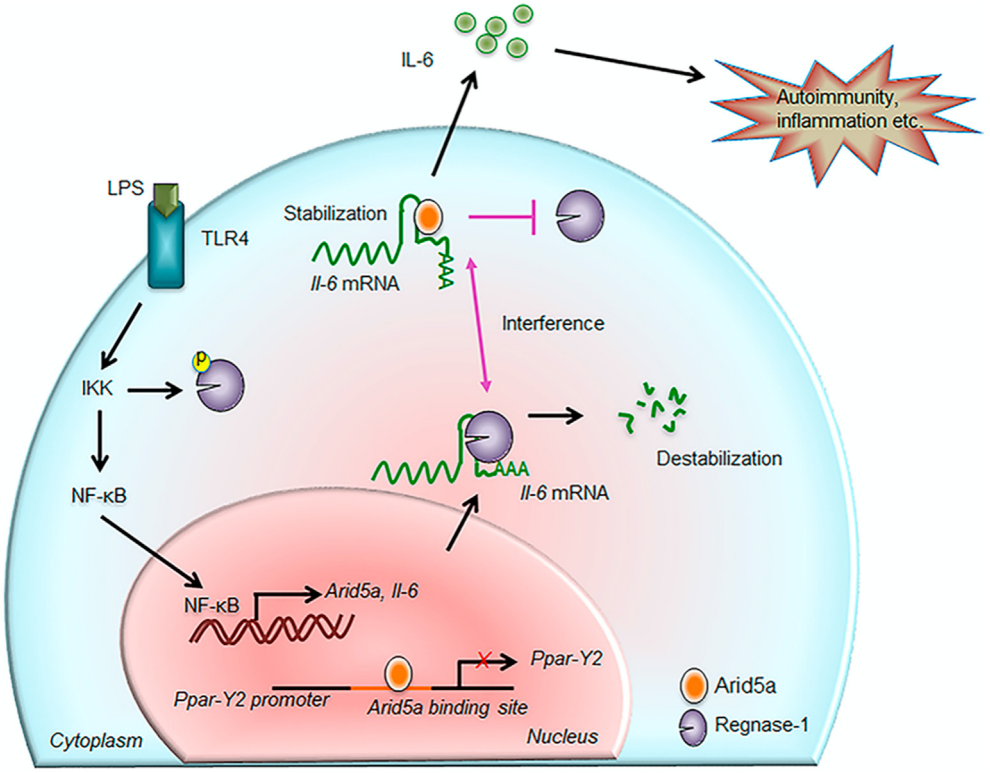

Figure 1 Contribution of AT-rich interactive domain 5a (Arid5a) to interleukin (IL)-6 production and disease. The innate immune response is generated by pathogen-associated molecular patterns, which are recognized by pathogen-recognition receptors and lead to the expression of proinflammatory mediators. For example, toll-like receptor 4 recognizes lipopolysaccharide and activates the IKK/NF-κB signaling pathway. The IKK complex phosphorylates Regnase-1 and promotes transcription of *IL-6* and *Arid5a*. Regnase-1 binds to the *IL*-6 mRNA and degrades it. In the nucleus, Arid5a binds to genes encoding transcription factors, such as *Ppar-γ2*, to inhibit their expression. Furthermore, Arid5a is shuttled to the cytoplasm under inflammatory conditions, where it interferes with the destabilizing effect of Regnase-1. Arid5a is involved in *IL*-6 mRNA stabilization, and the resulting increase in IL-6 production is associated with inflammation and autoimmune diseases. "Reprinted from Frontiers in Immunology, 10, Kishan Kumar Nyati, Riddhi Girdhar Agarwal, Praveen Sharma, Tadamitsu Kishimoto, Arid5a regulation and the roles of Arid5a in the inflammatory response and disease, article 2790, copyright (December 2019), under the terms of the creative commons attribution license (CC-BY)", https://www.frontiersin.org/articles/10.3389/fimmu.2019.02790/full.

deficient mice was correlated with decreased expression of *IL-6*, *Stat3* and *Ox40*. Activated *Arid5a*-deficient $CD4^+$ T cells have been found to reduce IL-6, Stat3 and Ox40 concentrations, which are responsible for the amelioration of EAE (Fig. 2).[8,9,11,24,25]

Arid5a promotes IL-17 signaling by stabilizing the expression of several IL-17-dependent cytokine mRNA transcripts (*IL-6*, *Cxcl1*, and *Cxcl5*) by binding to their 3' UTR sequences. Arid5a can facilitate translation of two IL-17-dependent transcription factors, CCAAT-enhancer-binding proteins β (*C/ebpβ*) and *IκBζ*, allowing indirect transactivation of the *Lcn2* promoter by increasing the expression of the genes reliant on these transcription factors. Arid5a was found to increase *Lcn2* by enhancing *C/ebpβ* expression, and constructs with mutations in the C/EBP binding element failed to be activated by Arid5a. Silencing *Arid5a* strongly inhibited IL-17-induced expression of all C/EBP protein isoforms. Therefore, Arid5a can also promote the expression of certain IL-17-dependent genes (e.g., *Lcn2*) with no effect on mRNA stability. IL-17 stimulation of target cells increases the abundance of Arid5a and triggers recruitment of Arid5a to the adaptor TRAF2, forming a feed forward loop.[24–26]

Arid5a is highly expressed in the nucleus, but stimulation of TLR4 and IL-17 signaling induces its translocation to the cytoplasm.[7,26] In stromal ST2 cells, *Arid5a* was found to be increased only in cytoplasmic fraction after IL-17 stimulation. Although it is not known whether IL-17 similarly alters Arid5a subcellular localization, Arid5a occupancy with its target mRNAs occurs only in cytoplasmic extracts and not in nuclear extracts. Furthermore, Arid5a associations with *IL-6*, *Cxcl1*, *Cxcl5*, *Nfkbiz*, and *C/ebpβ* transcripts were found to be increased in cytoplasmic fractions after IL-17 stimulation, while these associations were not enriched in the control or nuclear fraction.[26] Collectively, these findings show that by inducing the expression of these key transcription factors, Arid5a amplifies the IL-17-driven signaling program (Fig. 2), which might reveal a strategy to treat IL-17-dependent diseases.[25]

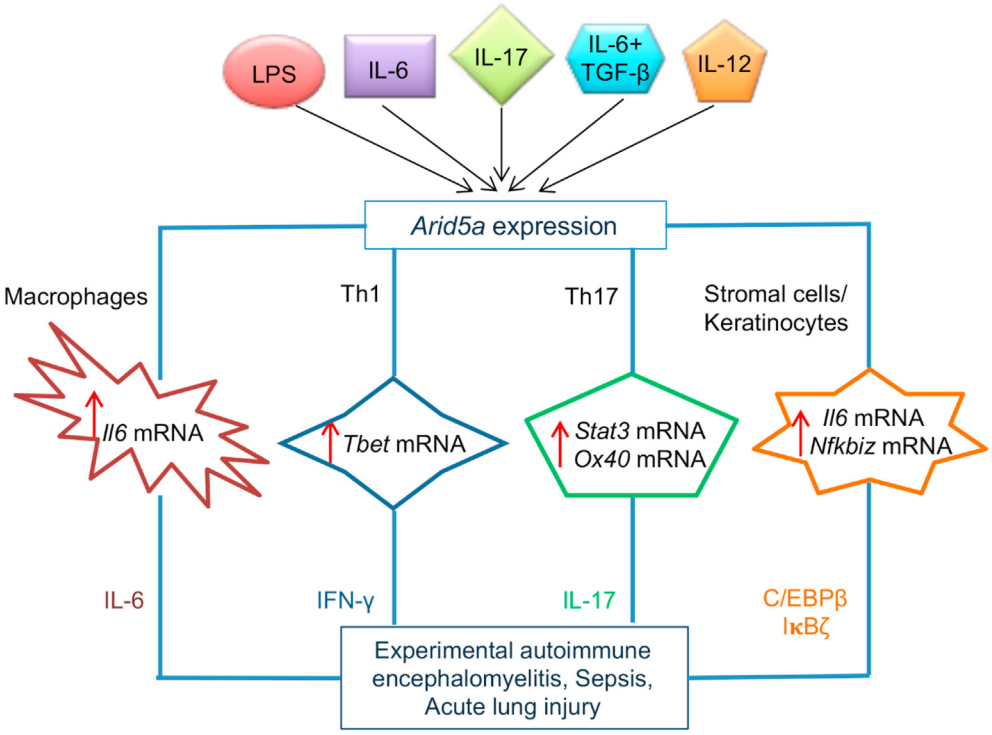

Figure 2 Role of AT-rich interactive domain 5a (Arid5a) in the pathogenesis of sepsis, acute lung injury (ALI), and experimental autoimmune encephalomyelitis (EAE) in mice. *Arid5a* expression is induced in many immune cells, such as macrophages, T helper (Th) 1 cells, Th17 cells, stromal cells, and keratinocytes, after stimulation with lipopolysaccharide (LPS), interleukin (IL)-6, IL-6 + transforming growth factor (TGF)-β, IL-17, or IL-12. Arid5a stabilizes a variety of inflammatory mRNAs, including *IL-6*, *Tbx21*, *Stat3*, *Ox40*, and *Nfkbiz*, in these cells. The stabilization of these target mRNAs results in overproduction of IL-6, interferon (IFN)γ, IL-17, CCAAT-enhancer-binding proteins (C/EBP)β, and inhibitor of κB (IκB)ζ, which triggers pathogenesis of sepsis, ALI, and EAE in mice. "Reprinted from Trends in Immunology, 41 (3), Kishan Kumar Nyati, Mohammad Mahabub-Uz Zaman, Praveen Sharma, Tadamitsu Kishimoto, Arid5a, an RNA-binding protein in immune regulation: RNA stability, inflammation, and autoimmunity, p255—268, copyright (March 2020), with permission from Elsevier".

Zaman et al.[10] previously showed that T cells from *Arid5a*-deficient mice were defective in expressing *IFN*γ under Th1 cell conditions when *Tbx21* mRNA expression was inhibited. Mechanistically, Arid5a bound to the conserved stem-loop structure of the 3' UTR of *Tbx21* and enhanced its mRNA stability (Fig. 2).[10] Additionally, *Arid5a* deficiency resulted in resistance to the effects of *Propionibacterium acnes*-derived LPS injection in mice, and the mice were unable to develop endotoxic shock. Interestingly, anti-IFNγ and anti-IL-6 treatments rescued wild-type mice from LPS-induced septic shock,[10] suggesting that IFNγ and IL-6 in Th1 cells were the major cytokines involved in Arid5a-mediated septic shock in mice. IL-6 has been shown to inhibit the differentiation of adipocytes, limiting obesity in mice,[15,27] and IL-6 levels are decreased in *Arid5a*-deficient mice.[8,10] Given the link between IL-6 and Arid5a signaling in adipogenesis, a recent study reported the regulation of adipogenesis and obesity through Arid5a signaling. Arid5a was found to inhibit adipogenesis by repressing the transcription of *Ppar-γ2*, which is the major regulator of adipogenesis, in the nucleus.[15] This study further showed that IL-6 treatment could not inhibit the differentiation of adipocytes in mouse *Arid5a*-deficient 3T3-L1 cells, while unstimulated *Arid5a*-deficient 3T3-L1 cells showed inhibition of adipocyte differentiation.[15] This was the first observation to suggest that IL-6 utilizes Arid5a to inhibit the differentiation of adipocytes. Moreover, *Arid5a* expression is induced by IL-6; therefore, it is likely that *IL-6*-deficient mice lack sufficient *Arid5a* expression, which leads to increased adipogenesis and obesity. Furthermore, Arid5a binds to the *Ppar-γ2* promoter and suppresses *Ppar-γ2* transcription, which ultimately restricts the process of adipogenesis in mice (Fig. 1). To date, most studies have indicated that Arid5a plays a crucial role in inflammatory and autoimmune diseases through transcriptional and posttranscriptional regulation of genes. Although Arid5a equally participates in the regulation of innate and adaptive immune signaling pathways, further investigations are needed to determine whether Arid5a has a significant role in immune regulation.

Identification of Arid5a functions in cancers

Pancreatic and colorectal cancer

Immunotherapy represents a fundamental change in the treatment of advanced cancers.[28] Immune checkpoint blockade, which can be effective even in metastasized cases and has shown significant suppression of tumor progression, is a particular focus currently. Unfortunately, most tumors appear to be resistant to immune checkpoint

blockade therapy,[29] possibly due to the plasticity and heterogeneity of tumors and the TME. In addition, increased activation of immune checkpoint pathways, such as the programmed death 1 (PD-1)-PD ligand 1 axis, or accumulation of immunosuppressive metabolites can sometimes cause an immune evasion mechanism by which tumors can evade the host's immune response.[30] Pancreatic and colorectal cancers, considered cold or nonimmunogenic tumors due to their insufficient quantities of tumor-infiltrating lymphocytes,[31,32] can avoid immunosurveillance. Increasing evidence shows that epithelial-to-mesenchymal transition (EMT) assists tumor cells in acquiring invasion and migration capacity and immunosuppressive properties; however, the precise molecular mechanisms relating mesenchymal tumor subtypes with resistance to immunosurveillance remain elusive.[29] Moreover, the tumor-intrinsic mesenchymal phenotype has been associated with accelerated immune evasion via crosstalk with stromal immune cells in the TME.[29] It is known that stromal and immune cells in the TME disturb tumor growth, likely owing to direct interaction with tumor cells and/or by altering innate and adaptive immunity.[33] Stromal and tumor cells secrete small molecules, such as chemokines, kynurenine, and adenosine, which can recruit immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), to the TME.[33,34] Furthermore, immune responses can be distorted by the inhibition of T cell activation or by the emergence of T cell exhaustion in the TME.[35,36] Therefore, immune metabolites and chemokines may have the potential to guide the development of novel strategies for cancer treatment.

Our group has recently demonstrated that *Arid5a* expression is associated with mesenchymal subtypes of colorectal and pancreatic (pancreatic ductal adenocarcinoma, PDAC) cancers, such as the CMS4 and QM subtypes, respectively.[21] Additionally, *Arid5a* expression was found to be significantly correlated with the levels of transforming growth factor (TGF)-β1, IL-6, and EMT-associated transcription factors (EMT-TFs), but not Stat3, in PDAC and colorectal cancers. This finding suggests that EMT-TFs are involved in the upregulation of Arid5a in PDAC and colorectal cancers of mesenchymal subtypes. However, the molecular mechanisms underlying the regulation of *Arid5a* expression in mesenchymal tumors need to be uncovered, and these mechanisms could be of great interest for future studies.

Arid5a participates in immune evasion by increasing tumor infiltration of granulocytic MDSCs (gMDSCs) and Tregs and suppressing antitumor effector T cell recruitment and activation in the TME.[21] Higher expression of *Arid5a* was observed in human and murine pancreatic cancer lines with EMT properties than in non-EMT cell lines. Remarkably, *Arid5a*-deficient tumor cells produced smaller tumors in immunocompetent mice than in immunodeficient mice. This result suggested the existence of Arid5a-mediated immunosuppression in the TME. Furthermore, *Arid5a* knockout tumors contained more effector $CD8^+$ T cells, fewer Tregs, and fewer MDSCs than wild-type tumors, indicating that Arid5a assists tumors in evading immune rejection. Mechanistically, Arid5a was found to enhance the expression of *Ido1* and C-C motif chemokine ligand 2 (Ccl2) by binding to their mRNAs in the 3' UTRs to stabilize them posttranscriptionally. Notably, IDO1 is known to degrade tryptophan into kynurenine, which results in decreased effector T cell proliferation and promotes Treg differentiation.[37,38] Moreover, Arid5a-mediated stabilization of *Ido1* mRNA increases IDO1 expression, which leads to local immunosuppression. Similarly, the increase in the expression of *Ccl2* due to Arid5a-facilitated stabilization of its mRNA augments the recruitment of MDSCs to the tumor.[21] These phenomena were verified in both pancreatic and colorectal tumor models, providing a better understanding of the link between EMT, Arid5a, and tumor immune invasion and indicating that Arid5a is a promising target for tumor immunotherapy. The molecular mechanisms underlying how Arid5a expression is regulated in mesenchymal tumors might be of future interest.

Lung cancer

Lung cancer causes the highest number of cancer-related deaths in men and women worldwide.[39] The 5-year survival rate of metastatic lung cancer is 5%, which is much lower than most of the other cancer types.[40] Surgery is the first line of treatment in lung cancer, but most clinically identified cases are inoperable. Chemotherapy and radiotherapy are the next alternatives; however, these therapies reduce the quality of life and disrupt normal tissue homeostasis. Recently, immune checkpoint blockade therapies, such as agents targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and PD-1, have produced results in lung cancer treatment, but only a subset of patients achieved a strong response with minimum toxicity with these immunotherapies.[41–44] Therefore, in-depth analysis of cells in the TME that contribute to lung cancer is required to identify new targeted therapies.

Macrophages have important prognostic value in the lung TME, as confirmed by experimental evidence.[45–47] Macrophages are classically split into two subtypes: LPS/IFNγ-generated M1 macrophages and alternative IL-4-activated M2 macrophages. Existing evidence indicates that the classical method of macrophage polarization and the extrinsic and intrinsic characteristics of macrophages are dependent on stimulatory conditions[48]; therefore, gene regulation in cytokine-stimulated macrophages is not necessarily similar to that in TAMs.[49,50] It is likely that the induction of an M1 versus M2 phenotype of macrophages based on cytokine stimulation is restricted and may act differently in the case of TAMs. TAMs receive a variety of activating signals, as they are located in the areas surrounding tumor cells and other tumor-infiltrating immune cells in the TME.[51,52] Sarode et al[19] recently reported a central role of β-catenin-mediated Wnt signaling and transcription of *Fos-like antigen 2 (Fosl2)* and *Arid5a* in the transition of tumor-inhibiting M1-like TAMs into tumor-promoting M2-like TAMs, identifying a role of TAM-specific signaling in immune evasion in lung cancer (Fig. 3). Moreover, β-catenin transcriptionally activates *Fosl2* and represses *Arid5a* expression in M2-like TAMs and partially regulates macrophage gene expression via *Tnf* and *Ccr2*, which leads to the suppression of lung tumor progression/

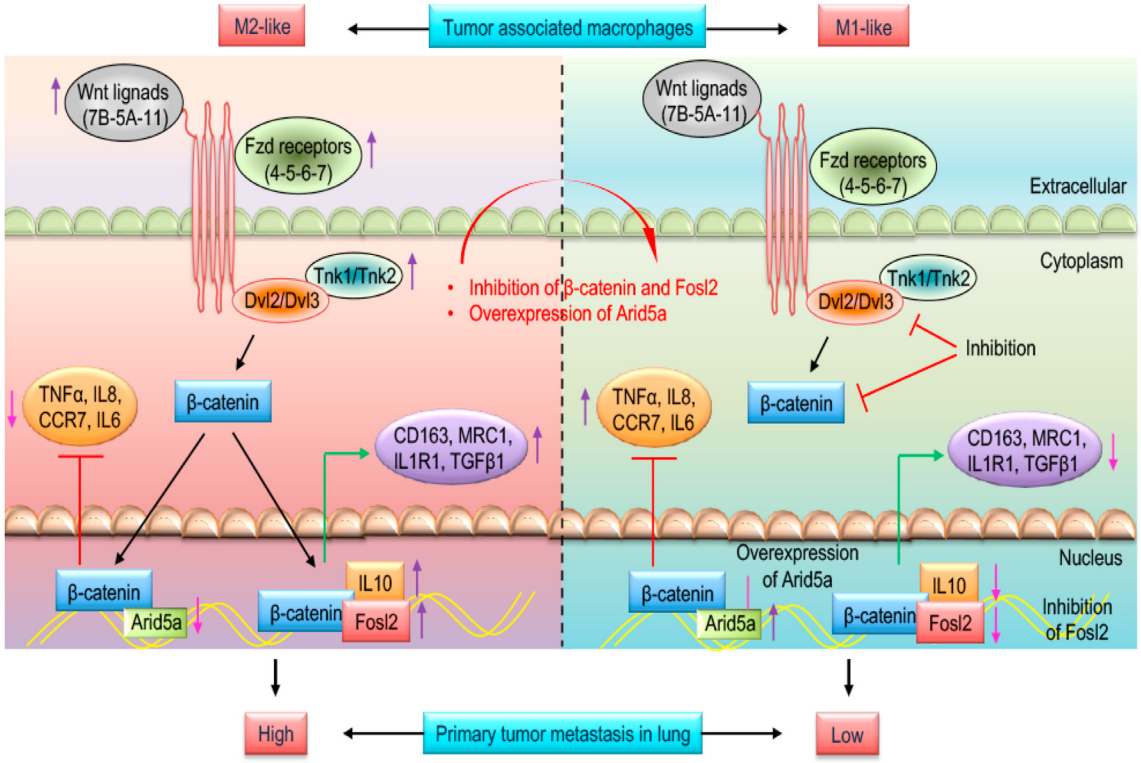

Figure 3 Reprogramming of M2-like TAMs to M1-like TAMs. Wnt ligands (Wnt5A-7B-11), frizzled receptors (Fzd4-5-6-8-9), disheveled (Dvl2-3), and Tnk (Tnk1-2) are upregulated in M2-like TAMs, and in this way, transcriptional activation of *β-catenin* occurs. β-catenin binds to the promoter region of M2 macrophage genes such as *IL-10* and to TF-activating M2 macrophage genes such as *Fosl2, CD163, MRC1, IL-1R1,* and *TGFβ1* and thus activates the M2 macrophage program. In contrast, β-catenin suppresses the M1 macrophage program by binding to TF-activating M1 macrophage genes such as *Arid5a, TNFα, IL-8, CCR7, and IL-6*. With inhibition of *β-catenin* and *Fosl2* and overexpression of *Arid5a*, M2-like TAMs are reprogrammed into M1-like TAMs; thus, reactivation of antitumor immunity in the tumor microenvironment occurs to restrict primary and metastatic lung tumor growth. "Reprinted from Frontiers in Immunology, 12, Kishan Kumar Nyati, Tadamitsu Kishimoto, Recent advances in the role of Arid5a in immune diseases and cancer, article 827611, copyright (January 2022), under the terms of the creative commons attribution license (CC-BY)", https://www.frontiersin.org/articles/10.3389/fimmu.2021.827611/full.

metastasis in lung cancer models, *in vitro*-trained TAMs and *ex vivo*-cultured TAMs isolated from mouse and human lung tumors (Fig. 3). Analysis of the transcriptomic data of lung cancer patients showed that upregulation of *β-catenin* and *Fosl2* and downregulation of *Arid5a* were correlated with poor prognosis. Future analyses should consider clinical TAM-specific *β-catenin/Fosl2/Arid5a* expression levels when measuring the survival advantage offered by a TAM-specific inhibitor of *β-catenin* and its transcriptional targets (*Fosl2* and *Arid5a*) in the treatment of lung cancer. Collectively, this study indicates that targeting β-catenin-dependent gene regulation in M2-like TAMs may be a new treatment strategy in lung cancer.[19]

Glioma

Glioma is considered a common intracranial malignant primary tumor and accounts for approximately 27% of all central nervous system tumors.[53] Gliomas have higher rates of morbidity, mortality, and recurrence than other nervous system tumors.[54,55] Low-grade gliomas (LGGs) include grade 2 and 3 gliomas that show slow growth and low malignancy, whereas grade 4 glioma, glioblastoma multiform (GBM), is an invasive tumor with high recurrence and mortality.[56,57] Eradication of gliomas is difficult owing to their high degree of malignancy and invasive growth.[54] Surgical resection, postoperative adjuvant radiotherapy, and temozolomide-based chemotherapy are the current options for the treatment of gliomas; however, the survival time of patients following treatment is still limited due to the high tumor recurrence rate and poor prognosis of patients.[58,59] As a strategy to identify alternative diagnoses and improve prognosis, next-generation gene sequencing has identified several molecular markers, even in gliomas. The two most critical molecular biomarkers for glioma, *isocitrate dehydrogenase (IDH)* mutation and 1p/19q combined deletion, have been widely used in clinical diagnosis and therapy.[60] Therefore, the identification of biomarkers that may help in determining cancer risk, improving prognosis, and predicting tumor recurrence is of great interest. Hence, it is of great significance to identify biomarkers for determining cancer risk, estimating the prognosis of patients, and predicting tumor recurrence.

In searching for a new molecular marker in glioma, only one study investigated the diagnostic and prognostic significance

of Arid5a and detected the possible biological functions and pathways of Arid5a.[20] Gene expression profiling interactive analysis (GEPIA) analysis of the LGG and GBM datasets in the cancer genome atlas (TCGA) database showed that higher expression of *Arid5a* was negatively correlated with the prognoses of LGG and GBM, indicating that high expression of *Arid5a* is probably a marker of poor prognosis in glioma. In contrast, low expression of *Arid5a* in lung cancer was previously found to be associated with poor prognosis.[19] Analysis of the genotype-tissue expression (GTEx) database revealed lower levels of *Arid5a* expression in normal human brain tissues than in most other tissues. Based on Chinese glioma genome atlas (CGGA) and TCGA RNA sequencing data and clinical and molecular characterization data, it was found that the expression level of *Arid5a* increased with increasing glioma tumor grade, as classified by WHO criteria. In addition, *Arid5a* expression was found to be significantly higher in *IDH*-wild-type gliomas than in *IDH*-mutant gliomas and in gliomas without 1p/19q codeletion than in 1p/19q codeletion gliomas. Earlier studies reported that wild-type *IDH*, lack of 1p/19q codeletion, and higher tumor grade were associated with poor prognosis in glioma.[61,62] Another study indicated that higher *Arid5a* expression was associated with higher tumor malignancy,[20] suggesting that Arid5a is a marker for detecting the degree of tumor malignancy.

Gene set enrichment analysis (GSEA) of glioma samples (from CGGA datasets) with low and high expression of *Arid5a* revealed that cell adhesion molecules (CAMs), ECM receptor interactions, the JAK-STAT signaling pathway, leukocyte transendothelial migration, and the p53 signaling pathway were enriched in the high *Arid5a* expression group, whereas analysis of TCGA datasets revealed enrichment of apoptosis, cytokine−cytokine receptor interactions, the JAK-STAT signaling pathway, leukocyte transendothelial migration and the toll-like receptor signaling pathway in the high *Arid5a* expression group. It has been reported that *IL-6* and *Stat3* mRNAs are stabilized by Arid5a,[8,9,24] and Stat3 or IL-6 can modulate *p53* gene expression and protein degradation.[63,64] Therefore, it is likely that Arid5a may affect the occurrence, development and clinical prognosis of glioma by regulating the p53 signaling pathway and JAK-STAT signaling pathway in glioma patients, and cell apoptosis and the immune response in glioma might be regulated by a high level of *Arid5a* expression. Gene ontology analysis showed that the inflammatory response, immune response, and IFNγ-mediated signaling pathway were highly correlated with higher *Arid5a* expression in glioma, revealing potential mechanisms affecting the growth and proliferation of cancer cells. IFNγ performs a dual function in cancer. It can enhance tumor growth by supporting an immunosuppressive TME65; on the other hand, it suppresses angiogenesis and enhances immunogenicity in tumors66. As discussed above, Arid5a can enhance the production of IFNγ by increasing *T-bet* mRNA stability.[10,16] Therefore, Arid5a may modulate the IFNγ-mediated signaling pathway to induce the formation of the TME. However, studies of Arid5a in glioma have been based on database mining; therefore, a comprehensive study of cell lines and animal/patient samples is required to confirm the role of Arid5a and its underlying mechanism in glioma.

Prostate cancer

Prostate cancer is known as one of the most common and lethal neoplasms in the urologic system, resulting in approximately 260,000 deaths every year in men globally.[67] Due to the continuously increasing numbers of patients with prostate cancer in the past few decades in developing countries, prostate cancer has become a great burden on public health systems.[68] Serum prostate-specific antigen (PSA) levels and pathological stage are the only major monitoring indicators of prostate cancer. Therefore, new biomarkers are required to assist in the diagnosis and timely treatment of prostate cancer. Approximately 30% of prostate cancer patients experience recurrence and metastasis after surgery,[69] even with advances in medical research. Several prostate cancer patients eventually develop aggressive castration-resistant prostate cancer,[70,71] even after androgen deprivation therapy is applied. Therefore, the identification of valuable molecular markers might be of great importance to improve the prognosis and diagnosis of prostate cancer patients.

Previously, it was found that knockdown of *Arid5a* expression inhibits the proliferation of dihydrotestosterone (DHT)-stimulated LNCaP prostate cancer cells by lessening global protein synthesis.[72] Inhibition of *Arid5a* causes DHT-stimulated cell cycle arrest at the G1 phase, which further decreases DHT-induced lipid accumulation. Knockdown of *Arid5a* decreased the expression of cell survival, proliferation, and cycle regulation proteins, such as HIF1a, cyclin D1, and cyclin D3, but it did not affect mRNAs, suggesting that Arid5a affects protein levels at the translational and/or posttranslational level. Furthermore, *Arid5a* deficiency in LNCaP cells increased the phosphorylation of eukaryotic translation initiation factor 2a (eIF2a) by activating general control nonderepressible 2 kinase (GCN2) and RNA-dependent protein kinase (PKR)-like endoplasmic reticulum kinase (PERK).[72] However, the study showed only preliminary findings on Arid5a regulation of proliferation and global protein synthesis in prostate cancer, and it would be of further interest to study how Arid5a regulates GCN2 and PERK kinases, tumorigenesis, and tumor progression in prostate cancer.

Breast cancer

Breast cancer is the most common cause of cancer-associated death in women worldwide, with an estimated incidence rate of 279,100 new cases per year in the United States alone. Tumor recurrence and metastasis are the major problems; therefore, despite substantial improvements in diagnosis and treatment, the path to reach complete remission in breast cancer is complex. Some genes have been approved as targets for the treatment of breast cancer; however, the clinical efficacy of agents targeting these genes is limited. Furthermore, the serious health issues caused by breast cancer globally increase the demand for new biomarkers and therapeutic targets.

A recent study based on database mining assessed the mRNA expression of arid family members, including Arid5a, in breast cancer based on TCGA data and analyzed the

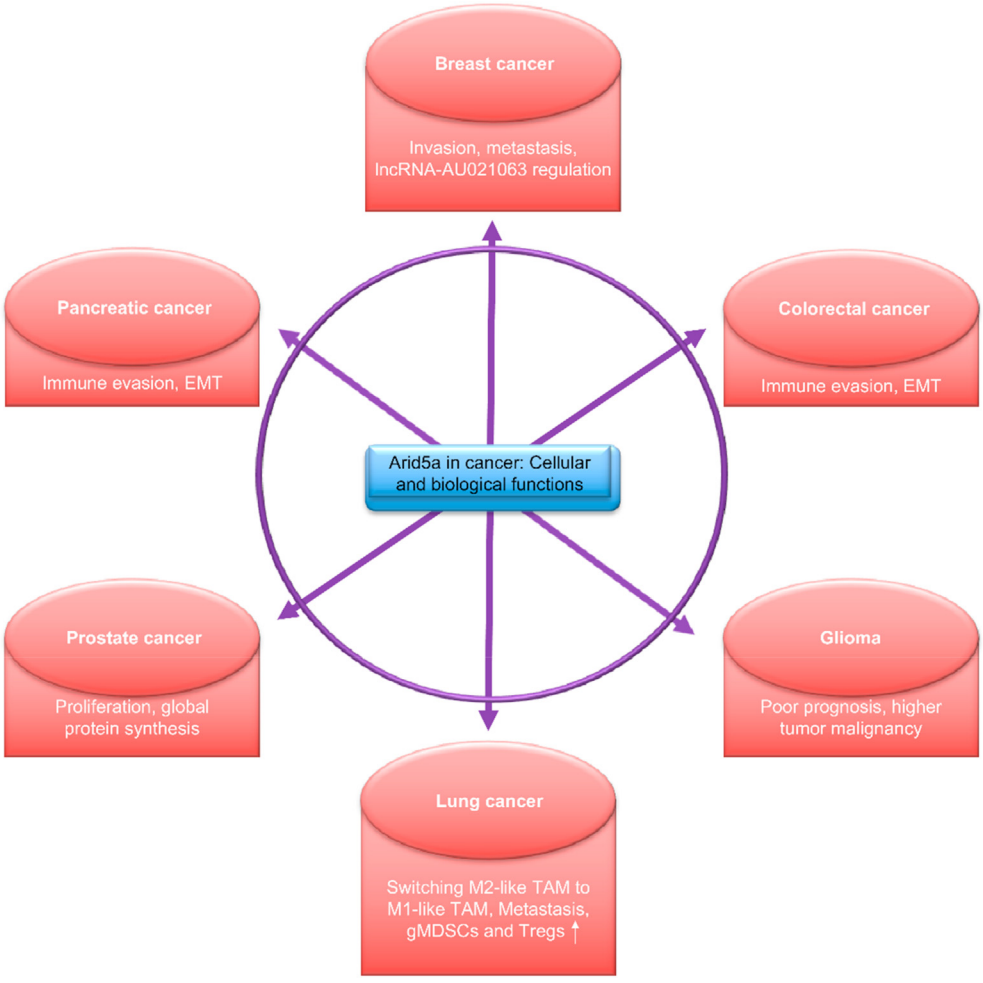

Figure 4 Functions of AT-rich interactive domain 5A (Arid5a) in cancer. Arid5a regulates various cellular processes via transcriptional and posttranscriptional modifications and is associated with the regulation of various cellular activities, as depicted above. "Reprinted from Frontiers in Immunology, 12, Kishan Kumar Nyati, Tadamitsu Kishimoto, Recent advances in the role of Arid5a in immune diseases and cancer, article 827611, copyright (January 2022), under the terms of the creative commons attribution license (CC-BY)", https://www.frontiersin.org/articles/10.3389/fimmu.2021.827611/full.

prognostic role of each member in breast cancer patients through Kaplan–Meier plotter.[22] In the TCGA data analysis of tumor and normal breast tissues, the mRNA expression of *Arid3a, Arid3b, Arid4b, Jarid1b, Jarid1c*, and *Jarid2* was higher, whereas *Arid1b, Arid3c, Arid4a, Arid5a, Arid5b*, and *Jarid1a* mRNA expression was lower in tumor tissues. Furthermore, the expression of *Arid1a, Arid1b, Arid2, Arid3a, Arid4a,* and *Arid4b* in nonluminal subtypes of breast cancer was lower than that in luminal subtypes; conversely, *Arid3c, Arid5a,* and *Jarid2* mRNA expression was higher in nonluminal subtypes of breast cancer tissues. Lower mRNA expression of *Arid5a* was correlated with poor overall survival in luminal type and all breast cancer patients according to Kaplan–Meier plotter analysis. Based on an analysis of online datasets, one study identified Arid5a as a good candidate for tumor treatment in breast cancer[22]; however, the study lacked experimental evidence, suggesting that further study is necessary.

IL-6 is a well-known inflammatory cytokine and is being increasingly appreciated as a mediator of cancer progression, invasion, and metastasis.[73–75] *IL-6* expression in breast tumors increases with tumor grade, and increased serum IL-6 levels are associated with poor survival of breast cancer patients. IL-6 induces *Arid5a* mRNA expression in macrophages and mouse embryonic fibroblasts (MEFs).[8,76] Furthermore, *Arid5a* mRNA expression is inhibited in *IL-6*-knockdown MEFs activated by LPS,[76] although *Arid5a* mRNA expression cannot be induced in *Stat3*-knockdown MEFs, even upon LPS stimulation. These findings suggest that Stat3 plays an essential role in *Arid5a* expression under canonical IL-6 signaling. Further investigation revealed that phosphorylated Stat3 binds to the promoter region of *Arid5a*, increasing its expression. Furthermore, IL-6–STAT3 signaling has also been shown to act synergistically with LPS signaling to induce *Arid5a* expression.[76] However, as discussed above, a correlation of *Arid5a* expression with *Stat3* was not observed in PDAC and colorectal cancers, suggesting different mechanisms of Arid5a regulation in tumors.[21]

Our group recently found that lncRNA-*AU021063*, the expression of which is induced by IL-6–Arid5a signaling,

regulates breast cancer invasion and metastasis by stabilizing the Trib3 protein and activating the MAPK pathway.[16] Analysis of transcriptomics and genomics data revealed that the expression of lncRNA-*AU021063* was significantly higher in breast cancer 4T1 cells than in other tumor cell lines under IL-6 treatment. Furthermore, a fluorescent *in situ* hybridization study verified that the relative expression level of lncRNA-*AU021063* was significantly decreased in *Arid5a*-deficient breast cancer cells but increased in *Arid5a*-overexpressing breast cancer cells stimulated with IL-6 compared to controls. Additionally, lncRNA-*AU021063* expression was observed in both the nucleus and cytoplasm, as was *Arid5a* expression. Arid5a is involved in the transcriptional and posttranscriptional regulation of genes and mRNA transcripts and thus contributes to the development of a variety of human diseases.[8,10,15] Luciferase assays and ChIP assays coupled with ChIP sequencing data analysis further suggested that Arid5a binds to the promoter region of lncRNA-*AU021063* and thereby increases the transcription of lncRNA-*AU021063*. Furthermore, induction of *IL-6* expression in lncRNA-*AU021063*-deficient and *Arid5a*-deficient breast cancer cells inhibited invasion in a Matrigel invasion assay. *In vivo* imaging data demonstrated that lncRNA-*AU021063*-deficient and *Arid5a*-deficient breast cancer cells had significantly inhibited lung metastasis ability in mice. Some lncRNAs have been identified to regulate the MAPK pathway[77] and to regulate genes through transcriptional, posttranscriptional, translational and/or posttranslational regulation to further control biological processes.[78] In our study, experiments with a pharmacological inhibitor of protein synthesis, cycloheximide, identified that 4T1 cells with overexpressing of lncRNA-*AU0*21063 had increased Trib3 protein levels compared with control cells under IL-6 stimulation. In addition, the 26S proteasome inhibitor MG132 rescued the reduction in Trib3 protein that was caused by lncRNA-*AU021063* inhibition in 4T1 cells, suggesting that lncRNA-*AU021063* enhances the levels of Trib3 protein in response to IL-6 by preventing the degradation of Trib3.[16]

Evidence suggests that IL-6 stimulates *Trib3* expression in breast cancer cells[79] and activates the MAPK pathway, which augments cancer processes, including invasion and metastasis.[79–82] In line with earlier evidence, our data also identified prolonged activation of Mek1/2 and Erk1/2 kinases along with higher levels of Trib3 protein in IL-6-induced lncRNA-*AU021063*-overexpressing breast cancer cells than in unstimulated cells. The invasiveness of IL-6-treated 4T1 breast cancer cells was significantly reduced following the inhibition of *Trib3* expression, indicating that the downregulation of *Trib3* expression could inhibit the invasion of 4T1 breast cancer cells under IL-6 signaling even in the case of overexpression of lncRNA-*AU021063*. This finding signified that Trib3 is necessary downstream of lncRNA-*AU021063* to mediate the invasion activity of breast cancer cells under IL-6 signaling. In addition to identifying the metastatic effects of Trib3 in breast cancer cells, the study also found that nude mice carrying 4T1 cells with repressed Trib3 expression had significantly decreased metastasis into the lungs compared to control mice, which further highlighted Trib3 involvement in the promotion of metastasis of breast cancer 4T1 cells. However, it would be of interest to identify their binding fragments and determine the underlying mechanism of Trib3 and MEK/ERK signaling mediated by lncRNA-*AU021063*. Taken together, the data show that the IL-6—Arid5a—lncRNA-AU021063 axis acts as a regulator of breast cancer metastasis via Trib3, increasing the validity of strategies employing Arid5a and lncRNA for therapeutic purposes in breast cancer.[16]

Conclusion

In summary, the role of Arid5a in inflammation and autoimmunity accomplished through its transcriptional and posttranscriptional regulation of inflammatory genes and mRNAs has already been established. In reality, Arid5a has multiple roles, such as modulating innate and adaptive immune responses, regulating cell proliferation, inducing differentiation of Th1 and Th17 cells, stabilizing mRNA, and regulating transcription factors. A better understanding of the Arid5a protein and its interaction with mRNAs and/or genes may help to decipher Arid5a signaling in diseases and improve therapeutic and diagnostic modalities targeting Arid5a. Recent advances have revealed crucial roles of Arid5a in numerous cellular processes, such as invasion, metastasis, reprogramming M2-like TAMs to M1-like TAMs, regulation of lncRNAs, and immune suppression in the TME, in a variety of cancers (Fig. 4), suggesting its potential as a candidate for cancer targeted therapy. However, an in-depth understanding of Arid5a involvement in biological processes in the TME and associated signaling pathways in cancers requires further research. Moreover, studying the function of Arid5a in cancers and the tumor immune microenvironment is of great significance for better understanding tumorigenesis and could result in the identification of new gene-targeted immunotherapies. Taken together, Arid5a is a novel molecule involved in various human carcinomas, but the functions and molecular mechanisms are still not fully characterized and deserve to be further elucidated in the future.

Author contributions

Kishan Kumar Nyati: Conceptualization and Investigation.
Kishan Kumar Nyati: Roles/Writing — Original draft including literature search, reading, and figure preparation.
Kishan Kumar Nyati and Tadamitsu Kishimoto: Writing — review & editing.
Kishan Kumar Nyati, Tadamitsu Kishimoto: Funding acquisition, Supervision, Visualization.

Conflict of interests

T.K. holds a patent for tocilizumab and has received royalties for Actemra. All authors declare no conflict of interests.

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