

The Role of ARID1A in Endometrial Cancer and the Molecular Pathways Associated With Pathogenesis and Cancer Progression

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Abstract. *AT-rich interaction domain 1A gene (ARID1A) encodes for a subunit of the switch/sucrose non-fermentable (SWI/SNF) complex, a chromatin remodeling complex, and it has been implicated in the pathogenesis of various cancer types. In this review, we discuss how ARID1A is linked to endometrial cancer and what molecular pathways are affected by mutation or inhibition of ARID1A. We also discuss the potential use of ARID1A not only as a prognostic biomarker, but also as a target for therapeutic interventions.*

The dynamic modification of chromatin structure in a temporal- and spatial-specific manner determines cell fate by regulating expression levels of specific genes. The complexity of this process is further highlighted when considering all the endogenous and exogenous signals received by each cell during development and throughout its life. Numerous molecules (proteins and RNA) and macromolecular complexes are responsible for the organization of nucleosomes (Figure 1), epigenetic modifications, the dynamic change between the ‘relaxed’ or ‘tight’ conformation of chromatin (euchromatin and heterochromatin, respectively) and the accessibility of gene promoters determining cellular activities such as gene

transcription, DNA repair and cell differentiation. Thus, disruption of normal chromatin remodeling impairs cellular development and homeostasis, and it has been associated extensively with tumorigenesis [reviewed in (1)].

The switch/sucrose non-fermentable (SWI/SNF) complex is a nucleosome-remodeling factor found in both eukaryotes and prokaryotes. It is involved in gene expression through transcriptional regulation and plays a pivotal role in carcinogenesis (2). This complex changes the DNA conformation in nucleosomes, allowing recruitment of transcription factors or other complexes responsible for DNA repair, replication and proliferation. Thus, when the SWI/SNF complex is disrupted, aberrant cell cycling is observed, as well as a loss of control of proliferation (3). SWI/SNF is a multi-subunit complex and many of its subunits, such AT-rich interaction domain 1A (ARID1A), ARID1B, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 2 (SMARCA2) and SMARCA4 (Figure 2), have been incriminated as driving mutations in various cancer types due to the high mutation frequencies observed (4). In particular, when considering human primary cancer cases with mutations in the SWI/SNF complex, most of the mutations seen are encountered in the gene encoding ARID1A (5-7). *ARID1A* and *ARID1B* genes encode DNA-targeting subunits, while *SMARCA2* and *SMARCA4* encode ATPase enzymes. The mutation frequency of these subunits in different cancer types seems to be tumor type-specific indicating that there is probably differential participation of the complex in gene regulation in different tissues (4). Loss of ARID1A has been shown in numerous human malignancies, such as uterine endometrioid carcinoma (8-10), ovarian endometrioid carcinoma (11), gastric cancer (12, 13), esophageal adenocarcinoma (14), pancreatic cancer (15) and colorectal cancer (16).

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ARID1A

ARID1A gene has been characterized as a tumor suppressor, and the majority of the mutations seen in human cases are frame-shift or nonsense mutations (17). It encodes a protein with both nuclear and cytoplasmic localization, however, it was shown that nuclear ARID1A is unstable, as it is rapidly degraded by the nuclear ubiquitin-proteasome system (17, 18). It is known that *ARID1A* expression is regulated by somatic mutations, copy number and methylation of its promoter (19). In-frame deletions disrupting the nuclear export signal lead to reduced ARID1A levels, due to the nuclear retention of the protein and its subsequent degradation (17, 18). As the majority of *ARID1A* mutations result in truncated proteins and proteins prone to degradation, its mutation in cancer highly correlates with loss of its protein expression, which can be assessed by immunohistochemistry (12, 15, 20). In addition, missense mutations in the DNA-binding domain of ARID1A impaired the activity of the SWI/SNF complex by reducing its genomic occupancy in mouse embryos, which resulted in embryonic lethality due to cardiovascular development defects (21). Furthermore, loss of ARID1A promoted colon cancer in a mouse model of human colorectal cancer (16) indicating its involvement in different tissues. According to next-generation sequencing data, mutations in *ARID1A* were not only found in endometrial cancer, but at different frequencies in a variety of human malignancies, such as 3.2-3.5% in breast carcinoma (22), 9.1-15% in esophageal adenocarcinoma (14, 23), 8-27% in gastric carcinoma (24), 8% in pancreatic carcinoma (25), 10-13% in hepatocellular carcinoma (26), 13% in transitional cell carcinoma of the bladder (27), 6% in neuroblastoma (28), and 17% in Burkitt lymphoma (29).

The extensive list of human malignancies found to have mutated ARID1A highlights the importance of this molecule and suggests that regulating its expression might be a viable therapeutic strategy. In fact, restoring ARID1A expression in ovarian cancer cells expressing mutant ARID1A resulted in suppression of proliferation and tumor growth in mice, whereas *ARID1A* silencing in a mouse tumor xenograft model increased cellular proliferation and tumorigenicity (8). Similar findings were also shown in cell lines of esophageal, breast and gastric cancer, with silencing of *ARID1A* leading to increased proliferation and restoration of its expression in cells carrying the mutant form leading to suppression of proliferation (23, 24). In addition, further characterization in a murine preosteoblast cell line showed that ARID1A inhibition enhanced proliferation by preventing cell-cycle arrest through the regulation of c-MYC expression (30). Furthermore, using a high-throughput genetic screening approach, it was shown that inhibition of ARID1A not only enhanced proliferation, but also reduced apoptosis of Jurkat

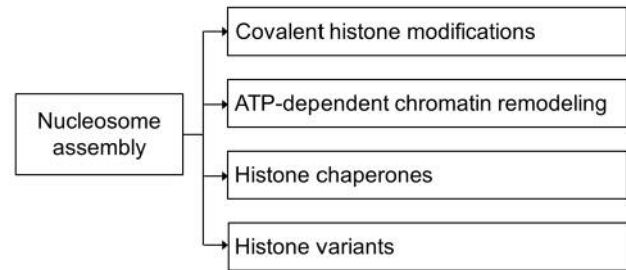


Figure 1. Levels of nucleosome assembly. Nucleosome assembly depends on histone modifications, ATP-dependent chromatin remodeling, the action of histone chaperons and the involvement of different histone variants.

leukemia cells by inhibiting FAS-mediated cell death (31). When considering tumor progression, it was shown that loss of ARID1A was associated with reduced progression-free survival in ovarian clear cell carcinoma (32), as well as deep myometrial invasion in endometrial carcinoma (33). A role of ARID1A in tumor initiation was also supported by the identification of *ARID1A* mutations and expression loss in precancerous lesions of esophageal adenocarcinoma, with higher frequency of loss in lesions with severe dysplasia (14). All these studies suggest that ARID1A acts as a tumor suppressor and has an important role in tumor initiation, disease progression and apoptosis through its regulation of cellular proliferation in multiple cancer types, including endometrial cancer (32).

In direct contrast to cancer cells, where *Arid1a* loss promoted proliferation and halted cellular differentiation, its loss in healthy embryonic stem cells had the opposite effect by impairing the maintenance of the pluripotent characteristics of the cells, as well as cell proliferation (34). In particular, ablation of ARID1A in early mouse embryos resulted in developmental arrest and failure of mesodermal layer formation. In addition to defective development, loss of pluripotency, inhibition of self-renewal and promotion of differentiation into primitive-endoderm-like cells were seen. This study suggested that ARID1A has a key role in differentiation with lineage-specific characteristics, as *in vitro* development of neurons and skeletal muscle was permitted, but development of cardiomyocytes and adipocytes was inhibited. Thus, ARID1A function and expression should be considered in a spatial and temporal context in relation to therapeutic and diagnostic potential applications.

Endometrial Cancer and ARID1A

One of the most common and invasive types of gynecological cancer is endometrial cancer, which in 2015 accounted for 40% of all gynecological cancer cases

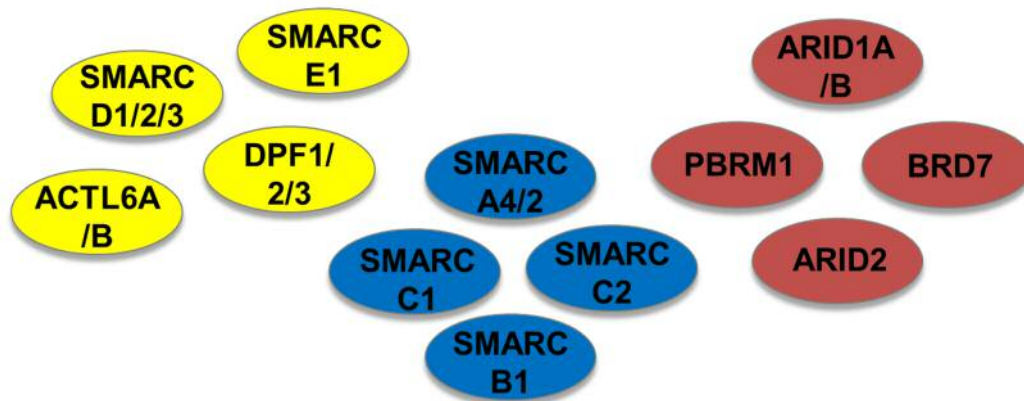


Figure 2. Switch/sucrose non-fermentable (SWI/SNF) complex consists of the core elements SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily A, member 4/2 (SMARCA4/2), SMARCC1, SMARCC2 and SMARCB1 (shown in blue); with the additional subunits SMARCD1/2/3, SMARCE1, actin-like 6A/B (ACTL6A/B) and double PHD fingers 1/2/3 (DPF1/2/3) (shown in yellow), and the variant components AT-rich interaction domain 1A/B (ARID1A/B), polybromo 1 (PBRM1), bromodomain-containing 7 (BRD7) and ARID2 (shown in red).

worldwide (35). Endometrial cancer has been divided into two major groups according to clinical, pathological and molecular features: type I and type II. Type I encompasses endometrioid and estrogen-related cancer cases, and is the most frequent form, as it appears in 80% of patients suffering from endometrial cancer. It is characterized by unopposed estrogen stimulation, early onset of symptoms (young women) and relatively favorable prognosis. In contrast, type II endometrial cancer (non-endometrioid and non-estrogen-related) usually presents as serous and clear cell carcinomas, and this type of cancer is characterized by reduced association with hormonal risk factors, late onset symptoms and aggressive clinical course (36).

Epigenetic defects have been identified in endometrial carcinomas and have been implicated in the pathogenesis of these carcinomas (37). In particular, *ARID1A* has been found mutated in all types of endometrium-associated tumors, including undifferentiated and dedifferentiated endometrial carcinomas (38-40). More specifically, *ARID1A* mutations were found in 57% of ovarian clear-cell carcinomas (41), 40% of uterine endometrioid carcinomas (42), and between 20% and 36% of uterine carcinosarcomas (43); however, they were found to be rare in endometrial serous carcinoma (44). Furthermore, a study investigating the *ARID1A* loss in patients with endometrioid carcinoma reported that no *ARID1A* loss was seen in complex atypical hyperplasia, with loss increasing to 25% and 44% of patients with low-grade and high-grade endometrioid carcinomas, respectively (9). The differential mutation rates and expression levels of *ARID1A* in endometrial and ovarian cancer may denote that distinct processes might be involved in their tumorigenesis or disease progression. Thus, it is of great importance to

study the role of *ARID1A* more not only in the pathogenesis of endometrial cancer, but also in its effect on the downstream molecular pathways in order to pinpoint the clinical relevance of the gene for both diagnostic and therapeutic interventions.

ARID1A has also been used as a prognostic marker in endometrial cancer. A significant association of reduced *ARID1A* expression has been found with shorter progression-free survival in patients suffering from endometrium-related cancer and, especially from ovarian clear-cell carcinoma, as well as with higher FIGO stage of both endometrial and ovarian cancer (45). Furthermore, the very rare occurrence of *ARID1A* mutations in complex atypical hyperplasia cases compared to endometrioid endometrial carcinoma (9, 46), in conjunction with evidence linking *ARID1A* to tumor initiation and progression suggest that it might play a significant role in the transition from complex atypical hyperplasia to carcinoma through somatic inactivating mutations (47).

Molecular Pathways

ARID1A mutations affect the activity of SWI/SNF complexes, which, in turn, lead to transcriptional dysfunction resulting in aberrant transcriptional signatures in diverse pathways (6). Loss of components of SWI/SNF complex, including *ARID1A*, was found to disrupt not only the physical assembly of the complex, but also its association with genomic loci and the recruitment of interacting partners (co-activators or co-repressors), thereby impeding its remodeling activity (48). For example, under normal conditions, *ARID1A* protein interacts with topoisomerase

Ila, which plays an important role in chromosome segregation during mitosis (49, 50). Furthermore, it was shown that ARID1A is essential in maintaining chromatin accessibility through histone modifications at enhancers and this function is shared with ARID1B, a recently found homolog of ARID1A (51), highlighting the importance of enhancer architecture in health and disease (52). Loss of ARID1A was shown to induce neoplastic transformation in non-tumorigenic endometriotic cells due to alterations in histone modifications around AP-1 motifs at enhancers, indicating that ARID1A loss could be an early stage event in oncogenic transformation (53). When association was sought with other components of the SWI/SNF complex and ARID1A, reduced SMARCD3 expression was significantly associated with human tumors also exhibiting ARID1A loss, such as lung, pancreatic and kidney carcinomas and sarcomas (54-58).

In endometrioid endometrial carcinogenesis, activation of WNT signaling pathway has been observed, potentially induced by various molecular events such as inhibition of phosphatase and tensin homolog (PTEN), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene (*PIK3CA*) mutations, *KRAS* proto-oncogene GTPase gene (*KRAS*) mutations, microsatellite instability (MSI), tumor protein P53 gene (*TP53*) mutations or combinations of these defects (59). Apart from the high percentage of cases presenting with *ARID1A* mutations (40% of low-grade endometrioid carcinomas), loss of ARID1A expression was observed in 26-29% of low-grade and up to 39% of high-grade endometrioid carcinomas (20, 46). In addition, co-occurrence of *ARID1A* mutations has been found in carcinomas exhibiting mutations of *PTEN* and *PIK3CA*, and ARID1A-deficient cancer cells exhibited significantly increase sensitivity to PI3K and protein kinase B (AKT) inhibition (60). Furthermore, impairment in the PI3K pathway is a very common feature of endometrioid carcinoma, accounting for more than 80% of cases, and ARID1A regulates this pathway through the phosphorylation of AKT (61). Due to the important effect of ARID1A deregulation in endometrial carcinogenesis, ARID1A has been used in addition to eight other genes (protein phosphatase 2 scaffold subunit Aalpha (*PPP2R1A*) gene, *PTEN*, *PIK3CA*, *KRAS*, catenin beta 1 (*CTNNB1*) gene, TP53, B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene and *PPP2R5C*) to sub-classify endometrial carcinomas based on mutational profile (62). ARID1A has also been associated with MSI and mismatch repair (MMR) deficiency due to silencing of MMR genes in gastric carcinoma and uterine endometrioid carcinoma (13, 59, 63). In particular, loss of ARID1A was seen in sporadic MSI in significantly more cases than in other conditions, and ARID1A-regulated epigenetic silencing of mutL homolog 1 (*MLH1*) gene through promoter hypermethylation has been suggested to be the cause of MSI (59). Lately, converging pathways were identified for

endometrial and ovarian carcinogenesis, through genetic and epigenetic analyses in Lynch syndrome, which is associated with hereditary defects in DNA repair resulting in increased MSI (64), while ARID1A loss seems to arise in early stages of carcinogenesis (65). Such a link of ARID1A and MSI was also described in gastric cancer, further supporting the hypothesis of mutated ARID1A-driven MSI (12, 13, 66). When considering the MMR pathways, ARID1A has been found to interact with MMR protein mutS homolog 2 (*MSH2*) and ARID1A deficiency contributes significantly to MMR impairment (67). Furthermore, Niskakoski *et al.* found a final diagnosis of endometrial cancer was given to all patients that presented with loss of either *ARID1A* gene or any of the four MMR genes *MLH1*, *PMS2*, *MSH6* or *MSH2* (64).

On the other hand, the molecular landscape in non-endometrioid cancer (type II) is characterized by high frequency of *TP53* mutations, up-regulation of p16, human epidermal growth factor receptor 2 (*HER2*) gene amplification, global loss of heterozygosity and alterations in e-cadherin signaling (68-70). It has been shown that p53 protein directly interacts with the ARID1A-SMARCA4 complex and this interaction regulates the transcription of various genes including cyclin-dependent kinase inhibitor 1A (*CDKN1A*) gene and SMAD family member 3 (*SMAD3*) (8). It has been proposed that when ARID1A is lost, the *CDKN1A* and *SDMA3* pathways are disrupted and PI3K/AKT pathway is aberrantly activated (59). Although loss of ARID1A and aberrant p53 expression have been described extensively in clear cell cancer (71-73), examination of ovarian clear-cell carcinoma, uterine carcinoma and endometrial carcinoma samples showed that mutations in both *ARID1A* and *TP53* were mutually exclusive (59, 63). ARID1A, p53 and β -catenin can be used as prognostic biomarkers in both clear-cell and endometrioid carcinoma, however, a significant correlation has been established only between ARID1A and β -catenin expression in endometrioid tumors (74). In a recent study, the estrogen receptor cofactor nuclear receptor interacting protein 1 (*NRIP1*) was found to be mutated in 12% of patients with metastatic endometrial cancer and these mutations were driving oncogenesis. In the same study, *ARID1A* mutations were not in agreement with the finding that driver events might be common in primary and metastatic tumors, demonstrating considerable heterogeneity within endometrial cancer cases and relative homogeneity in metastatic tissues (75).

Since tumors with *ARID1A* mutations are seen frequently in hormone-responsive tissues, it is worth considering the role of ARID1A in the regulation of hormonal signaling. Increased transcriptional activation through the glucocorticoid, estrogen, and androgen receptors was seen when ARID1A expression was restored in ARID1A-deficient breast cancer cells (76). Regarding other pathways affected by ARID1A, in ARID1A-deficient endometrial cancer cells, a significant increase in the level of forkhead box O1 (FOXO1) was observed along

with down-regulation of the mitogen-activated protein kinase pathway and the insulin-like growth factor-1 signaling pathway (77). Although a systematic study investigating all pathways affected by mutant ARID1A is not yet available, the importance of such a study is emphasized by the fact that synthetic lethality was generated when enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) inhibitors were used as therapeutic agents in *ARID1A*-mutated cancer, through targeting the phosphoinositide-3-kinase interacting protein 1 (PIK3IP1), an ARID1A-regulated molecule of the PI3K/AKT pathway (78), while a new inhibitor of PI3K α , showed positive results in human trials (79). Through synthetic lethality, suppression of cells growth and promotion of apoptosis are achieved, whereas ARID1B, might have potential as a therapeutic target in *ARID1A*-mutated cancer cells in a molecular-targeted therapeutic approach (51).

Conclusion

Endometrial cancer is one of the most common types of gynecological cancers, with carcinoma incidence increasing in every year worldwide. ARID1A loss has been found in every type of endometrial cancer, indicating its important role in initiation and progression of this disease. ARID1A, as member of SWI/SNF chromatin remodeling complex, interacts with numerous of transcription factors and other signaling molecules, while its association with several molecular pathways has been shown. Due to the fact that defects in ARID1A can affect the expression levels of various downstream genes, a better understanding is needed to elucidate which of the pathways affected are important in the pathogenesis and progression of cancer, and how these pathways can be targeted. Thus, the mechanism of action of ARID1A in initiation and progression of cancer cells needs to be clarified in order to develop new diagnostic tools and design new, more effective, therapeutic approaches.

Conflicts of Interest

All Authors declare that no conflict of interest exists in regard to this study.

Authors' Contributions

CT and ENK researched and wrote the article. AL, IT, TT, SK, LI, XA and GT helped with the writing of the article, offered scientific advice and proof-read the article.

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