ARID1A gene mutation in ovarian and endometrial cancers (Review)

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Abstract. The AT-rich interacting domain-containing protein 1A gene (*ARID1A*) encodes ARID1A, a member of the SWI/SNF chromatin remodeling complex. Mutation of *ARID1A* induces changes in expression of multiple genes (*CDKN1A, SMAD3, MLH1 and PIK3IP1*) via chromatin remodeling dysfunction, contributes to carcinogenesis, and has been shown to cause transformation of cells in association with the PI3K/AKT pathway. Information on *ARID1A* has emerged from comprehensive genome-wide analyses with next-generation sequencers. *ARID1A* mutations have been found in various types of cancer and occur at high frequency in endometriosis-associated ovarian cancer, including clear cell adenocarcinoma and endometrioid adenocarcinoma, and also occur at endometrial cancer especially in endometrioid adenocarcinoma. It has also been suggested that *ARID1A* mutation occurs at the early stage of canceration from endometriosis to endometriosis-associated carcinoma in ovarian cancer and also from atypical endometrial hyperplasia to endometrioid adenocarcinoma in endometrial cancer. Therefore, development of a screening method that can detect mutations of *ARID1A* and activation of the PI3K/AKT pathway might enable early diagnosis of endometriosis-associated ovarian cancers and endometrial cancers. Important results may also emerge from a current clinical trial examining a multidrug regimen of temsirolimus, a small molecule inhibitor of the PI3K/AKT pathway, for treatment of advanced ovarian clear cell adenocarcinoma with *ARID1A* mutation and PI3K/AKT pathway activation. Also administration of sorafenib, a multikinase inhibitor, can inhibit cancer proliferation with *PIK3CA* mutation and resistance to mTOR inhibitors and GSK126, a molecular-targeted drug can inhibit proliferation of *ARID1A*-mutated ovarian clear cell adenocarcinoma cells by targeting and inhibiting EZH2. Further studies are needed to determine the mechanism of chromatin remodeling dysregulation initiated by *ARID1A* mutation, to develop methods for early diagnosis, to investigate new cancer therapy targeting *ARID1A*, and to examine the involvement of *ARID1A* mutations in development, survival and progression of cancer cells.

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Contents

1. Introduction

Several mutations in genes encoding chromatin remodeling complexes have been found in recent years using comprehensive genome-wide analyses with next-generation sequencers. Chromatin remodeling is a molecular mechanism of regulation of gene expression levels based on changes to chromatin structure; that is, regulation of the interaction of proteins with double-stranded DNA by changing the nucleosome structure in an ATP-dependent manner. This mechanism has impacts on transcription, replication, repair, methylation, and recombination of DNA (1). Dysfunction in the mechanism is likely to contribute to carcinogenesis, and aberrations in chromatin remodeling have been found in approximately 10% of all human cancers (2). Chromatin remodeling complexes alter the structure of nucleosomes by local ATP-dependent sliding of nucleosomes or by modification of histones (3,4). In sliding, the loosened chromatin structures appear to facilitate binding of proteins to double-stranded DNA, while the mechanism

of histone modification is unclear (3). Chromatin remodeling complexes are also predicted to be involved in regulation of higher-order chromatin structures.

There are several types of chromatin remodeling complexes, including the SWItch/sucrose non-fermentable (SWI/SNF) complex, imitation SWI (ISWI) complex, INO80 complex and chromodomain helicase DNA-binding protein (CHD) complex. The SWI/SNF complex is involved in activation or inhibition of transcription, and plays a crucial role in carcinogenesis. Isakoff *et al* showed that inactivation of *SNF5p* (*SNF5*) in murine fibroblasts leads to both increased and decreased expression of genes (5). *SNF5* encodes SNF5, a core member of the SWI/SNF complex, and these results suggest that the SWI/SNF complex is involved in activation and inhibition of transcription. Medina *et al* found that ectopic expression of *SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily a, member 4* (*SMARCA4)* in *SMARCA4*-deficient cells altered expression of ~1% of all genes (6). *SMARCA4* encodes BRG1, which is also a core member of the SWI/SNF complex, and these findings suggest that the SWI/SNF complex induces changes in gene expression and may play a crucial role in carcinogenesis.

The SWI/SNF complex is composed of many subunits, including an ATP-dependent catalytic subunit and a core subunit that is involved in construction of the complex and contains ARID1A (7-11). In this review, we focus on the relationships of *ARID1A* mutations with ovarian and endometrial cancers, and we discuss the possible use of ARID1A as a molecular target in diagnosis and treatment.

2. What is *ARID1A*?

ARID1A is located on chromosome 1p36.11 and encodes ARID1A, a core member of the SWI/SNF complex (12). This complex plays a crucial role in carcinogenesis, and thus *ARID1A* is viewed as a cancer-inhibiting gene, of which mutation may be involved in onset and progression of several cancers. Next-generation sequencers have enabled genome-wide analyses, and mutation of *ARID1A* in ovarian clear cell carcinoma and ovarian endometrioid carcinoma was first reported in 2010. Since then, *ARID1A* mutations have been found in many human cancers and sarcomas, with mutation frequencies of 34% in renal clear cell carcinoma (13), 8-27% in stomach cancer (14-16), 13% in transitional cell carcinoma of the bladder (16), 9.1-15% in esophageal adenocarcinoma (17,18), 10-13% in hepatocellular carcinoma (19,20), 9% in esophageal carcinoma (21), 8% in lung adenocarcinoma (22), 8% in prostate cancer (14), 4-8% in pancreas cancer (14,23,24), 2-4% in breast cancer (14,25,26), 14-17% in Burkitt lymphoma (27,28), 6% in neuroblastoma (29) and 2% in medulloblastoma (14). *ARID1A* mutation is especially common in gynecologic cancer, with rates of 46-57% in ovarian clear cell adenocarcinoma (30,31), 30% in ovarian endometrioid adenocarcinoma (31) and 40% in uterine endometrioid adenocarcinoma (32) (Table I). Most of these *ARID1A* mutations are frameshift or nonsense mutations. There are two types of hotspot for mutations. One is the mutations around nuclear export signal sequence resulting in reduced nuclear export of ARID1A, and another is the mutations affecting interactions between ARID1A and the other SWI/SNF subunits disturbing the stability of the whole protein complex (33). Recent meta-analysis indicated that loss of ARID1A was associated with cancer-specific mortality and cancer recurrence (34).

Table I. Tumors with *ARID1A* mutations (13-32).

Tumor	Rate (%)
Ovarian clear cell carcinoma	46-57
Ovarian endometrioid carcinoma	30
Low-grade endometrioid carcinoma	40
Renal clear cell carcinoma	34
Gastric carcinoma	8-27
Transitional cell carcinoma of the bladder	13
Esophageal adenocarcinoma	9.1-15
Hepatocellular carcinoma	10-13
Esophageal carcinoma	9
Pulmonary adenocarcinoma	8
Prostate carcinoma	8
Pancreatic carcinoma	2-8
Breast carcinoma	2-4
Burkitt lymphoma	14-17
Neuroblastoma	6
Medulloblastoma	2

Many reports have suggested that *ARID1A* mutation is involved in onset and progression of cancer. Guan *et al* found that suppression of wild-type *ARID1A* in ovarian cancer cells with *ARID1A* mutation was sufficient to inhibit cell proliferation and tumor growth in mice, whereas silencing of *ARID1A* in non-transformed epithelial cells enhanced cellular proliferation and tumorigenicity in mice (35). Similarly, Streppel *et al* found enhanced cell proliferation following *ARID1A* knockdown in esophageal adenocarcinoma cells, whereas increased *ARID1A* expression in *ARID1A*-deficient cells significantly inhibited cell proliferation (18). Moreover, Guan *et al* showed that *ARID1A* promotes formation of the SWI/SNF chromatin remodeling complex containing BRG1, and with p53 regulates transcription of downstream effectors, including proteins encoded by *cyclin-dependent kinase inhibitor 1A (CDKN1A)* and *SMAD family member 3 (SMAD3). CDKN1A* encodes p21, which acts as a regulator of cell cycle progression in G1 phase (35). *SMAD3* encodes SMAD3, which acts on transforming growth factor β (TGF-β) and serves as a regulator of differentiation, migration, and adhesion of cells. Briefly, mutation of *ARID1A* inactivates ARID1A/BRG1/p53 complex and they silence the transcription of CDKN1A and SMAD3. Finally the mutation of *ARID1A* inactivates these downstream effectors and causes tumor growth.

3. *ARID1A* mutation in ovarian cancers

ARID1A mutations occur in ovarian cancers at high frequency, and a close association between endometriosis-associated ovarian cancer and *ARID1A* mutation has been suggested in multiple studies. *ARID1A* mutations are found in 46-57% of ovarian clear cell carcinomas (30,31)

and in 30% of ovarian endometrioid carcinomas (31), but not in ovarian high-grade serous adenocarcinomas or ovarian mucinous adenocarcinomas (31,32), which are both closely associated with endometriosis. Loss of ARID1A expression is more frequent in endometriosis-associated ovarian clear cell carcinomas compared to those that are non-endometriosis-associated (36), with loss of ARID1A in 61% of cystic ovarian clear cell carcinomas compared to 43% of adenofibromatous ovarian clear cell carcinomas (36). Ovarian clear cell carcinomas can be divided into subgroups of cystic and adenofibromatous carcinomas (37), and cystic ovarian clear cell carcinoma is more closely associated with endometriosis and has a better prognosis. Endometrioid tumors are also associated with loss of ARID1A expression, which occurs at rates of 33 and 13% in borderline malignant tumors of the mucinous endocervical and endometrioid types, respectively, but not in those of the mucinous intestinal epithelium or serous types (38).

Multiple reports also suggest that *ARID1A* mutation occurs at the early stage of canceration from endometriosis to ovarian cancer. Yamamoto *et al* found that locations of ovarian cancer and endometriosis were associated with loss of *ARID1A* protein expression; that is, among endometrial lesions adjacent to *ARID1A*-deficient ovarian carcinomas, 86-100% were *ARID1A*-deficient. In contrast, solitary endometriosis and endometriosis distant from *ARID1A*-deficient ovarian carcinomas retained *ARID1A* expression (36). Similarly, Ayhan *et al* found loss of *ARID1A* expression in endometrial epithelia adjacent to *ARID1A*-deficient clear cell adenocarcinomas and endometrioid adenocarcinomas, whereas endometriotic cyst epithelia distant from *ARID1A*-deficient ovarian carcinomas retained *ARID1A* expression (39). The mechanism of transformation from endometriosis to ovarian cancer is unclear; however, the microenvironment around the endometrium is likely to have abundant iron-induced free radicals, and repeated damage and repair due to these radicals may lead to malignant transformation (40,41).

Recent studies have shown that *ARID1A* mutation is involved in carcinogenesis through multiple mechanisms, including via the phosphatidylinositol-3-kinase (PI3K)/AKT pathway. Activation of this pathway stimulates several mechanisms that cause progression to cancer, including proliferation of cancer cells, inhibition of apoptosis of cancer cells. These processes occur mainly via activation of tyrosine kinase receptors and somatic mutation of specific components of signal transduction, including loss of *phosphatase and tensin homolog* (*PTEN*), a cancer-suppressor gene, and activation of mutation of *phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit* α (*PIK3CA*). *PTEN* dephosphorylates phosphatidylinositol-3-phosphate (PIP3) into phosphorylated phosphatidylinositol-2-phosphate (PIP2), and competitively inhibits the PI3K/AKT pathway. *PIK3CA* encodes p110α, a catalytic subunit of PI3K. The mammalian target of rapamycin complex 1 (mTORC1), a major downstream effector activated by signaling of AKT, plays a central role in growth and proliferation of cells. To investigate the effect of *ARID1A* on the PI3K/AKT pathway, Guan *et al* produced and compared *ARID1A* knockout mice (n= 9) and *ARID1A*/PTEN double knockout mice (n=22). Of the *ARID1A*/PTEN double knockout mice, 60% developed poorly differentiated ovarian carcinoma with intraperitoneal dissemination and development of ascites, and the other 40% showed hyperplasia of the ovarian surface epithelium. In contrast, *ARID1A* knockout mice did not develop discernable histopathological changes, which suggests that mutation of *ARID1A* alone does not cause development and progression of cancer, but that a combination of *ARID1A* inactivation and a PI3K/AKT pathway aberration is sufficient to initiate tumorigenesis (42). *PTEN* knockout mouse (loss of PTEN alone) is not sufficient to initiate ovarian or endometrial tumorigenesis. However, loss of PTEN appears to potentiate tumorigenesis in ovaries with mutations of other genes like *ARID1A* or *APC* (43). *PIK3CA* is mutated in 33-46% of ovarian clear cell adenocarcinomas (44,45) and Yamamoto *et al* found that *PIK3CA* is frequently mutated in endometrial epithelia adjacent to ovarian clear cell adenocarcinomas (45) and that *PIK3CA* mutation and loss of ARID1A expression occur simultaneously (36,46).

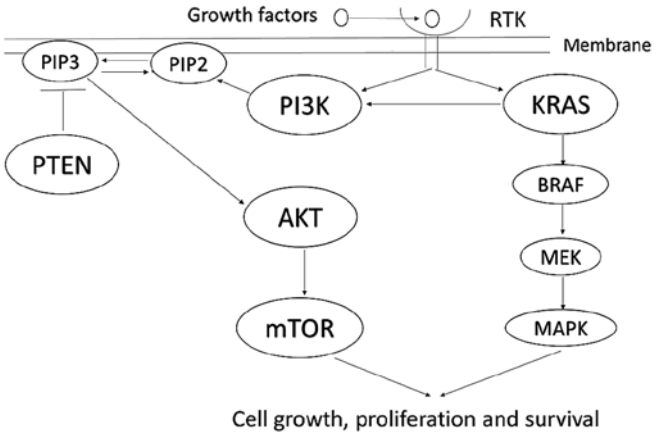

Figure 1. The PI3K/AKT pathway. Activation of receptor tyrosine kinase (RTK) leads to activation of KRAS and PI3K. KRAS also activates PI3K. PI3K phosphorylates PIP2 to PIP3, whereas PTEN dephosphorylates PIP3 to PIP2. PIP3 in turn activates AKT and then mTOR, which leads to stimulation of cell growth, proliferation and survival. KRAS also contributes to these processes through another pathway.

4. *ARID1A* mutation in endometrial carcinomas

ARID1A is mutated at high frequency in both ovarian cancers and endometrial carcinomas (32). Aberrations in the PI3K/AKT pathway are present in ≥80% of uterine endometrioid adenocarcinomas (47). Endometrioid adenocarcinoma is a type I uterine endometrial carcinoma, and this type has frequent mutations in *KRAS*, *PTEN* and *PIK3CA* (48). *KRAS* mutation is involved in cell proliferation and activates growth factors and the PI3K/AKT pathway. Since *KRAS*, *PTEN* and *PIK3CA* play roles in regulation of the PI3K/AKT pathway, it is likely that uterine endometrioid adenocarcinomas have many gene mutations associated with this pathway (Fig. 1).

An association between loss of ARID1A protein expression and activation of the PI3K/AKT pathway has also been found in type I endometrial carcinomas. *ARID1A* mutations are present in 40% of low-grade endometrioid adenocarcinomas, and loss of ARID1A expression occurs in 26-29% of low-grade and 39% of high-grade endometrioid adenocarcinomas (32,49). Moreover, in a classification of endometrial

carcinomas based on mutations in 9 genes, including *ARID1A*, *PTEN*, *PIK3CA*, *KRAS*, *P53* and *BRAF*, *ARID1A* mutation was detected in 47% of low-grade endometrioid adenocarcinomas, 60% of high-grade endometrioid adenocarcinomas, 11% of serous adenocarcinomas, and 24% of carcinosarcomas (50). Mutations of *PTEN* and *PIK3CA* also frequently occur in uterine endometrial carcinomas with *ARID1A* mutation, and these mutations induce aberrant activation of PI3K, phosphorylation of AKT, and inhibition of cell survival and apoptosis (51).

Another characteristic of type I endometrial carcinomas is induction of microsatellite instability (MSI). The cause of MSI may be a defect in DNA mismatch repair function, and loss of ARID1A expression may be associated with MSI in uterine endometrioid adenocarcinomas. Bosse *et al* found a strong association between ARID1A loss and sporadic MSI, and concluded that ARID1A may be a causative gene for MSI through a role in epigenetic silencing of the *mutL homolog 1* (*MLH1*) gene in endometrial cancer (52).

In addition to its role in cancer development, ARID1A may also have a crucial role in progression of cancer. In immunohistochemical staining of atypical endometrial hyperplasia and uterine endometrioid carcinomas with an anti-ARID1A antibody, Mao *et al* defined the lack of staining in focal tumor areas as 'clonal loss', whereas the absence of ARID1A immunoreactivity in almost all tumor cells was defined as 'complete loss'. Clonal loss occurred at rates of 16% in atypical endometrial hyperplasia, 24% in uterine low-grade endometrioid carcinomas and 9% in uterine high-grade endometrioid carcinomas, whereas the respective rates of complete loss were 0, 25 and 44% in these diseases (53). This suggests that loss of ARID1A expression plays important roles in the early phase of tumor development and progression.

Uterine endometrial clear cell carcinoma (UCCC) is a rare disease that accounts for <5% of all endometrial carcinomas. The genetic basis of UCCC is mostly unknown, but downregulation of ARID1A has been found in 14-22% of UCCC cases, with these rates being lower than those in ovarian clear cell carcinoma (54-57).

5. *ARID1A* in molecular-targeted therapy and as a prognostic marker

The apparent importance of *ARID1A* mutation at the early stage of carcinogenesis from endometriosis to ovarian cancers suggests that detection of *ARID1A* mutation may be useful for early diagnosis of endometriosis-associated ovarian cancers. Practical application of *ARID1A*-dependent early diagnosis requires understanding of the molecular mechanism underlying transformation to cancer, advances in methods for detection of *ARID1A* mutation, and epidemiological examination of the relationship between *ARID1A* mutation and carcinogenesis. Greater clarity on the mechanisms through which *ARID1A* mutation causes transformation via aberrant activation of the PI3K/AKT pathway is likely to contribute to development of more convenient markers, while improved detection of *ARID1A* mutations is required for low-cost use of convenient samples such as cyst aspirates. Frequent *ARID1A* mutation in ovarian cancers has been reported, but cancer incidences in cases with *ARID1A* mutation have not been investigated. Efficient screening tests require high positive and negative predictive values (58), which will require epidemiological studies of the relationship between *ARID1A* mutation and carcinogenesis.

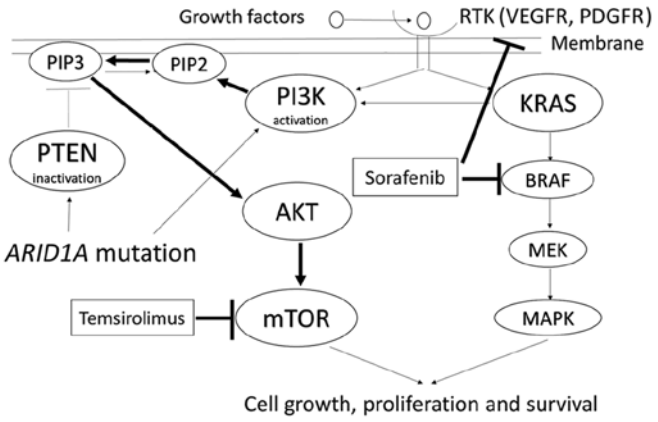

Figure 2. Effects of *ARID1A* mutation and anticancer agents on the PI3K/AKT pathway. *ARID1A* mutations frequently co-occur with mutations of *PTEN* and *PIK3CA*. PTEN mutation inactivates *PTEN* and *PIK3CA* mutation activates PI3K, which lead to stimulation of cell growth, proliferation and survival. Temsirolimus inhibits the PI3K/AKT/mTOR signaling pathway by binding to the mTORC1 complex (65). Sorafenib is a multikinase inhibitor that targets the mitogen-activated protein kinase (MAPK) pathway, and also inhibits vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR).

Improved understanding of the carcinogenetic mechanism of *ARID1A* mutation is also likely to facilitate development of new therapies using molecules targeted against the effects of the *ARID1A* mutation. Molecular targeted therapy for ovarian clear cell adenocarcinoma is currently being examined. Takano *et al* found that combination therapy with temsirolimus, an mTOR inhibitor, and trabectedin, a new anticancer drug, for recurrent ovarian clear cell adenocarcinomas showed efficacy in a subset of patients and caused only mild adverse reactions (59). *ARID1A* mutation induces aberrant activation of PI3K and phosphorylation of AKT, which then targets mTOR, and in turn mTOR affects cell division, cell death and angiogenesis, and is involved in proliferation of cancer cells. Trabectedin is an alkylating agent that modifies guanine bases in DNA (60,61), and combination therapy of temsirolimus and trabectedin for recurrent ovarian clear cell adenocarcinomas is currently under examination in a phase II clinical trial. At the case report level, administration of sorafenib, a multikinase inhibitor, resulted in partial remission in a patient with stage IIIc ovarian clear cell adenocarcinoma with *PIK3CA* mutation and resistance to mTOR inhibitors (62) (Fig. 2).

In many cases, the *ARID1A* mutation is a frameshift or nonsense mutation. Thus, an anticancer drug that can repair these mutations may have broader efficacy and fewer adverse reactions compared with those of current molecular targeted drugs. However, most current drugs solely inhibit molecules with aberrant expression in cancer cells, and those targeting gene mutations remain at the research level.

A novel treatment strategy directly targeting enhancer of zeste homolog 2 (EZH2) has recently been reported. EZH2 is often overexpressed in ovarian clear cell adenocarcinomas and

generates the lysine 27 trimethylation on histone H3. GSK126, a small molecule and highly selective inhibitor of EZH2 methyltransferase, dose-dependently decreases the level of H3K27Me3 in ovarian clear cell adenocarcinoma cells with loss of *ARID1A* expression and inhibits their growth (63). The effect of GSK126 is reduced when expression of *ARID1A* is restored in these cells. An association with PI3K-interacting protein 1 gene (*PIK3IP1*), a direct target of *ARID1A* and EZH2 that is also often mutated in ovarian clear cell adenocarcinoma with *ARID1A* mutations. Mutation of *ARID1A* is related to reduced expression of PIK3IP1, and administration of GSK126 or restoration of *ARID1A* expression led to increased expression of PIK3IP1. GSK126 suppresses EZH2, and thus has the opposite effect of *ARID1A* or EZH2. Both *ARID1A* and EZH2 act on PIK3IP1, but *ARID1A* is more dominant than EZH2. With *PIK3IP1* overexpression, PIK3IP1 inhibits cell proliferation and induces apoptosis in ovarian clear cell adenocarcinomas. Thus, *ARID1A* or *EZH2* regulate expression of *PIK3IP1* and a high rate of mutation of these genes in ovarian clear cell adenocarcinoma enhances cell proliferation and anti-apoptotic effects. GSK126 is a molecular-targeted drug that should inhibit proliferation of *ARID1A*-mutated ovarian clear cell adenocarcinoma cells by targeting and inhibiting EZH2. In mice, GSK126 also affects peritoneal dissemination (63). In the present study, the number of tumors after treatment with GSK126 was significantly lower than that in untreated mice after *ARID1A*-mutated ovarian clear cell adenocarcinoma cells were injected into the abdominal cavity (63). Based on all of these findings, GSK126 is likely to be among the most efficient molecular-targeted drugs against ovarian clear cell adenocarcinoma with *ARID1A* mutations.

ARID1B, a homolog of *ARID1A*, is also a possible target in molecular-targeted therapy (64). Knockdown of *ARID1B* in wild-type cells did not impair expression of the SWI/SNF complex, but knockdown in cells with *ARID1A* mutation led to loss of SMARCA4, the main subunit of ATPase, and other subunits. That is, co-occurrence of *ARID1A* and *ARID1B* mutations may be required for carcinogenesis, and a study of 297 *ARID1A*-mutant primary cancer samples identified 30 (10.1%) that also contained *ARID1B* mutations, with this rate being significantly higher than that of 3% in primary cancer samples without *ARID1A* mutation. This finding suggests that molecular-targeted therapy against ARID1A and ARID1B may produce better therapeutic effects.

Associations between ARID1A expression and prognosis have recently been reported in stomach cancer, bladder cancer, bowel cancer, and renal cell cancer, which suggests that *ARID1A* expression may serve as a prognostic marker (65-68). Meta-analysis also confirmed loss of *ARID1A* is associated with cancer-specific mortality and cancer recurrence (34). However, this association has only rarely been reported in gynecologic cancers, including in a clinically advanced stage and with tumor progression in uterus endometrioid adenocarcinomas (53). Thus, the association of *ARID1A* and prognosis in UCCC remains uncertain (55-57).

On the contrary, in a study conducted between 2006 and 2011 in 46 patients with International Federation of Gynecology and Obstetrics (FIGO) stage (1988) III and IV epithelial ovarian cancers, Yokoyama *et al* found that the expression level of *ARID1A* was correlated with prognosis after chemotherapy. Twelve patients with a significantly lower level of ARID1A expression did not achieve complete response (CR). Of 34 patients who achieved CR, 21 patients who subsequently relapsed had relatively low levels of ARID1A (69). In addition, shorter progression-free survival after chemotherapy was found in the 11 patients with complete loss of ARID1A expression compared to 35 patients with ARID1A expression (69). In 112 patients with ovarian clear cell adenocarcinoma, Itamochi *et al* found an association between ARID1A expression and prognosis, and a relationship between ARID1A expression and each FIGO (1988) stage (70). Thus, the 5-year survival rate for FIGO stage I or II patients with positive tumor expression of ARID1A was 91%, while that for patients with negative tumor expression of ARID1A was 74%. However, this difference was not observed in FIGO stages III or IV. Based on these findings, ARID1A may be a biomarker that is predictive of prognosis of patients with FIGO stage I and II ovarian clear cell adenocarcinoma (70).

6. Conclusion

Advances in comprehensive genome analysis have permitted identification of mutations in multiple genes encoding chromatin remodeling factors in human cancers. Genes encoding proteins making up the SWI/SNF chromatin remodeling complex have been found to have particularly inactivating mutations at high frequency, and this complex has been suggested to inhibit malignant transformation. One such gene is *ARID1A*, and *ARID1A* mutations that eliminate expression of ARID1A protein produce abnormalities in chromatin remodeling and contribute to canceration from endometriosis to endometriosis-associated ovarian cancers. Since chromatin remodeling is involved in regulation of expression of multiple genes and in genome instability, its dysregulation is likely to have multiphase and significant impacts on development, survival, and progression of endometriosis, but the detailed mechanisms remain unclear. Further studies are needed to determine the mechanism of chromatin remodeling dysregulation initiated by *ARID1A* mutation, to develop methods for early diagnosis via detection of *ARID1A*, to investigate new cancer therapy targeting *ARID1A*, and to examine the involvement of *ARID1A* mutations in development, survival and progression of cancer cells.

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