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Aberrant chromatin remodeling in gynecological cancer (Review)

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Abstract. Epigenetic regulatory mechanisms are a current focus in studies investigating cancer. Chromatin remodeling alters chromatin structure and regulates gene expression, and aberrant chromatin remodeling is involved in carcinogenesis. AT-rich interactive domain-containing protein 1A (ARID1A) and SWItch/sucrose non-fermentable-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4 are remodeling factors that are mutated in numerous types of cancer. In gynecological cancer, *ARID1A* mutations have been identified in 46-57% of clear cell carcinoma and 30% of endometrioid carcinoma. Mutations of chromodomain helicase, DNA-binding protein 4 have been detected in 17-21% of endometrial serous cancer, and mutations of *ARID1A* and mixed-lineage leukemia 3 occur in 36 and 27% of uterine carcinosarcoma, respectively. These data suggest that aberrant chromatin remodeling is a potential cause of cancer, and have led to the development of novel proteins targeting these processes. Additional accumulation of information on the mechanisms of chromatin remodeling and markers for these events may promote personalized anticancer therapies.

Contents

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1. Introduction

Epigenetics involves the regulation of gene expression without a change in DNA sequence. Somatic cells retain and transfer epigenetic information based on DNA methylation, histone methylation, acetylation, ubiquitination, ADP ribosylation, histone modification, small RNAs unrelated to genetic codes and modification of chromatin structure through chromatin remodeling. The term 'chromatin remodeling' refers to the alteration of chromatin structure from a closed state to a loosened one, which is termed 'euchromatin' (1). There are a few types of chromatin remodeling complexes, including the SWItch/sucrose non-fermentable (SWI/SNF) complex, which has several subunits, including ARID1A and brahma homologue (BRM)-related gene 1 (BRG1; also referred to as SMARCA4) (2). Through the interaction between subunits, chromatin remodeling complexes change chromatin structure, and this determines gene expression levels via the regulation of the interaction between proteins with double-stranded DNA (3). This change in accessibility may be achieved by adenosine triphosphate (ATP)-dependent complexes modulating histone-DNA association and by covalent modification of core nucleosomal histones mediating the transcriptional activity (4). Epigenetics is also associated with intracellular communication (5). These are key events in cell growth, and thus epigenetic abnormalities may induce carcinogenesis, developmental defects and multifactorial disease. The association between aberrant chromatin remodeling with gynecological cancer is discussed in the present review.

2. Chromatin remodeling

In eukaryotes, almost all genomic DNA is packaged by core histones to form chromatin structures. These structures change in events such as transcription, replication, modification and recombination of genomic DNA (6). The requirement for different chromatin structures is fulfilled by chromatin remodeling, which is an important factor in the regulation of gene expression.

Chromatin remodeling is performed by two enzyme groups: Histone modifiers, which chemically alter histones; and ATP-dependent chromatin remodeling factors, which bind

to nucleosome cores and surrounding DNA to change the chromatin structure. Using energy from ATP dephosphorylation, remodeling factors alter nucleosomal structure, transiently loosen binding with DNA, and coordinate with specific chaperones, exchanging specific or all nucleosome cores (4). The nucleosomal structure is dynamically changed by remodeling factors, resulting in prompt changes in the chromatin structure (6). Several types of ATP-dependent remodeling factors are known, including a number of high-molecular-weight protein complexes with >10 subunits (6). The activity of these complexes is regulated and they are transferred to specific DNA sites to regulate gene expression by changing the chromatin structure (6,7). ATP-dependent remodeling factors are classified into several families: SWI/SNF, imitation SWI (ISWI), INO80, SWR1, nucleosome remodeling deacetylase (NuRD)/Mi2/CHD and nucleosome remodeling factor (7).

3. Aberrant chromatin remodeling and cancer

Chromatin remodeling factors regulate epigenetic gene expression, and aberrations in this process may induce carcinogenesis. A large-scale study of genome sequences has identified mutations of genes encoding remodeling factors in a number of types of human cancer, including those for the SWI/SNF complex, which has led to the suggestion that SWI/SNF complexes are protective against cancer (7,8). Mutations in SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4 *(SMRCA4/BRG1*), which encodes the ATPase subunit of the SWI/SNF complex, has been detected in >30% of non-small cell lung carcinoma (NSCLC) (7). Similarly, mutations in the ARID1A, which encodes an additional subunit of the SWI/SNF complex, has been detected in 46-57% of clear cell carcinoma and 30% of endometrioid carcinoma in ovarian cancer (9). *ARID1A* mutations also occur in 13% of hepatocellular carcinoma (HCC), 9.6% of gastrointestinal adenocarcinoma and 2.5% of malignant melanoma (7). Chromodomain helicase, DNA-binding protein 4 (CHD4), which forms the nucleosome remodeling and deacetylase (NuRD) complex, is overexpressed or mutated in serous endometrial cancer, and metastasis-associated protein 1 overexpression has been detected in breast cancer (10).

Deleted regions encoding mixed-lineage leukemia protein 3 (MLL3) produce chromosomal aberrations that are frequently associated with acute myeloid leukemia (AML) (11). Similar gene mutations are identified in medulloblastoma, HCC (12), bladder carcinoma (13), prostate cancer (14), colorectal cancer (15), gastric adenocarcinoma (16), NSCLC (17), breast cancer (18) and pancreatic cancer (19) and in AML (11). Je *et al* (20) revealed mutations causing a frameshift of *MLL3* in 28.1% of cases of gastric cancer and 7.5% of cases of colon cancer.

4. Chromatin remodeling-associated gene mutations and carcinogenic mechanism

ARID1A is located at 1p35.3 and encodes an ~250-kD protein that is involved in interactions between numerous proteins, including the SWI/SNF complex. The SWI/SNF complex has multiple activities, including the following: The promotion of binding of transcription factors, coactivators and compressors; mobilization of histone-modifying enzymes; promotion of binding of nucleosomes with promoter and enhancer regions; and promotion of chromatin loop formation to induce interactions of enhancers and promoters (Fig. 1) (7,21). The SWI/SNF complex and ARID1A also regulate transcription to induce steroid hormones: It has been suggested that ARID1A may be involved in recruiting SWI/SNF to regulate genes through its ability to stimulate steroid hormone receptor-mediated transcriptional activation (22,23). Wu and Roberts (21) proposed three activities of *ARID1A* in the repression of tumors, namely, proliferation, differentiation and apoptosis. Gastrointestinal and breast cancer cells demonstrate a tendency to grow following *ARID1A*-knockdown, and growth rates decrease subsequent to re-expression of *ARID1A*. Ovarian epithelial cells and mouse preosteoblast cells indicated similar proliferation behaviors following *ARID1A*-knockdown. With regard to differentiation, *ARID1A*-knockdown eliminated self-renewal of ES cells and inhibited the differentiation of neurons and osteocytes *in vitro*. For apoptosis, the Fas apoptotic pathway in Jurkat cells was inhibited by knockdown of *ARID1A*. These results demonstrate that an *ARID1A* deficit has those three effects on tumor suppression (21). An *ARID1A* deficit has also been associated with the activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, and with the amplification of zinc-finger protein 217 (ZNF217), which are involved in cancer development (24).

Dynamic regulation of chromatin structures to allow transcription factors to bind to DNA is necessary for gene transcription, duplication and repair. Two complexes, BRG1-associated factor (BAF) and polybromo-associated BAF (PBAF), in the SWI/SNF family, perform this role in eukaryotes (22). BRG1 and BRM are subunits containing ATPase domains that hydrolyze ATP to provide energy for translocation of nucleosomes and changes in chromatin structure (25). BRG1 binds to BRCA1 and regulates cluster of differentiation 44 expression as part of the epithelial-mesenchymal transition in cancer (25). *BRG1* (also referred to as *SMARCA4*) is located at p13.2 on the short arm of chromosome 19 (19p13.2). *BRG1* regulates DNA transcription and serves a role in tumor suppression due to remodeling of the chromatin structure. Therefore, mutations and deletions of this gene are identified in a number of cancer types, including ovarian small cell carcinoma, rhabdoid tumors (kidney and brain), medulloblastoma, lung adenocarcinoma, mantle cell lymphoma, Burkitt's lymphoma, HCC, esophageal adenocarcinoma, melanoma, non-melanoma skin cancer and intraductal papillary mucinous neoplasms of the pancreas (26).

Chromodomain helicase DNA-binding protein 4 (CHD4) is located on the short arm of chromosome 12 (12p13) and its transcription product is a molecule in the SNF2/RAD54 helicase family. CHD4 serves a key role in epigenetic transcription suppression, as it acts in nucleosome remodeling in an ATP-dependent manner, and is the major protein involved in the formation of a deacetylase complex. CHD4 exhibits tandem chromodomains in the N-terminal region and an ATPase-helicase domain in the central region. The chromodomains recognize and bind to nucleosomes and regulate interactions with chromatin, whereas the ATPase-helicase domain is involved in DNA transcription, duplication,

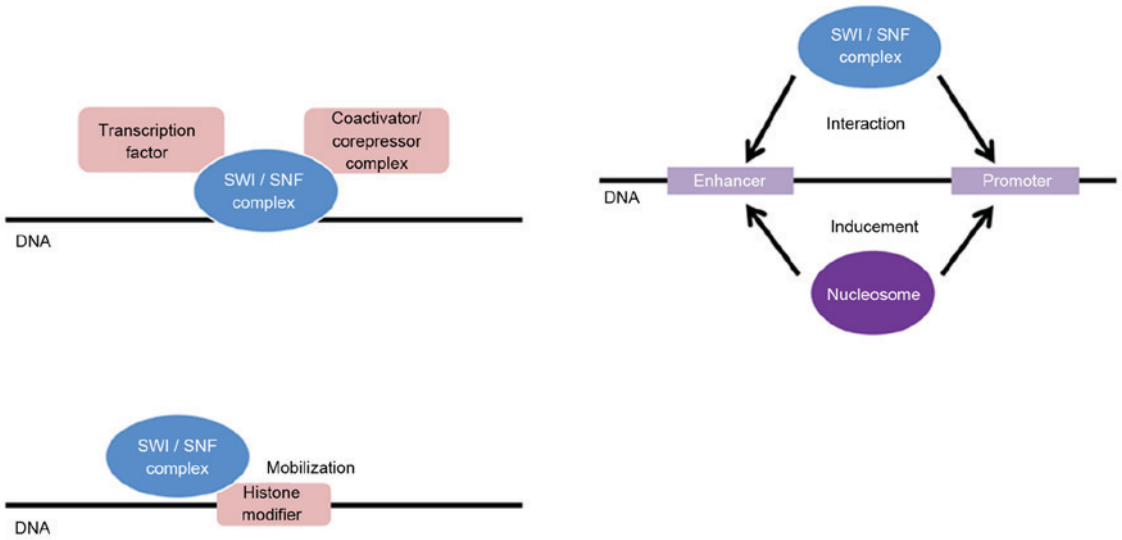

Figure 1. Actions of SWI/SNF complexes on chromatin structure that affect transcriptional regulation. The SWI/SNF complex recruits coactivator/corepressor complexes and transcription factors, and induces nucleosome formation at promoter and enhancer regions. The SWI/SNF complex also mobilizes histone-modifying enzymes and enhances interactions between enhancers and promoters. SWI/SNF, switch/sucrose non-fermentable complex.

recombination and repair (27). Mutations in these domains cause hyposegmentation in cells, indicating that the two domains are required for CHD4 function (27).

Mutations of *CHD4* have been identified in several cancer types, and particularly in serous endometrial carcinoma: Zhao *et al* (28) revealed that 11/52 patients exhibited a heterozygous somatic *CHD4* mutation. Le Gallo *et al* (29) also identified a somatic mutation in *CHD4* in 17% of patients with serous endometrial cancer. CHD4 is characterized by 'signature' motifs that contain important amino acid residues required for ATP hydrolysis and helicase activity. The normal function of CHD4 is eliminated by R957Q, R1127G and R1162W mutations in these residues (30). In an immunohistological examination of lesion tissues in gastric cancer and colorectal cancer, Kim *et al* (30) identified no CHD4 expression in 56.4% of patients with gastric cancer and 55.7% with colorectal cancer. Insertion or deletion of 1 to 2 bases caused a somatic mutation in *CHD4*, with the resulting frameshift causing elimination of normal *CHD4* expression (30).

MLL3 belongs to a gene cluster of the MLL family and is also called lysine N-methyltransferase 2C (KMT2C). *MLL3* exhibits a histone methyltransferase SET domain, a HMG-binding domain, a nuclear receptor binding domain and 5 zinc fingers, and acts as a nuclear receptor coactivator in mammals (11). The MLL family transfers 1, 2 or 3 methyl groups to lysine K4 of methyl histone H3, and MLL3 particularly methylates H3K4 in enhancer regions (11). In a study of familial nasopharyngeal carcinoma, Sasaki *et al* (31) proposed that the mechanism of carcinogenesis involves the action of acquired factors such as somatic mutation and Epstein-Barr virus infection in regions containing germline mutations that frequently cause a stop codon in *MLL3*. In an analysis of gene mutations in patients with Lynch syndrome, Villacis *et al* (32) also suggested that a *MLL3* mutation increases the risk of colorectal cancer.

Enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*) encodes proteins in the polycomb group (PcG) family and is located on chromosome 7 (7q35-q36). PcG proteins contribute to the epigenetic regulation of gene expression, for example: EZH2 methylates histone H3 core protein lysine 27 and inhibits gene transcription (33). *EZH2* demonstrates high expression in numerous types of cancer, including breast cancer, melanoma and lung cancer (33). In gynecological cancer, high *EZH2* expression occurs in uterine fibroids and cervical lesions. Yang *et al* (34) proposed a mechanism in which EZH2 inhibits the expression of the DNA mismatch repair gene Mutator S protein homolog 2 (*MSH2)* and develops uterine fibroids. Cai *et al* (35) revealed that *EZH2* was expressed more frequently in cervical cancer tissues compared with normal tissues, and that cisplatin resistance in cervical cancer was increased by the inhibition of endogenous *EZH2* expression with short hairpin RNA. Furthermore, an overexpression of *EZH2* has been identified in 66% of tumors and 67% of endothelial cells of tumor vessels in patients with ovarian cancer (36). Patients with high expression of *EZH2* in tumors exhibited a significantly poorer prognosis compared with those without high expression. The inactivation of *EZH2* expression increases apoptosis of cancer cells, decreases the number of vessels in tumor tissues and reduces the growth of ovarian cancer cells (36).

5. Aberrant chromatin remodeling and ovarian cancer

Ovarian clear cell carcinoma (OCCC) is a chemoresistant cancer due to delayed cell division (37). OCCC exhibits two carcinogenic pathways, which are referred to as the adenofibroma-carcinoma and endometriosis-carcinoma sequences (38,39). The differences in the genetic backgrounds of these two pathways are unclear, but the *ARID1A* mutation has been suggested to be involved in the onset of OCCC via the endometriosis-carcinoma sequence, rather than via the adenofibroma-carcinoma sequence (38,39). Jones *et al* (9) detected *ARID1A* mutations in 24 (57%) of 42 patients with OCCC, and concluded that *ARID1A* is a tumor suppressor

Table I. Aberrant chromatin remodeling-associated genes in cancer.

Gene name	Mutation ratio, %	Gene abnormality	Type of cancer	(Refs.)
ARID1A	46-57	MS, NS, FS	Ovarian clear cell carcinoma	(9)
	30	MS, NS, FS	Ovarian endometrioid carcinoma	(2)
	13	MS, NS, FS	HCC	(7)
	9.6	MS, NS, FS	Gastrointestinal adenocarcinoma	(7)
	2.5	MS, NS, FS	Malignant melanoma	(7)
	36	Mutation	Endometrial serous carcinoma	(29)
	36	Mutation	Uterine CS	(57)
CHD4	56.4	FS	Gastric cancer	(30)
	55.7	FS	Colorectal cancer	(30)
	21	Mutation	Endometrial serious carcinoma	(28)
	7	OE	Endometrial carcinoma	(29)
	4	OE	Endometrial clear cell carcinoma	(29)
EZH2	66	OE	Ovarian cancer	(36)
	Unknown	OE	Melanoma, BC, lung cancer, cervical cancer	(33,34)
MLL3	<5	MS, NS, FS	Bladder carcinoma	(13)
	8	MS, NS, FS	Prostate cancer	(14)
	13	MS, NS, FS	Gastric adenocarcinoma	(16)
	27	Mutation	Uterine CS	(57)
	14	FS	Colorectal cancer	(15)
	28.1	FS	Gastric cancer	(20)
	7.5	FS	Colon cancer	(20)
	Unknown	Deletion	AML	(21)
	Unknown	MS, NS, FS	BC, medulloblastoma, pancreatic cancer, HCC, NSCLC	(12,17-19)
SMARCA4/	10	GM, NS, FS	Lung adenocarcinoma	(49)
BRG1	31.3	GM, NS, FS	Lung large cell carcinoma	(49)
	36.4	GM, NS, FS	Lung pleomorphic carcinoma	(49)
	94	GM, NS, FS	SCCOHT	(26,45-47)
	<30	Mutation	NSCLC	(7)
	10-20	Mutation	Melanoma, esophageal adenocarcinoma, intraductal papillary mucinous neoplasms of the pancreas	(26)
	Unknown	Mutation	OSCC, rhabdoid tumor, mantle cell lymphoma, Burkitt lymphoma, non-melanoma skin cancer	(26)

MS, missense mutation; NS, nonsense mutation; FS, frameshift mutation; OE, overexpression; GM, germline mutation; HCC, hepatocellular carcinoma; BC, breast cancer; NSCLC, non-small cell lung carcinoma; AML, acute myeloid leukemia; OSCC, ovarian small cell carcinoma; CS, carcinosarcoma; SCCOHT, small cell carcinoma of the ovary hypercalcemic type; *SMARCA4*/*BRG1*, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4; *MLL3*, mixed-lineage leukemia 3; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit; *CHD4*, chromodomain helicase, DNA-binding protein 4; *ARID1A*, AT-rich interaction domain 1A.

gene and that *ARID1A* mutation inactivates gene products through the aberrant chromatin remodeling associated with OCCC pathogenesis. *ARID1A* encodes a component of the SWI/SNF complex, which regulates cell growth, controls cell cycle regulation and cell division and repairs DNA (40,41).

Wiegand *et al* (42) detected an *ARID1A* mutation in 55 (46%) of 119 patients with OCCC and identified a deficit in *BAF250a*, a protein encoded by *ARID1A*, in 36% of these patients (Table I). BAF250a gives specificity to the SWI/SNF complex and enables regulation of gene expression (22). Furthermore, *ARID1A* mutations and *BAF250a* deficits were identified in OCCC and adjacent endometriotic lesions, but not in distant lesions, which suggests that this mutation and resultant *BAF250a* deficit are events in the early stage of neoplastic transformation of endometriosis (2,42). A previous study confirmed that an *ARID1A* deficit was also an early phenomenon in endometriosis-associated ovarian cancer (EAOC) and endometriotic ovarian cysts, together with AKT protein activation and a histone H2A variant (γH2AX) (43). An *ARID1A* deficit has also been identified as a poor prognostic factor in

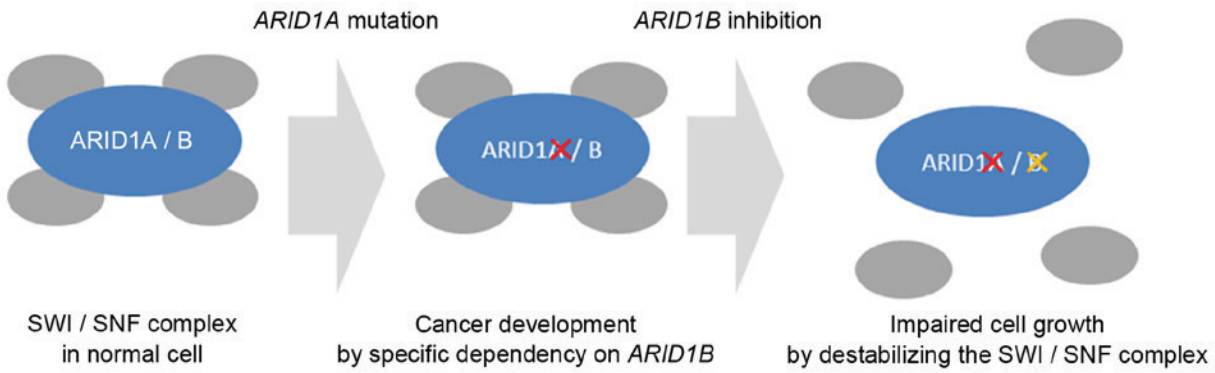

Figure 2. Coordinated carcinogenic effects of *ARID1A/B*. If *ARID1A* is mutated, the *ARID1B* mechanism enhances cancer development. *ARID1B* inhibition destabilizes the SWI/SNF complex, which leads to inhibition of cell proliferation. ARID1B, AT-rich interaction domain 1A; SWI/SNF, switch/sucrose non-fermentable complex.

patients with stage I/II OCCC, and may be a useful biological marker for the prediction of prognosis (42).

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) associated with hypercalcemia is a rare disease and is considered to be a rhabdoid tumor (26). SCCOHT is a poorly differentiated tumor associated with a poor prognosis that develops in young females (44). In an immunohistological study, Conlon *et al* (44) measured loss of *SMARCA4* expression in 94% of patients with SCCOHT, whereas loss of *SMARCA4* expression is usually identified in <5% of patients with ovarian cancer (44). Therefore, these data are considered to be specific to SCCOHT (44). In SCCOHT, germline mutations have been revealed in one allele of *SMARCA4*, and expression is deleted due to an inactivating germline mutation and frameshift and nonsense mutations in the other allele (26,45-47). Rhabdoid tumors that develop in organs other than the ovary, including the kidney and brain, have germline and somatic expression of *SMARCA4* (48). Immunostaining for the expression of *SMARCA4* in tumor tissues of patients with lung cancer revealed downregulation of *SMARCA4* in no patients with squamous cell carcinoma, in 10% with adenocarcinoma, in 31.3% with large cell carcinoma and in 36.4% with pleomorphic carcinoma (49), and somatic mutation and deletion of *SMARCA4* are present in these types of cancer (26). SMARCA4 is a subunit of the BAF and PBAF complexes, and mutation and deletion produces incomplete complexes and abnormal subunits that may cause dysregulation of genes and induce disease (50).

6. Aberrant chromatin remodeling and endometrial cancer

Endometrial cancer includes endometrioid carcinoma and serous carcinoma, which is less common compared with endometrioid carcinoma and has a relatively poor prognosis (51). Almost all serous carcinomas are poorly differentiated type 2 endometrial cancer with myometrial, vascular and extrauterine invasion (51). In exome sequencing of endometrial serous carcinomas in 53 patients, Le Gallo *et al* (29) detected *CHD4* mutations in 9 (17%) cases, and identified mutation of chromatin remodeling genes, including *ARID1A*, in 19 (36%) (29) (Table I). Similarly, Zhao *et al* (28) identified *CHD4* mutations in 11 (21%) of 52 patients with endometrial serous carcinomas. *CHD4* is a catalytic subunit of the NuRD complex that inhibits transcription and repairs DNA damage (52). *CHD4* overexpression has also been revealed in 7% of endometrioid carcinomas and 4% of endometrial clear cell carcinomas, with half of *CHD4* mutations affecting the ATPase/helicase domain or helicase domain, which is suspected to be the cause of endometrial cancer (29).

Carcinosarcoma (CS) is an extremely rare gynecological disease with a poor prognosis (53). Histological results of CS demonstrate mixed epithelial carcinoma and non-epithelial sarcoma (53). CS occurs commonly in the uterine body, but has also been identified in the ovary, uterine cervix and vagina (54-56). The incidence in the United States is 2 per 100,000, and the 5-year survival rates are 35-65% in the early stage and ~10% in stage IV (53). In 22 patients with uterine CS, Jones *et al* (57) revealed *ARID1A* mutations in 8 (36%) cases, mutations of histone methyltransferase *MLL3* in 6 (27%) cases, mutations of speckle-type POZ protein (SPOP), which is involved in chromatin remodeling, in 3 (14%) cases, and mutations of chromatin remodeling-associated genes in 14 (64%) cases (57). *ARID1A* serves an important role in the regulation of cell growth, and *MLL3* is a coactivator of tumor protein p53 (*TP53*), a tumor suppressor p53 gene (2,58). SPOP is a transcriptional repressor of p53 via the bric-a-brac/tramtrack/broad complex protein (59). Jones *et al* (57) suggested that a specific tissue-type of uterine CS depends on aberrant chromatin remodeling. Therefore, a complete understanding of genetic mutations in this cancer will be useful for diagnosis, early detection and treatment.

7. Therapy targeting aberrant chromatin remodeling

Cancer cells with an *ARID1A* deficit are highly sensitive to small molecule inhibitors in the PI3K/AKT signal transduction pathway. Therefore, drugs that inhibit this pathway are effective in patients with cancer with an *ARID1A* deficit (60). Therapy targeting epigenetic regulatory mechanisms in cancer cells is also under development. Bitler *et al* (61) focused on the activity of EZH2, a methylation factor in cancer with *ARID1A* mutation, and identified that proliferation of cells with an *ARID1A* mutation was selectively inhibited by the administration of an EZH2 inhibitor. This suggests that EZH2 inactivation is a potential therapy for cancer with *ARID1A* mutation, and EZH2 inhibition has been demonstrated to reduce the number

of ovarian tumors with *ARID1A* mutations *in vivo*. Therefore, pharmacological inhibition of *EZH2* expression may be a therapeutic strategy for cancer with an *ARID1A* mutation (61).

Guan *et al* (62) demonstrated that an *ARID1A* in-frame mutation prevented ARID1A transport from the nucleus to the cytoplasm (62). The ARID1A protein was then degraded by the ubiquitin-proteasome system and was not available downstream, resulting in the onset of cancer. Thus, ARID1A degradation may be inhibited by targeting the ubiquitin-proteasome system in cells with an *ARID1A* mutation, with potential recovery of the original cancer inhibitory effect (62).

ARID1B has recently been identified as an *ARID1A* homolog (63). In cells with an *ARID1A* deficit, *ARID1B* is independently expressed and its proliferation is enhanced, which suggests that *ARID1A* and *ARID1B* may interact in promoting carcinogenesis. However, blocking the mechanism of *ARID1B* in cells with an *ARID1A* deficit destabilizes the SWI/SNF complex and inhibits cell proliferation. Therefore, *ARID1B* is also a therapeutic target in cancer with *ARID1A* mutation (Fig. 2) (63). Immunohistochemical detection of *ARID1A* expression may be a useful marker for the evaluation of malignancy, prognosis and treatment effect (64).

8. Conclusion

ARID1A mutation is involved in gynecological cancer types such as OCCC and uterine cancer through the induction of aberrant chromatin remodeling and promotion of tumorigenesis. Germline mutations and epigenetic regulatory mechanisms, including chromatin remodeling, are involved in carcinogenesis. Therefore, there is a requirement for methods for identifying chromatin remodeling-associated gene mutations, including *ARID1A* and *BRG1*, and for therapy targeting the carcinogenic mechanisms of aberrant chromatin remodeling.

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