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ARID1A mutation in endometrial cancer: a review

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Summary

Endometrial carcinoma is the most frequent gynecological malignancy and a leading cause of cancer death in women worldwide. ARID1A, a gene participated in chromatin remodeling, is an emerging tumor suppressor gene. Accumulating evidence has reported somatic inactivating mutations of ARID1A and loss of its expression in many types of human cancers, especially in endometrium-derived tumors. The high prevalence of somatic mutations in endometrial cancers indicates a pivotal role of ARID1A in their development. Understanding the roles of ARID1A in the pathogenesis of endometrial carcinoma is fundamental for future translational studies aimed at designing new diagnostic tests for early detection and identifying critical molecular targets for new therapeutic interventions.

Key words: ARID1A; Mutation; Endometrial cancer; ARID1B.

Introduction

Endometrial cancer is the most common gynecological malignancy, it is a heterogeneous disease, comprised of multiple subtypes with differing risk factors, precursor lesions, and outcomes. ARID1A (AT-rich interacting domain-containing protein 1A gene) is viewed as a cancer-inhibiting gene and is an essential component of the SWI/SNF (mating type switching/sucrose non-fermenting) complex in selectively suppressing DNA synthesis. The SWI/SNF complex has been shown to play an essential role in controlling gene expression and is also involved in tissue development and cellular differentiation[1]. This mechanism has impacts on transcription, replication, repair, methylation, and recombination of DNA[2]. Inactivation of several components of this complex had been found to be associated with certain type of cancer. The SWI/SNF complex is involved in activation or inhibition of transcription, and is also predicted to be involved in regulation of higher-order chromatin structures. Several mutations in genes encoding chromatin remodeling complexes have been found in recent years using comprehensive genome-wide analyses with next-generation sequencers. As a member of SWI/SNF complexes, ARID1A is thought to contribute to specific recruitment of its chromatin remodeling activity by binding transcription factors and transcriptional coactivator/corepressor complexes. In this review, the authors focus on the relationships of ARID1A mutations with tissue-specific endometrial cancers, and suggesting key insights into the pathogenesis of endometrial cancer with implications for the development of targeted therapy.

ARID1A structure and expression

ARID1A is located on chromosome 1p36.11 and encodes two isoforms (2285 and 2086 amino acids) named BAF250A. ARID1A is post-translationally modified, including N-16-lysine acetylation and serine/threonine phosphorylation, potentially regulating protein expression or protein-protein interactions [3]. ARID1A belongs to a family of 15 proteins in humans that all contain a characteristic 100-amino acid DNA-binding ARID domain. Seven ARID subfamilies have based both upon degree of homology within the ARID domain as well as similarity between highly variable non-ARID domain structures [4]. The ARID domain of ARID1A does not demonstrate sequence-specific DNA binding and the only other protein homology domain, located within the C-terminus, has unknown function [5]. ARID1A forms a complex with either BRG (SMARCA4) or BRM (SMARCA2), which becomes part of SWI/SNF adenosine triphosphate-dependent chromatin-remodeling complexes [6]. Chromatin remodeling is a molecular mechanism of regulating the interaction of proteins with double-stranded DNA by changing the nucleosome structure in an ATP-dependent manner. The nucleosome remodeling activity is derived from the catalytic ATPase subunit (either SMARCA4/BRG1 or SMARCA2/BRM) and is enhanced by the non-catalytic subunits SMARCB1/SNF5, BAF155, and BAF170 [7]. The SWI/SNF complex is composed of many subunits, including an ATP-dependent catalytic subunit capable of sliding nucleosomes along a DNA template in vitro and a core subunit that is involved in construction of the complex and contains ARID1A [7, 8]. Chromatin remodeling complexes alter the structure of nucleosomes by local ATP-dependent sliding of nucleosomes or by modification of histones [9, 10].

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ARID1A mutations in cancer

Genome sequencing studies have detected ARID1A mutations or deletions in a wide variety of cancer types, with mutation frequencies of 34% in renal clear cell carcinoma [11], 8-27% in stomach cancer [12, 13], 13% in transitional cell carcinoma of the bladder [13], 9.1-15% in esophageal adenocarcinoma [14, 15], 10-13% in hepatocellular carcinoma [16, 17], 8% in lung adenocarcinoma [18], 8% in prostate cancer [12], 4-8% in pancreas cancer [12, 19], and 2-4% in breast cancer [12, 20, 21]. ARID1A mutations are frequently seen in cancers occurring in hormone- responsive tissues, so it is especially common in gynecologic cancer, with rates of 46-57% in ovarian clear cell adenocarcinoma [22, 23], 30% in ovarian endometrioid adenocarcinoma [23], 47% of low-grade endometrioid adenocarcinomas, 60% of high-grade endometrioid adenocarcinomas, 11% of serous adenocarcinomas, 24% of carcinosarcomas [24-26], and 14-22% uterine endometrial clear cell carcinoma [27-29].

There are two types of hotspots 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 [30]. The vast majority of cancer-associated mutations in ARID1A (>97%) were inactivating, with nonsense or frameshift (rather than silent or missense) mutations detected throughout the gene. Array CGH analysis of primary breast tumors demonstrated loss of chromosomal material encoding one copy of ARID1A in 13% of samples, without identifying any ARID1A coding mutations in the remaining allele [31]. At the protein level, complete loss of ARID1A expression were characterized in only 1-3% of breast cancers [24, 32]. Nearly all of the ARID1A mutations were found to be heterozygous in hepatocellular carcinomas [33]. Jones *et al.* has postulated that post-transcriptional and/or post-translational mechanisms account for loss of ARID1A protein in OCCs harboring heterozygous mutations without loss of heterozygosity, based upon the finding that RNA sequencing detects both wild-type and mutant alleles in 30% of the OCCs with ARID1A mutations were both alleles affected [22, 23]. By immunohistochemistry, 73% of the ARID1A heterozygous tumors lacked protein expression, as did 5% of tumors not found to have coding mutations [23]. Mutations affecting ARID1A expression may occur in non-coding regions of the genome not assayed by exome sequencing techniques and epigenetic silencing might contribute. Conversely, 27% of the ARID1A heterozygous OCCs retain detectable protein expression. A similar situation occurs in gastric cancer, in which ARID1A mutations were biallelic in only 44% of ARID1A-mutant samples. Again, 25% of samples harboring heterozygous mutations retained ARID1A expression by IHC [13]. Heterozygosity for ARID1A in mice results in embryonic-lethality, suggesting that biologically relevant haploinsufficient effects are caused by loss of a single allele [34].

Tumor behavior of ARID1A in endometrial cancers

Many reports have suggested that ARID1A mutation is involved in onset and progression of cancer. Studies have suggested roles for ARID1A in three processes relevant to tumor suppression – proliferation, differentiation, and apoptosis – with mixed results. Mao *et al.* defined clonal loss of ARID1A occurred at rates of 16% in atypical endometrial hyperplasia, 24% in uterine low-grade endometrioid adenocarcinomas and 9% in uterine high-grade endometrioid adenocarcinomas, whereas the respective rates of complete loss of ARID1A were 0%, 2%5, and 44% in these diseases [35]. This suggests that ARID1A mutation occurs at the early stage of canceration from atypical endometrial hyperplasia to endometrioid adenocarcinoma in endometrial cancer. Cases with loss of ARID1A were significantly high in late stages of endometrial clear cell carcinomas, but had no association with reduced overall or progression-free survival [28, 29]. Investigators have found that nuclear ARID1A is unstable as compared to cytoplasmic ARID1A by using biochemistry approaches, because the protein is rapidly degraded by the ubiquitin-proteasome system in the nucleus. In-frame deletions that disrupt the consensus nuclear export signal are associated with a reduced steady-state protein level of ARID1A due to its retention in the nuclei and subsequent degradation, which delineate the basic biological mechanism regulating ARID1A subcellular distribution and protein stability [24]. It has been reported that knock-down of ARID1A significantly elevated AKT phosphorylation levels in three cell lines (KLE, ESS1, and MFE280) expressing wild-type ARID1A. In contrast, up-regulation of AKT phosphorylation was not observed in the EFE184 cell line in which ARID1A protein is not present. Depletion of wild type ARID1A by siRNA considerably increased phosphorylation of AKT and decreased apoptosis rate was markedly detected in comparison to the control cells that expressed normal levels of ARID1A [36]. Expression of ARID1A varies during the cell cycle, highest during G0/G1, and significantly diminished in S and G2/M phases [37]. At the molecular level, mutation of ARID1A inactivates ARID1A/BRG1/p53 complex and they silence the transcription of cyclin-dependent kinase inhibitor 1A (CDKN1A) and SMAD family member 3 (SMAD3), which acts as a regulator of cell cycle progression in G1 phase, and causes tumor growth [38]. Loss of ARID1A may have many effects on SWI/SNF complexes that lead to transcriptional dysfunction, including disruption of nucleosome sliding activity, assembly of variant SWI/ SNF complexes, targeting to specific genomic loci, and/or recruitment of coactivator/corepressor activities. With respect to chromatin remodeling, ARID1A is thought to be dispensable for the in vitro nucleosome remodeling activity of SWI/SNF, as measured by DNase hypersensitivity patterns of reconstituted nucleosomal arrays [7].

ARID1A is recurrently and specifically mutated on one allele but expressed from the other allele, have raised the possibility that reduced levels of ARID1A may mediate a haploinsufficient effect in promoting cancer. Knockdown studies in a variety of cell types, having only partial loss of ARID1A, showed increased cell proliferation and colony formation [13, 16, 31, 39], impaired differentiation [34, 39], as well as decreased apoptosis [40]. Different mutation patterns among cancer subtypes imply tissue-specific mutational effects, which may limit the extent to which observations in one cancer type or cell line may be applied to other model systems.

Relationship between ARID1A and other genes

The relationship between loss of ARID1A and microsatellite instability (MSI) in endometrial endometrioid carcinoma has been recently demonstrated and loss of ARID1A is associated with mismatch repair deficiency [41, 42]. MSI phenotype is characterized by a higher frequency of mutations at some short nucleotide repeats within the genome, which results from unrepaired errors during DNA replication in a defective DNA mismatch repair (MMR) system [43]. The prevalence of the high levels of MSI (MSI-H) is ~20% in unselected endometrial tumours, and is higher in endometrioid adenocarcinomas than in non-endometrioid adenocarcinomas [44]. Melissa *et al.* determined the MSI status of 241/276 low-grade EECs and 13/30 high-grade EECs [26].

Recent studies have shown that ARID1A mutation is involved in carcinogenesis through multiple mechanisms, including activation the phosphatidylinositol-3-kinase (PI3K)/AKT pathway, which stimulates several mechanisms that cause progression to cancer, including proliferation of cancer cells and inhibition of apoptosis of cancer cells. ARID1A mutations co-occur with mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (PIK3CA), phosphatase and tensin homolog (PTEN), and KRAS in endometrioid adenocarcinoma [26, 45]. These mutations induce aberrant activation of PI3K, phosphorylation of AKT, and inhibition of cell survival and apoptosis [46]. PIK3CA was candidate preferentially necessary for the growth of ARID1A-mutated cancer cell lines [36]. PTEN is a cancer-suppressor gene, dephosphorylates phosphatidylinositol-3-phosphate (PIP3) into phosphorylated phosphatidylinositol-2-phosphate (PIP2), and competitively inhibits the PI3K/AKT pathway. Aberrations in the PI3K/AKT pathway are present in ≥80% of uterine endometrioid adenocarcinomas [47]. It is becoming increasingly evident that the majority of endometrioid carcinomas acquire ARID1A and/or PTEN, and a significant subset of clear cell carcinomas acquire ARID1A mutations as early oncogenic events, whereas these mutations in serous carcinoma are very rare[48].

Co-existent PTEN and PIK3CA mutations were identified in 28.6% low-grade endometrial endometrioid cancers; 86.8% low-grade endometrial endometrioid cancers had ARID1A mutations within PTEN and/or PIK3CA mutations [26]. Huang *et al.* evaluated molecular alterations including MSI, loss of expression of MMR protein, ARID1A and PTEN, as well as mutation of PTEN, KRAS, CTNNB1, and PIK3CA in endometrial tumors [49]. 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 [50]. 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 [51].

ARID1A controls tumor growth by collaboration with p53 and regulates p53 downstream targets [38]. Mutations of ARID1A and TP53 were mutually exclusive in endometrial carcinomas [41, 42]. ARID1A/BRG1 complex has been shown to directly interact and collaborate with p53 to transcriptionally regulate several downstream effectors including those encoded by CDKN1A (p21) and SMAD3 [26]. Using biochemistry approaches, investigators have found that ARID1A acts as a nucleocytoplasmic protein whose stability depends on its subcellular localization [27]. To determine the mutation frequencies in various subtypes of endometrial carcinomas, Melissa *et al.* identified that low-grade EECs have high to moderate frequencies of mutations in PTEN, ARID1A, PIK3CA, and CTNNB1, with a higher frequency of mutations of PTEN, ARID1A, PIK3CA, KRAS, PPP2R1A, and TP53 seen in high-grade EECs. The comparison of high-grade EECs to endometrial serous carcinomas revealed significantly different mutation frequencies for ARID1A, PTEN, PIK3CA, CTNNB1, PPP2R1A, and TP53 [26].

ARID1A and ARID1B

The ARID1 subfamily contains two members, ARID1A and ARID1B, which share approximately 80% amino acid homology within their ARID domains and 50% homology throughout, have been reported to have opposing functions in cell cycle arrest, and are mutually exclusive since individual SWI/SNF chromatin relationship between ARID1A and ARID1B in cancer [52]. Immunoprecipitation of the SMARCC1 (BAF155) core both wildtype and ARID1A-mutant cells, indicating that intact ARID1B-containing complexes are present in both wildtype and ARID1A-mutant cells [7]. Partial loss of ARID1 function via mutation of ARID1A or ARID1B alleles can drive cancer growth but at the same time create a specific vulnerability compared to non-mutant cells. Helming *et al.* compared 18 ARID1A-mutant and 147 cell lines wildtype for ARID1A, of 9,050

genes interrogated, ARID1B scored as the top candidate preferentially required for the growth of ARID1A-mutant cancer cell lines, which suggested co-occurrence of ARID1A and ARID1B mutations may be required for carcinogenesis[53].

Since ARID1A and ARID1B have been characterized as mutually exclusive members of BAF variant SWI/SNF complexes, meaning the two proteins do not coimmunoprecipitate [54]. Following induction of differentiation in a non-transformed osteoblast model, ARID1A and ARID1B have opposing effects on cell cycle arrest caused by serum deprivation - knockdown of ARID1A delayed arrest while ARID1B knockdown had no effect [55]. Furthermore, ARID1A and ARID1B were found to have differential interactions with E2F family members [39]. Collectively, such findings could suggest a tumor suppressor model by which the unopposed actions of ARID1B-containing SWI/SNF complexes disrupt cell cycle control and predispose to transformation.

Clinical Implications of ARID1A mutation

Several studies have attempted to analyze the prognostic significance of ARID1A mutations. Ultimately, larger prospective studies, ideally assessing not only ARID1A sequence, but also loss of heterozygosity and protein expression, will be required to adequately address the prognostic significance of ARID1A mutations. Importantly, Shen *et al.* speculated that ARID1A deficiency sensitizes cancer cells to PARP inhibitors *in vitro* and *in* vivo, PARP inhibitor BMN673 selectively inhibits ARID1A-deficient tumors in xenograft models [56]. Ronald *et al.* found that ARID1A inactivation is not sufficient for tumour formation, but requires concurrent activation of PIK3CA. Remarkably, therapeutic treatment with the pan-PI3K inhibitor, BKM120, prolongs ovarian clear-cell carcinoma model survival by inhibiting the tumour cell growth [57]. Thus, PARP inhibitors in combination with PI3K–AKT inhibitors may provide new therapeutic avenues for patients with ARID1A- mutant tumors.

Conclusion

In summary, recently published studies provided new evidence that the mechanistic basis by which ARID1A alters chromatin structure, contributes to SWI/SNF activity, modulates transcription, and ultimately suppresses cancer formation. Ultimately, several lines of evidence support classification of ARID1A as a tumor suppressor gene. Haploinsufficient tumor suppressor effects have ample precedent, and their identification and interpretation require synthesis of human sequencing data, as well as cell culture and animal modeling systems. Moreover, several findings demonstrate a synthetic lethal relationship between PIK3CA, PTEN, P53, and ARID1B interacted with ARID1A in endometrial cancer and co-affected cell function. Furthermore, it will be of interest to determine whether inactivation of chromatin remodelers, such as ARID1A can be therapeutically exploited by targeting downstream and potentially reversible epigenetic consequences of remodeler mutation.

References

[1] Ho L., Crabtree G.R.: “Chromatin remodelling during development”. *Nature*, 2010, *463*, 474.

[2] Clapier C.R., Cairns B.R.:”The Biology of Chromatin Remodeling Complexes”. *Annu. Rev. Biochem.*, 2009, *78*, 273.

[3] Beausoleil S.A., Gygi S.P.: “Large-scale characterization of HeLa cell nuclear phosphoproteins”. *Proc. Natl. Acad. Sci. U S A.*, 2004, *101*, 12130.

[4] Wilsker D., Probst L., Wain H.M, Maltais L., Tucker P.W., Moran E.: “Nomenclature of the ARID family of DNA-binding proteins”. *Genomics*, 2005, *86*, 242.

[5] Dallas P.B., Pacchione S., Wilsker D., Bowrin V., Kobayashi R., Moran E.: “The human SWI-SNF complex protein p270 is an ARID family member with non-sequence-specific DNA binding activity”. *Mol. Cel. Biol.*, 2000, *20*, 3137.

[6] Reisman D., Glaros S., Thompson E.A.: “The SWI/SNF complex and cancer”. *Oncogene*, 2009, *28*, 1653.

[7] Phelan, Michael L., Saïd, Narlikar, Geeta J., Kingston R.E.:”Reconstitution of a Core Chromatin Remodeling Complex from SWI/SNF Subunits”. *Mol. Cel.*, 1999, *3*, 247.

[8] Wang X., Nagl N.G., Wilsker D., Scoy M.V., Pacchione S., Yaciuk P., *et al.*: “Two related ARID family proteins are alternative subunits of human SWI/SNF complexes”. *Biochem. J.*, 2004, *383*, 319.

[9] Saha A., Wittmeyer J., Cairns B.R.:”Chromatin remodelling: the industrial revolution of DNA around histones”. *Nat. Rev. Mol. Cell. Biol.*, 2006, *7*, 437.

[10] Lorch Y., Maierdavis B., Kornberg R.D.: “Mechanism of chromatin remodeling”. *Proc. Natl. Acad. Sci. U S A*, 2010, *107*, 3458.

[11] Varela I., Tarpey P., Raine K., Huang D., Ong C.K., Stephens P.,*et al.*: “Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma”. *Nature*, 2011, *469*, 539.

[12] Jones S., Li M., Parsons D.W., Zhang X., Wesseling J., Kristel P.,*et al.*: “Somatic mutations in the chromatin remodeling gene ARID1A occur in several tumor types”. *Human. Mutat.,* 2012, *33*, 100.

[13] Zang Z.J., Cutcutache I., Poon S.L., Zhang S.L., Mcpherson J.R., Tao J.,*et al.*: “Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes”. *Nat. Genet.*, 2012, *44*, 570.

[14] Agrawal N., Jiao Y., Bettegowda C., Hutfless S.M., Wang Y., David S., *et al.*: “Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma”. *Cancer. Discov.*, 2012, *2*, 899.

[15] Streppel M.M., Lata S., DelaBastide M., Montgomery E.A., Wang J.S., Canto M.I., *et al.*: “Next-generation sequencing of endoscopic biopsies identifies ARID1A as a tumor-suppressor gene in Barrett’s esophagus”. *Oncogene*, 2013, *33*, 347.

[16] Huang J., Deng Q., Wang Q., Li K.Y., Dai J.H., Li N., *et al.*: “Exome sequencing of hepatitis B virus-associated hepatocellular carcinoma”. *Nat. Genet.,* 2012, *44*, 1117.

[17] Fujimoto A., Totoki Y., Abe T., Boroevich K.A., Hosoda F., Nguyen H.H., *et al.*: “Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators”. *Nat. Genet.,* 2012, *44*, 760.

[18] Imielinski M., Berger A., Hammerman P., Hernandez B., Pugh T., Hodis E., *et al.*: “Mapping the Hallmarks of Lung Adenocarcinoma with Massively Parallel Sequencing”. *Cell*, 2012, *150*, 1107.

[19] Biankin A.V., Waddell N., Kassahn K.S., Gingras M.C., Muthuswamy L.B., Johns A.L., *et al.*: “Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes”. *Nature*, 2012, *491*, 399.

[20] Cornen S., Adelaide J., Bertucci F., Finetti P., Guille A., Birnbaum D.J., *et al.*: "Mutations and deletions of ARID1A in breast tumors". *Oncogene*, 2012, *31*, 4255.
[21] Stephens P.J., Tarpey P.S., Davies H., Van L.P., Greenman C., Wedge D.C., *et al.*: "The landscape of cancer genes and mutational processes in breast cancer". *Nature*, 2012, *486*, 400.
[22] Jones S., Wang T.L., Iem S., Mao T.L., Nakayama K., Roden R., *et al.:* "Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma". *Science*, 2012, *330*, 228.
[23] Wiegand K.C., Shah S.P., Alagha O.M., Zhao Y., Tse K., Zeng T., *et al*.: "ARID1A Mutations in Endometriosis-Associated Ovarian Carcinomas". *N. Engl. J. Med.,* 2010, *363*, 1532.
[24] Guan B., Mao T.L., Panuganti P.K., Kuhn E., Kurman R.J., Maeda D., *et al*.: "Mutation and loss of expression of ARID1A in uterine low-grade endometrioid carcinoma". *Am. J. Surg. Pathol.*, 2011, *35*, 625.
[25] Le G.M., O'Hara A.J., Rudd M.L., Urick M.E., Hansen N.F., O'Neil N.J., *et al*.: "Exome sequencing of serous endometrial tumors identifies recurrent somatic mutations in chromatin-remodeling and ubiquitin ligase complex genes". *Nat. Genet.*, 2012, *44*, 1310.
[26] Mcconechy M.K., Ding J., Cheang M.C., Wiegand K., Senz J., Tone A.A., *et al*.: "Use of mutation profiles to refine the classification of endometrialcarcinomas". *J. Pathol.*, 2012, *228*, 20.
[27] Hoang L.N., Mcconechy M.K., Meng B., Mcintyre J.B., Ewanowich C., Gilks C.B., *et al*.: "Targeted mutation analysis of endometrial clear cell carcinoma". *Histopathology*, 2015, *66*, 664.
[28] Fadare O., Renshaw I.L., Liang S.X.: "Does the Loss of ARID1A (BAF-250a) Expression in Endometrial Clear Cell Carcinomas Have Any Clinicopathologic Significance? A Pilot Assessment". *J. Cancer*, 2012, *3*, 129.
[29] Fadare O., Gwin K., Desouki M.M., Crispens M.A., Jones H.W., Khabele D., *et al.*: "The Clinicopathologic Significance of p53 and BAF-250a (ARID1A) Expression in Clear Cell Carcinoma of the Endometrium". *Mod. Pathol.*, 2013, *26*, 1101.
[30] Guan B., Gao M., Wu C.H., Wang T.L., Shih I.M., *et al.*: "Functional analysis of in-frame indel ARID1A mutations reveals new regulatory mechanisms of its tumor suppressor functions". *Neoplasia,* 2012, *14*, 986.
[31] Mamo A., Cavallone L., Tuzmen S., Chabot C., Ferrario C., Hassan S., *et al*.: "An integrated genomic approach identifies ARID1A as a candi date tumor-suppressor gene in breast cancer". *Oncogene*, 2011, *31*, 2090.
[32] Wiegand K.C., Lee A.F., Al-Agha O.M., Chow C., Kalloger S.E., Scott D.W., *et al*.: "Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas". *J. Pathol.*, 2011, *224*, 328.
[33] Guichard C., Amaddeo G., Imbeaud S., Ladeiro Y., Pelletier L., Maad I.B., *et al*.: "Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma". *Nat. Genet.*, 2012, *44*, 694.
[34] Gao X., Tate P., Hu P., Tjian R., Skarnes W.C., Wang Z.:"ES cell pluripotency and germ-layer formation require the SWI/SNF chromatin remodeling component BAF250a". *Proc. Natl. Acad. Sci. U S A.*, 2008, *105*, 6656.
[35] Mao T.L., Ardighieri L., Ayhan A., Kuo K.T., Wu C.H., Wang T.L.,et al.: "Loss of ARID1A expression correlates with stages of tumor progression in uterine endometrioid carcinoma". *Am. J. Surg. Pathol.*, 2013, *37*, 1342.
[36] Gagnon V., Mathieu I., Sexton E., Leblanc K., Asselin E., *et al*.: "AKT involvement in cisplatin chemoresistance of human uterine cancer cells". *Gynecol. Oncol.*, 2004, *94*, 785.
[37] Flores-Alcantar A., Gonzalez-Sandoval A., Escalante-Alcalde D., Lomelí H.: "Dynamics of expression of ARID1A and ARID1B subunits in mouse embryos and in cells during the cell cycle". *Cell. Tissue. Res.*, 2011, *345*, 137.
[38] Guan B., Wang T.L., Shih I.M.:"ARID1A, a Factor That Promotes Formation of SWI/SNF-Mediated Chromatin Remodeling, Is a Tumor Suppressor in Gynecologic Cancers". *Cancer. Res*., 2011, *71*, 6718.
[39] Nagl N.G. Jr., Wang X., Patsialou A., Van S.M., Moran E.: "Distinct mammalian SWI/SNF chromatin remodeling complexes with opposing roles in cell-cycle control". *EMBO J.*, 2007, *26*, 752.
[40] Luo B., Cheung H.W., Subramanian A., Sharifnia T., Okamoto M., Yang X., *et al*.: "Highly parallel identification of essential genes in cancer cells". *Proc. Natl. Acad. Sci. U S A*., 2008, *105*, 20380.
[41] Bosse T., ter Haar N.T., Seeber L.M., Pj V.D., Hes F.J., Vasen H.F., *et al*.: "Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer". *Mod. Pathol.*, 2013, *26*, 1525.
[42] Allo G., Bernardini M.Q., Wu R.C., Shih I.M., Kalloger S., Pollett A., *et al.*: "ARID1A loss correlates with mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas". *Mod. Pathol.*, 2013, *27*, 255.
[43] Burgart L.J.: "Testing for defective DNA mismatch repair in colorectal carcinoma: a practical guide". *Arch. Pathol. Lab. Med.*, 2005, *129*, 1385.
[44] Esteller M., Catasus L., Matias-Guiu X., Mutter G.L., Prat J., Baylin S.B., *et al*.: "hMLH1 Promoter hypermethylation is an early event in human endometrial tumorigenesis". *Am. J. Pathol.*, 1999, *155*, 1767.
[45] Llobet D., Pallares J., Yeramian A., Santacana M., Eritja N., Velasco A., *et al.*: "Molecular pathology of endometrial carcinoma: practical aspects from the diagnostic and therapeutic viewpoints". *J. Clin. Pathol.*, 2009, *62*, 777.
[46] Liang H., Cheung L.W., Li J., Ju Z., Yu S., Stemke-Hale K., *et al.*: "Whole-exome sequencing combined with functional genomics reveals novel candidate driver cancer genes in endometrial cancer". *Genome. Res.*, 2012, *22*, 2120.
[47] Cheung L.W., Hennessy B.T., Li J., Yu S., Myers A.P., Djordjevic B., *et al*.: "High Frequency of PIK3R1 and PIK3R2 Mutations in Endometrial Cancer Elucidates a Novel Mechanism for Regulation of PTEN Protein Stability". *Cancer. Discov.,* 2011, *1*, 170.
[48] Hoang L.N., Mcconechy M.K., Köbel M., Han G., Rouzbahman M., Davidson B., *et al.*: "Histotype-genotype correlation in 36 high-grade endometrial carcinomas". *Am. J. Surg. Pathol.*, 2013, *37*, 1421.
[49] Huang H.N., Lin M.C., Tseng L.H., Chiang Y.C., Lin L.I., Lin Y.F., *et al*.: "Ovarian and endometrial endometrioid adenocarcinomas have distinct profiles of microsatellite instability, PTEN expression, and ARID1A expression". *Histopathology*, 2015, *66*, 517.
[50] Guan B., Rahmanto Y.S., Wu R.C., Wang Y., Wang Z., Wang T.L., *et al.*: "Roles of Deletion of Arid1a, a Tumor Suppressor, in Mouse Ovarian Tumorigenesis". *J. Natl. Cancer. Inst.*, 2014, *106*, 766.
[51] Tanwar P.S.: "PTEN loss and HOXA10 expression are associated with ovarian endometrioid adenocarcinoma differentiation and progression". *Carcinogenesis,* 2013, *34*, 893.
[52] Wu J.N., Roberts C.W.: "ARID1A mutations in cancer: another epigenetic tumor suppressor?".*Cancer. Discov.*, 2013, *3*, 35.
[53] Helming K.C., Wang X., Wilson B.G., Vazquez F., Haswell J.R., Manchester H.E., *et al.*: "ARID1B is a specific vulnerability in ARID1A-mutant cancers". *Nat. Med.*, 2014, *20*, 251.
[54] Martens J.A., Winston F.: "Recent advances in understanding chromatin remodeling by Swi/Snf complexes". *Curr. Opin. Genet. Dev.,* 2003, *13*, 136.
[55] Nagl N.G. Jr, Patsialou A., Haines D.S., Dallas P.B., Beck G.R. Jr, Moran E.: "The p270 (ARID1A/SMARCF1) subunit of mammalian SWI/SNF-related complexes is essential for normal cell cycle arrest". *Cancer. Res.*, 2005, *65*, 9236.
[56] Shen J., Peng Y., Wei L., Zhang W., Yang L., Lan L., *et al*.: "ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors". *Cancer. Discov*., 2015, *5*, 752.
[57] Chandler R.L., Damrauer J.S., Raab J.R., Schisler J.C.,Wilkerson M.D., Didion J.P., *et al*.: "Coexistent ARID1A-PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signalling". *Nat. Commun.*, 2015, *6*, 6118.

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