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The SWI/SNF complex mutations in gynecologic cancers: molecular mechanisms and models

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Abstract

The SWI/SNF (Mating Type SWitch/Sucrose Non-Fermentable) chromatin remodeling complexes interact with histones and transcription factors to modulate chromatin structure and control gene expression. These evolutionarily conserved multi-subunit protein complexes are involved in the regulation of many biological functions, such as differentiation and cell proliferation. Genomic studies have revealed frequent mutations of genes encoding multiple subunits of the SWI/SNF complexes in a wide spectrum of cancer types, including gynecologic cancers. These SWI/SNF mutations occur at different stages of tumour development and are restricted to unique histologic types of gynecologic cancer. Thus, the SWI/SNF mutations have to function in the appropriate tissue and cell context to promote gynecologic cancer initiation and progression. In this review, we will summarize the current knowledge of SWI/SNF mutations in gynecologic cancer development to provide insights into both molecular pathogenesis and possible treatment implications for these diseases.

Keywords

SCCOHT; DDEC; clear cell carcinoma of the ovary; SWI/SNF; SMARCA4; ARID1A

1. INTRODUCTION

Gynecologic cancer, also referred to as cancer of the female reproductive tract, includes malignancies arising from the cervix, fallopian tubes, ovaries, uterus, vulva and vagina. Among these cancers, whilst uterine cancer is the most common, ovarian cancer is the most

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common cause of death. Both ovarian and uterine cancers are composed of several distinct histologic subtypes. Many of these histologic subtypes are believed to arise from distinct cellular origins in addition to having distinct and sometimes pathognomonic mutations. Recent genomic studies have revealed that each histologic subtype is often associated with a distinct mutational landscape and signature, such as the homologous recombination signature characteristic of BRCA-deficient high-grade serous cancer of the ovary. In addition to finding common well-studied tumor suppressors and oncogenes, genomic analysis of gynecologic cancers has identified frequent mutations of genes encoding subunits of the SWI/SNF (Mating Type SWItch/Sucose Non-Fermentable) chromatin remodeling complex. Some mutations, such as *SMARCA4/BRG1*, occur as a germline event and function as a classic tumor suppressor and key driver in small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Other mutations occur either early during the transformation or as a late event during the progression of gynecologic cancer. These studies suggest specific roles of mutations in the SWI/SNF complex during multiple steps of gynecologic cancer development. In this review, we will summarize the current knowledge of SWI/SNF mutations in gynecologic cancer development to provide insights into both molecular pathogenesis and the potential treatment implications of these disease.

2. BIOLOGY OF THE SWI/SNF COMPLEXES

The SWI/SNF complexes were first discovered in *S. cerevisiae*. They are evolutionarily conserved multi-subunit protein complexes that interact with histones and transcription factors. They are composed of 10 to 15 subunits with many possible combinations of subunits, resulting in the presence of numerous distinct sub-complexes in a single cell (Figure 1) (1–5). Two major types of the SWI/SNF complexes have been well documented in mammalian cells, the canonical BAF (BRG1 associated factors) complex that contains a mutually exclusive ARID1A or ARID1B subunit, and the PBAF (Polybromo-associated BAF) complex that incorporates ARID2, PBRM1 and BRD7 as its signature subunits (6–8). Recently, a third type of SWI/SNF complex, discovered independently by Alpsoy *et al.* and Mashtalir *et al.* recently, does not include ARID1A/B and ARID2 and instead contains BRD9 and either GLTSCR1 (glioma tumor suppressor candidate region gene 1) or GLTSCR1L (GLTSCR1-like) as its unique subunits and are therefore called as either the GBAF or the non-canonical BAF complex (8, 9). All these SWI/SNF complexes include a catalytic ATPase subunit (mutually exclusive SMARCA4/BRG1 or SMARCA2/BRM) and core subunits including SMARCC and SMARCD proteins (10). Assembly of these complexes occurs in a highly ordered and modular fashion, through which the core module acts as an essential platform for recruiting complex-specific subunits and subsequently the pre-assembled ATPase module caps (8).

The SWI/SNF complexes are believed to bind to DNA regions via ARID1A and ARID1B, two mutually exclusive accessory subunits of the complex with non-selective DNA binding activities (11), and/or interaction with general or specific transcription factors (12). They utilize the energy of ATP hydrolysis to mobilize nucleosomes to control chromatin accessibility (1–5). These complexes are therefore crucial for gene transcription, cell fate control, and lineage specification, all of which are frequently perturbed in cancer (13–15). Although it remains unclear whether and how each class of the SWI/SNF complexes

functions differently, Pan *et al.* have recently demonstrated that both the non-catalytic and the ATPase activities of the ATPase module cap determine the divergent localization of each class of SWI/SNF complexes to their genomic loci (16). Furthermore, Michel *et al.* mapped the SWI/SNF complexes on chromatin and unveiled that each class of the SWI/SNF complexes has differential preference on chromatin localization (17). The BAF complex displayed a strong enrichment in active enhancers (H3K27ac and H3K4me1) and primed enhancers (H3K4me1), suggestive of their key roles in enhancer regulation, whereas the PBAF complex had the strongest presence in active promoters (H3K27ac and H3K4me3) (17). In contrast, a great portion of the GBAF complex binds to CTCF sites (17), which are known to play important roles in the maintenance of DNA architecture (18). These findings highlight the diverse functions of the SWI/SNF complexes.

Given its pivotal role in regulating diverse pathways, it is not surprising that mutations impacting SWI/SNF function occur in a broad spectrum of cancers. Indeed, data from The Cancer Genome Atlas (TCGA) has shown that mutations of the SWI/SNF subunits are found in about 20% of all cancers (19, 20), a rate that approaches the frequency of *TP53* mutations. At least 9 subunits of this complex are recurrently mutated, suggesting a conserved/shared mechanism at the heart of its tumor suppressor activity. Genomic, functional and genetically engineered mouse model (GEMM) studies all strongly support that SWI/SNF subunits are *bona fide* tumor suppressors (21–24). However, specific subunits are mutated in different malignancies across the body, suggesting the subunit-, complex- and/or context-dependent functions of the SWI/SNF complexes. The mechanisms by which inactivating mutations in distinct SWI/SNF subunits promote oncogenic transformation and progression remains largely unaddressed. Investigating the function of specific mutations in relevant contexts with appropriate biological models will help design novel strategies for the management of a large number of malignancies with defects in this complex.

3. MUTATIONS OF THE SWI/SNF COMPLEX IN GYNECOLOGIC CANCERS

Mutations in the SWI/SNF complexes have been reported in multiple types of gynecologic cancers (Figure. 2). These mutations, which impact different subunits of the complex, arise at different stages of tumor development and thus may play distinct roles in each tumor type. For example, the inactivating mutations of the *SMARCA4* gene, the only recurrent genetic event in SCCOHT, are considered as the driver event of SCCOHT development. In contrast, the inactivating mutations of *SMARCA4*, *SMARCB1* or *ARID1A/B* genes are late events in the development of endometrial cancer that may promote disease progression. In this section, we will summarize the current understanding of SWI/SNF mutations in gynecologic cancers. We will order this review by the point in time in which the SWI/SNF deficiencies operate during disease development and progression: a driver event, an early event or a progression event.

3.1 Gynecologic cancers with SWI/SNF deficiency as a driver event

SCCOHT is a rare type of ovarian cancer that primarily affects young women with a median age of diagnosis in the mid-twenties (25–29). About two thirds of SCCOHT patients display hypercalcemia, which resolves upon removal of tumor. Various mechanisms have been

proposed that may account for the paraneoplastic hypercalcemia, including elevated levels of parathyroid hormone (PTH) and PTH related peptide (PTHrP), but none have yet to be fully substantiated (30, 31). Patient outcomes are abysmal with a 65% recurrence rate and a 2-year survival rate less than 35% (32–34). While standard treatment includes surgery and aggressive multi-agent chemotherapy, SCCOHT exhibits guarded responses to conventional treatment, which highlights the urgent need to develop novel tumor-specific treatment strategies.

Histologically, the SCCOHT tumours most often grow as sheets of closely packed small to intermediate sized cells with scant cytoplasm, hyperchromatic nuclei and prominent nucleoli. Follicle-like spaces containing eosinophilic fluid are seen in 80% of cases. A minority of cases will have mixed architectural patterns including nests, cords and single cells. Glands or cysts lined by mucinous epithelium can be seen in 10% of cases and signet ring cells in 1% of cases. The stroma varies from fibrous, myxoid and edematous. Approximately half of these tumours contain larger cells, some of which have rhabdoid features (eccentric nucleus, prominent nucleolus and abundant eosinophilic cytoplasm). Contrary to what its name implies, SCCOHT are actually comprised of cells which are mostly intermediate in size. Dr. Robert E. Scully coined the name SCCOHT to highlight the “small size” of the cells compared to the typical undifferentiated carcinoma of the ovary, which was composed of conspicuously large cells (34). In addition, some SCCOHT are comprised of exclusively large or rhabdoid cells, and are given the paradoxical name of “SCCOHT, large cell variant” (29). Diagnosis was historically challenging due to nonspecific poorly-differentiated histology and lack of diagnostic immunohistochemical (IHC) markers (32, 34–36). The majority of SCCOHT are positive for WT1 and CD10 and variably positive for cytokeratins, EMA and calretinin, which does not reliably distinguish SCCOHT from other ovarian tumors. It was not until the molecular underpinnings of SCCOHT were discovered that specific IHC markers were uncovered for diagnostic use.

We and others have discovered that, unlike most common ovarian malignancies, the genome of SCCOHT is diploid with inactivating germline and/or somatic mutations of the *SMARCA4* gene as the only recurrent feature and the likely driver event in ~90% of SCCOHT tumors (37–40). In addition, SCCOHT does not express SMARCA2 (41, 42), the alternative ATPase of the SWI/SNF chromatin-remodelling complex, a surprising finding given that SMARCA2 is essential for the survival of most other SMARCA4-deficient cancer cells (43, 44). Through IHC analysis of over 3000 primary gynecologic tumors, we further demonstrated that loss of SMARCA4, either alone or together with SMARCA2, is highly sensitive and specific for the diagnosis of SCCOHT (41), thus providing a definitive tool for SCCOHT diagnosis. Furthermore, claudin-4, an epithelial differentiation marker that distinguishes epithelial originated tumors from sarcomas exhibiting “epithelioid” morphology, was not expressed in any of the 10 SCCOHT examined (45), suggesting that SCCOHT does not fit as a bona fide epithelial tumor. SCCOHTs share both histological and genetic similarities to malignant rhabdoid tumors of the kidney, soft tissues and brain, which are tumors caused by mutations in *SMARCB1* (46). As such, SCCOHT has been proposed to be essentially a rhabdoid tumor of the ovary (47) and has now been included in rhabdoid tumour predisposition syndrome 2 (RTPS2, MIM: 603254; OMIM: 613325). Although the removal of the term “small cell” may circumvent confusion with neuroendocrine “small cell

carcinomas”, it is our opinion that changing the name to “rhabdoid tumor of the ovary” will still lead to confusion rather than clinical clarity, unless SCCOHT shares a unique and effective treatment with rhabdoid tumours.

3.2 Gynecologic cancers with SWI/SNF deficiency as an early event

3.2.1 *ARID1A* mutations in endometriosis-associated ovarian cancer—Clear cell ovarian carcinoma (CCOC) and endometrioid ovarian carcinoma (ENOC) are strongly associated with endometriosis (48), a common complication affecting 10% of women with functional endometrial tissue outside the endometrial cavity of the uterus that likely arises from retrograde menstruation (49). ENOC represents about ~10% of ovarian carcinomas, while CCOC represents 5–12% ovarian carcinomas with a higher frequency in some Asian countries (50–53). CCOC tends to be diagnosed at a younger age and an earlier stage than the more common high-grade serous ovarian cancer (HGSOC), but, unlike the majority of other ovarian cancer subtypes, CCOC is inherently resistant to standard platinum/taxane chemotherapy (54). In the absence of an alternative, however, platinum/taxane-based chemotherapy is still the standard of care for this disease.

Although both CCOC and ENOC arise from ovarian endometriotic cysts, these two cancers are quite distinct. ENOC is composed of columnar cells with eosinophilic cytoplasm, glandular or solid architecture and is mostly estrogen receptor (ER) positive, while CCOC is composed of cuboidal cells with usually clear cytoplasm, tubulocystic/papillary architecture and is predominantly ER negative. Our genomic interrogation of these cancers revealed that though there are no specific mutations found exclusively in either subtype, there are some genomic features that differentiate these cancers, such as the APOBEC signature found in 26% of CCOC and microsatellite instability found in 28% of ENOC (55). Interestingly, CCOC and its atypical endometriosis precursor have histological and immunophenotypic similarities to the Arias-Stella reaction (56), a distinct and benign morphological change to the endometrium, induced by high levels of estrogen/progesterone from pregnancy or exogenous hormone use, that cytologically resembles a malignancy. It has also been observed that the Arias-Stella reaction and CCOCs have similar gene expression patterns (56).

Research from our group and others has shown that somatic mutations in the *ARID1A* gene, encoding an accessory subunit of the SWI/SNF chromatin remodeling complex, commonly occur in both CCOC and ENOC, resulting in complete loss of ARID1A protein expression in ~50% of CCOC and 30% of ENOC (57, 58). ARID1A protein can also be lost in the endometriotic cysts adjacent to ARID1A-deficient CCOC (59). Yamamoto and colleagues confirmed that ARID1A protein loss occurred frequently in precancerous lesions adjacent to ARID1A-deficient CCOC, including 86% (12/14) of the non-atypical endometriosis, 100% (14/14) of the atypical endometriosis, benign (3/3) and borderline (6/6) clear-cell adenofibroma components, but was absent in the 22 solitary endometriosis and 10 endometriosis distant from carcinomas (60). Another study from the same group further confirmed that ARID1A was also lost in endometriotic cysts adjacent to ARID1A-deficient ENOC (61). Furthermore, ARID1A loss has also been recently discovered in 8% (3/66) of histologically benign ovarian endometriotic cysts (62) and at low frequency in deep

infiltrating endometriosis (63, 64), which has nearly no risk of malignant transformation. Thus, although *ARID1A* inactivation occurs early during the transformation, it appears that ARID1A loss by itself is insufficient for malignant transformation. Moreover, ARID1A loss is significantly associated with genetic alterations that activate the PI3K/AKT signaling pathway in CCOC, such as PTEN loss and/or gain-of-function mutations of *PIK3CA* gene (60, 65, 66), suggesting a cooperative role of ARID1A inactivation and PI3K/AKT activation in malignant transformation of premalignant lesions.

3.2.2 *ARID1A* mutations in endometrial cancer—Endometrial cancer is the most common and second most lethal gynecological cancer. It is composed of endometrioid endometrial carcinoma (EEC), the most common subtype and an estrogen-dependent cancer type, and estrogen-independent subtypes including high grade serous endometrial carcinoma (HGSEC) and clear cell endometrial carcinoma (CCEC). The genomic landscapes of sporadic EECs and HGSECs have been elucidated by TCGA and ourselves, in which mutations of *ARID1A* occurs in about 30–50% of low grade EEC, 40–60% of high grade EEC and a much lower frequency in HGSEC and endometrial carcinosarcoma (67, 68). We further validated that ARID1A protein is lost in 29% (29/101) of low grade EEC, 39% (44/113) of high grade EEC, 18% (17/95) of HGSEC and 26% (6/23) of CCEC (69). Similarly, Guan *et al.* reported a comparable rate of ARID1A loss in 26% (15/58) of low-grade EEC, but not in any of 12 HGSEC or 5 carcinosarcoma (70). The mutation landscape of pure CCEC has been described by DeLair *et al.* recently (71). Mutation of *ARID1A* was observed in 22% (7/32) of CCEC along with protein loss (71), in agreement with an earlier report by Fadare *et al.* (72). Thus, *ARID1A* mutations occurs at differential frequencies in most common types of endometrial carcinomas, with a significant enrichment in EEC.

EEC is believed to arise from atypical hyperplasia (AH), which is sometimes referred to as endometrial intraepithelial neoplasia (EIN). Mao *et al.* analyzed ARID1A expression by IHC in 246 cases of benign endometrium, hyperplasia and endometrioid carcinoma at different stages of progression, of which ARID1A was intact in all 65 benign endometrial tissues, but was lost clonally in 16% (6/38) of EIN/AH and either completely or clonally in 25% (22/88) and 24% (21/88) of low grade EEC and 44% (24/55) and 9% (5/55) of high-grade EEC, respectively (73). This was supported by a study from Werner *et al.* that reported a similar frequency of ARID1A loss in EIN/AH, but not benign hyperplasia (74), suggesting that ARID1A loss is likely an important driver event for transition of EIN/AH into carcinoma. Accordingly, Yen *et al.* unveiled that the detection of complete or heterogeneous ARID1A loss by IHC from biopsy/curettage predicted EEC in subsequent hysterectomy in 94% (15/16) of patients but only 15% of patients with retained ARID1A developed EEC (75), thus supporting a predictive value of ARID1A loss in the diagnosis of sporadic cases of EEC. Furthermore, Mao *et al.* uncovered a significant increase of complete loss of ARID1A in the high grade component of 19 cases of high-grade EEC that contained concurrent low-grade carcinomas with 26% (5/19) of them showing progressive loss of ARID1A from retention or clonal loss in low grade components to complete loss in high-grade areas (73), arguing that ARID1A loss may also play an important role in the progression of EEC, which requires further validation.

Patients with Lynch syndrome, one of the most prevalent hereditary cancer predisposition syndromes arising from a germline mutation in one of the four microsatellite repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), have a 40–60% lifetime risk of developing ECs (76, 77). The value of ARID1A loss in predicting malignant transformation in Lynch Syndrome patients has been also studied. Using IHC, Niskakoshi *et al.* discovered that ARID1A loss occurs in ~60% (14/23) of Finland Lynch syndrome EEC and appears in about 20% of the AH preceding the development of EEC (78), suggesting that ARID1A loss may predict the risk of EC development in Lynch syndrome patients. However, Bosse *et al.* reported that ARID1A loss was only seen in 14% (5/36) of Netherland Lynch syndrome EEC (79). This discrepancy may be attributed to the size and origin of different Lynch syndrome kindreds that may carry distinct mutations of mismatch repair genes. For example, 79% (52/66) of the Finland cohort carriers harbor the *MLH1* germline mutation (78), whereas the Netherland cohort carriers have germline mutations of either mismatch repair gene with the frequency being undisclosed (79). Therefore, additional studies are required for validating the significance of ARID1A loss in predicting the likelihood of malignant transformation of the gynecological tract in Lynch syndrome patients with distinct germline mutations.

3.3 Gynecologic cancers with SWI/SNF deficiency as a progression event

Dedifferentiated endometrial carcinoma (DDEC) occurs when an undifferentiated carcinoma arises abruptly within a clonally related low-grade EEC, which is often a microsatellite instable (MSI) tumor as seen in both Lynch syndrome and in sporadic cancer (80–82). The undifferentiated component shows sheet-like proliferations of monomorphic round to polygonal-shaped cells lacking cellular cohesion and evidence of epithelial architecture (absence of glands, nests or trabeculae). Rhabdoid-like cells can be seen in 20% of cases (83). In about 40% of cases, the low-grade component is eclipsed likely due to an outgrowth of the undifferentiated component, and the tumor overall appears as a pure undifferentiated endometrial carcinoma (UDEC) (80, 84). The endometrioid components usually express ER, PR and PAX8, whereas the undifferentiated components are negative for ER and PAX8 and express stem cell markers, i.e. SOX2. DDEC/UDEC (referred to as DDEC only hereafter) occurs in women with a peak of age of diagnosis at 55 years. DDEC is clinically aggressive and most patients quickly succumb to their diseases even when the undifferentiated component appears as a minor fraction of the tumor (80, 82). Its clinical behavior is worse than FIGO grade 3 EEC, the entity which DDEC is most often confused with. Although DDEC is relatively rare, its actual incidence is largely undetermined due to its late recognition, as it was only described by Dr. Elvio Silva and colleagues at MD Anderson in 2006 (80). Through reviewing 633 cases of endometrial adenocarcinoma accessioned in the Department of Pathology at The University of Texas MD Anderson Cancer Center in a 2-year period (2003 and 2004), Silva *et al.* identified that DDEC represented ~9% of cases (84), suggesting that the incidence of DDEC may be underestimated due to misdiagnosis or under-recognition.

The genomic landscape of DDEC remains largely undetermined. Espinosa *et al.* recently analyzed the immunophenotypic features and mutational status of a small panel of genes of 21 DDEC and described that DDEC with *POLE* exonuclease domain mutations are more often stage I diseases (7/9; 78% vs. 3/12; 25%; $p=0.023$) with favorable disease specific

survival over DDEC without *POLE* mutations (85). This finding has yet to be validated in larger series of DDEC. We and others have discovered three types of inactivating mutations occurring in subunits of the SWI/SNF complex in DDEC (86–89). These include inactivating mutations in *SMARCA4* resulting in loss of SMARCA4 protein in 30–40% of DDEC, inactivation of *SMARCB1* resulting in loss of SMARCB1 protein in 2–7% of DDEC, or co-inactivation of *ARID1A* and *ARID1B* resulting in concurrent loss of ARID1A and ARID1B proteins in 28% of DDEC (83, 86, 90–92). Loss of SMARCA4 or SMARCB1 is restricted to the undifferentiated component of DDECs. In such cases about half also exhibit loss of ARID1A expression in both components (90, 91). While loss of ARID1B is also restricted to the undifferentiated component of DDECs, it occurs concordantly with ARID1A loss that usually occurs in both low-grade and undifferentiated components (90, 91). Furthermore, mutational loss of *SMARCA4*, *SMARCB1* or *ARID1A/ARID1B* is often associated with loss of the expression of SMARCA2 protein, the alternative ATPase of the SWI/SNF complex, through non-genetic mechanisms (83, 90, 91). Such SWI/SNF mutations are also implicated in undifferentiated carcinomas of ovary (87), urinary tract (93), gastrointestinal tract (94) and kidney (95), suggesting that the SWI/SNF deficiency acquired during tumor progression may be a widespread mechanism that promotes cancer dedifferentiation. Furthermore, no apparent histologic differences have been observed between ARID1A/ARID1B co-inactivated tumours and SMARCA4 or SMARCB1-inactivated tumours, as the inactivation of these SWI/SNF proteins both coincided with an undifferentiated histology (87). However, ARID1A/ARID1B-dual deficient DDEC has intact PBAF and GBAF complexes and SMARCB1-deficient DDEC has functional GBAF complex, whereas SMARCA4-deficient DDEC likely loses the ATPase activity of all SWI/SNF complexes completely. Thus, it remains possible that DDEC driven by these distinct modes of mutations in the SWI/SNF complexes may result in abrogation of cell lineage determination differentially. Future digital histology analysis using advanced technologies, such as artificial intelligence, may help identify subtle difference among these cancers. Lastly, it has been showed that there is a greater propensity for MMR protein-deficient endometrioid carcinomas to give rise to either ARID1A/ARID1B co-deficient or SMARCA4 or SMARCB1 deficient DDEC with nearly 75% of them being MMR protein deficient (87, 91). Given the reported reliance of ARID1A-deficient cells on the presence of ARID1B (96), we speculated that a MSI tumor background may facilitate the acquisition of additional molecular aberrations required for the successful emergence of an ARID1A/ARID1B-dual deficient sub-clone.

The phenomenon of dedifferentiation has yet to be described in the context of CCEC or CCOC. Further studies are needed to determine why this phenomenon, either does not occur or alternatively, is lethal to CCEC and CCOC cells.

3.4 Gynecologic cancers with SWI/SNF deficiency NOT MAPPED TO DISEASE PROGRESSION

3.4.1 SMARCA4 mutations in undifferentiated uterine sarcoma—

Undifferentiated uterine sarcoma is a diagnosis of exclusion with limited molecular genetic data available. Recently, Kolin *et al.* discovered *SMARCA4* mutations and/or protein loss in 5 cases of undifferentiated uterine sarcoma with a median age of diagnosis of 33 years old

(97), close to that of SCCOHT. These tumors were composed of sheets of large atypical epithelioid cells with prominent rhabdoid morphology, indistinguishable from the large cell variant of SCCOHT. They were uniformly aggressive and all patients died of disease with a median survival of 7 months (range 1–43 months). Given that these tumors share similar age of diagnosis and histological and molecular features with SCCOHT, Kolin *et al.* suggested to name these tumors as a new identity, SMARCA4-deficient undifferentiated uterine sarcoma or malignant rhabdoid tumor of the uterus (97). Aside from age, SMARCA4-deficient uterine stromal tumours, which occur in younger women, is incredibly challenging to distinguish from SMARCA4-deficient DDEC with no identifiable low-grade components, which occur in older women. The SMARCA4-deficient undifferentiated uterine sarcoma did not express claudin-4, which is noted as an epithelial differentiation marker that distinguishes tumors of carcinoma origin from sarcoma in SWI/SNF-deficient malignancies (45). Kolin *et al.* suggest that claudin-4 expression can be a useful feature for the differential diagnosis. However, a recent study by Tessier-Cloutier *et al.* discovered that the undifferentiated components of DDEC always lost the expression of claudin-4, arguing that claudin-4 cannot be used to infer mesenchymal or epithelial tumour origin in the endometrium (98). Furthermore, all three SMARCA4-deficient undifferentiated uterine sarcomas with known MMR protein status were MSS tumors (97), whereas a majority of SMARCA4-deficient DDEC is MSI tumors (91). Whether the SMARCA4-deficient uterine stromal sarcoma has a stable genome requires further study. Therefore, a large number of cases are required to fully characterize the clinicopathologic, immunophenotypic and genomic features of this entity and understand the role of SMARCA4 loss in the development of the SMARCA4-deficient uterine stromal sarcoma.

3.4.2 *SMARCB1* mutations in epithelioid sarcoma and myoepithelioma-like tumors of vulvar—Epithelioid sarcoma and myoepithelial carcinoma are very rare malignancies in the vulvar region. Recently, Folpe *et al.* studied the clinicopathologic, IHC, and molecular genetic features of 14 *SMARCB1*-deficient vulvar neoplasms and uncovered that the proximal-type epithelioid sarcoma was the predominant subtype with *SMARCB1* deficiency, followed by myoepithelial carcinoma (99). The mean age of diagnosis was 46 years, with a range of 22 to 62 years. Follow up data of 13 patients (4–72 months, mean 31 months) indicated 3 patients died of disease, 1 was alive with unresectable metastatic disease, 1 was alive with radiographic evidence of extensive lymph nodal disease, and 8 were alive without disease (99). *SMARCB1* deficiency in myoepithelial carcinoma was further supported by a study from Yoshida *et al.*, in which such tumors, referred to as myoepithelioma-like tumors of the vulvar region, were diagnosed at a median age of 41 years (range 24–65 years) (100). Tumor cells of the myoepithelioma-like tumors of the vulvar region were well circumscribed, focally encapsulated, and lobulated and follow up data demonstrated that all 9 patients were alive without metastases at a mean follow-up of 66 months (100). Despite this, future study of a large number of cases are required to fully characterize the clinicopathologic, immunophenotypic and genomic features of these two entities and address whether *SMARCB1* inactivation is the only recurrent driver event, as seen in epithelioid sarcomas at other anatomic sites.

4. PROGNOSTIC AND CLINICOPATHOLOGICAL SIGNIFICANCE OF SWI/SNF MUTATIONS IN GYNECOLOGIC CANCERS

4.1 Does ARID1A loss have prognostic value in endometrial carcinoma or endometriosis-associated ovarian cancer?

As ARID1A inactivation appears in a portion of endometriosis-associated ovarian cancer and endometrial cancer, it has been of great interest to investigate the prognostic value of ARID1A loss. We have initially analyzed ARID1A expression in 132 CCOC and 125 ENOC by IHC and did not identify any correlation between ARID1A loss and patient age, disease stage and disease-specific survival in either cancer type (59). Accordingly, Maeda, Yamamoto, Lowery and their colleagues independently analyzed the expression of ARID1A by IHC in 149 CCOC, 90 CCOC and 82 CCOC/130 ENOC, respectively, and did not identify significant difference between ARID1A expression status and histopathologic features, i.e. age, clinical stage, tumor grade or overall survival (101–103). Supporting this, analysis of transcriptomic profiles from the ARID1A wild-type and mutant CCOC failed to identify a canonical signaling process that was distinct between wild-type and ARID1A mutant tumors (104). In contrast, Katagiri *et al.* found that loss of ARID1A was significantly correlated with advanced FIGO stage and high CA125 levels and a shorter progression-free survival in 60 patients of CCOC that received platinum-based chemotherapy (105). However, only 15% (9/60) of CCOC in the Katagiri study was deficient in ARID1A expression, raising the possibility that some cases in that study cohort may be misdiagnosed. Interestingly, Itamochi *et al.* examined the expression of ARID1A by IHC in 112 CCOC and discovered that although ARID1A loss was not correlated with patient age, FIGO stage, and status of residual tumor, it correlated with a lower 5-year overall survival rate in stage I/II CCOC (74% vs 91%) (106). This observation argues that loss of ARID1A protein expression may have some prognostic value among CCOC patients with early stage of the disease. Liu *et al.* have recently performed a meta-analysis on more than 600 CCOC from 7 studies, mostly patients from Japan and China, and concluded that ARID1A loss correlated with a shorter progression-free survival (HR, 1.97; 95% CI, 1.37–2.83, $P=0.000$), but not overall survival (107). In order to validate these findings in independent cohorts, most recently, our group has studied 1,024 ENOC and 595 ENOC from the Ovarian Tumor Tissue Analysis (OTTA) consortium and The Canadian Ovarian Experimental Unified Resource (COEUR). In this large study, we found no evidence that the ARID1A expression status is prognostically significant in either CCOC or ENOC (108).

The prognostic value of ARID1A loss in endometrial cancer has also been analyzed by several groups. Werner *et al.* analyzed a collection of 535 primary endometrial cancers as well as 77 metastatic endometrial cancers and documented a significant correlation between ARID1A loss and younger patient age and deeper myometrial infiltration, but not survival (74). Zhang *et al.* also failed to detect any association between ARID1A loss and clinical stage, the depth of myometrial invasion, lymph node metastasis or overall survival of patients with endometrial carcinoma (109). In contrast, Heckl *et al.* determined the expression of ARID1A in 59 EEC by IHC and reported a significant association between ARID1A loss and a worse 5-year survival (110). However, this EEC cohort had an unusual high rate of ARID1A loss (90%, 53/59) (110), arguing that whether such observation was a

consequence of unusual collection of EEC patients. Interestingly, using the data from the molecularly defined endometrial carcinoma cohort from TCGA, Shen *et al.* demonstrated that ARID1A mutations correlated with a better outcome in endometrial carcinoma (111). As MSI endometrial cancer displayed better prognosis than MSS endometrial cancer (111), Shen *et al.* further investigated whether such correlation reflects the enrichment of ARID1A mutations in MSI tumor. It was unveiled that ARID1A mutation status was not significantly associated with survival in patients with MSI tumors, but was associated with a better prognosis in patients with MSS tumors, implying that ARID1A mutation status may predict patient outcome in MSS endometrial cancer (111). Furthermore, Fadare *et al.* investigated 22 CCEC and found that ARID1A loss occurred restrictively in stage III and IV CCEC and was associated with worsen outcome (72). However, the sample volume of the Fadare study was small, highlighting a need for further investigation.

4.2 Prognostic values of SWI/SNF deficiency in DDEC

Although DDEC displayed a worse outcome than grade 3 endometrial cancer, our initial comparison between 15 DDEC with intact SMARCA4/SMARCB1 and 15 DDEC with loss of SMARCA4 or SMARCB1 did not identify significant differences in disease-specific survival (91). This may be due to the presence of ARID1A/ARID1B dual deficient cases in the SMARCA4/SMARCB1 intact category. Subsequently, we found that DDEC patients with any of the three types of SWI/SNF deficiency had worse outcome than those with intact SMARCA4, SMARCB1 or ARID1B (87). Both SMARCA4 or SMARCB1-deficient DDEC and ARID1A/ARID1B-dual deficient DDEC exhibited similar aggressive clinical behavior as >50% of the patients in both groups died of their disease within 2 years of initial diagnosis (87). In another study that only examined DDEC with no identifiable low-grade components, Kobel *et al.* confirmed that patients with any of the three types of SWI/SNF deficiency had much worse 1-year disease specific survival (26%) than those with intact SMARCA4, SMARCB1 or ARID1B (75%) (88). Therefore, clinically, the SWI/SNF complex deficiency defines a highly aggressive subset of DDEC.

5. UNDERSTANDING THE PATHOGENIC ROLES OF SWI/SNF MUTATIONS IN GYNECOLOGIC CANCER USING *IN VITRO* MODELS

5.1 Role of SMARCA4 loss in SCCOHT development

Despite the rarity of this cancer, there are three cell line models available for studying SCCOHT molecular pathogenesis. BIN67 cells were derived from a metastatic pelvic nodule of a primary SCCOHT (112). SCCOHT-1 cells were established from a recurrent chemotherapy-naïve SCCOHT (113). COV434 was established from a primary tumor that was initially diagnosed as granulosa cell tumor (114) and later re-classified as SCCOHT due to the absence of SMARCA4/SMARCA2 and through re-examining the original tumor material (Karnezis et al., in preparation). Re-expression of either SMARCA4 or SMARCA2 dramatically suppressed the growth of all three cell lines (41, 115), supporting the tumor suppressive role of the SWI/SNF complexes in the development of SCCOHT. In order to understand the oncogenic pathways that sustain the proliferation of SMARCA4-deficient SCCOHT cells, we and others have performed genetic screens and identified key oncogenic

features of SCCOHT. In agreement with the notion that the SWI/SNF complexes function antagonistically with the polycomb repressive complex 2 (PRC2) (116, 117), the master regulator depositing repressive histone marker H3K27Me₃, we discovered that SMARCA4 loss in SCCOHT leads to increased expression of EZH2, the catalytic subunit of PRC2 (118), resulting in a dependency of SCCOHT cells to the enzymatic activity of PRC2 and its companion histone deacetylases (HDACs) for maintaining their survival (115, 118, 119). Lang *et al.* performed a drugable genome siRNA in BIN67 cells and uncovered receptor tyrosine kinase (RTK) signaling as the top supportive oncogenic pathways in SCCOHT, including FGFRs, PDGFRs, and EGFRs alongside the AKT and MAPK signaling cascades downstream of these RTKs (120). These findings suggest that SMARCA4 loss mediates malignant transformation of precursor cells in part through PRC2-dependent epigenetic rewiring and activation of RTKs. Furthermore, although the cell origin of SCCOHT remains to be determined, extensive sectioning of two SMARCA4-deficient SCCOHT primary tumors identified minor foci of immature teratoma and/or yolk sac tumor that displayed the reduced protein expression of SMARCA4 in comparison to stromal cells (38). Restoring the expression of SMARCA4 triggered neuronal-like differentiation of SCCOHT cell lines (41, 115). Therefore, it is plausible to speculate that some SCCOHT may arise from the neuroepithelium of immature teratoma and/or from adult mesenchymal progenitor cells of the ovary, which hold the potential of differentiation into multiple lineages including neurons (121, 122), where complete inactivation of SMARCA4 may pause the differentiation of these putative precursor and drive their malignant transformation (Figure 3). Alternatively, as terminally differentiated neurons can undergo dedifferentiation upon activation of oncogenes (123), it is possible that SMARCA4 loss may unleash the suppression of genes essential for maintaining cell stemness (i.e. *EZH2*), thereby initiating the dedifferentiation and malignant transformation of sympathetic neurons in the ovary. However, because SMARCA4 is required for the maintenance of adult neural stem/progenitor cells and is only rarely mutated in brain cancers, such as atypical teratoid rhabdoid tumors (ATRT), the unique microenvironment of the ovary may be crucial for sustaining the viability of SMARCA4-deficient mesenchymal progenitor cells, neuronal cells or neural progenitor cells and foster their transformation.

5.2 Role of ARID1A loss in endometriosis-associated ovarian cancer and endometrial cancer

In order to understand the role of ARID1A loss in the development of gynecologic cancers, Guan *et al.* re-expressed ARID1A in OVISe, an ARID1A-null CCOC cell line, and demonstrated that restoring the expression of wild-type ARID1A, but not mutant ARID1A with naturally occurred in-frame indels, suppressed cell proliferation, in part through upregulating the expression of p21, and inhibited the growth of OVISe-xenografted tumors in mice (124, 125). Another study from the same group further described that ARID1A loss reversed the suppression of hTERT in endometrial epithelium cells and confers a survival advantage of tumor cells by maintaining their telomeres (126). Furthermore, Bilter *et al.* discovered that re-expression of ARID1A in OVISe cells reactivated the expression of PIK3IP1, a known negative regulator of the PI3K-Akt pathway, by recruiting the SWI/SNF complex (127). Although it was shown that the induction of PIK3IP1 was crucial for apoptosis of OVISe cells induced by GSK126 (127), an EZH2 inhibitor, it remains

undetermined whether suppression of PIK3IP1 is required for the proliferation of ARID1A-deficient CCOC cells. Utilizing a drug screen combined with target identification in a panel of CCOC cell lines with intact or no ARID1A expression, Miller *et al.* discovered that loss of ARID1A expression in CCOC created a dependency on YES1, a SRC tyrosine kinase that is involved in cell proliferation, migration and invasion (104). Lakshminarasimhan *et al.* knocked down ARID1A expression in an immortalized endometriosis cell line and identified altered expression of genes enriched in the integrin signaling and the paxillin pathways (128). Furthermore, Goldman *et al.* performed proteome analyses of an isogenic CCOC cell pair (OVCA429) with or without ARID1A expression and uncovered that ARID1A depletion impacted only 5% of the detected proteome with a significant enrichment in proteins of the mevalonate pathway, an important metabolic pathway involved in isoprenoid synthesis, cholesterol synthesis, and other downstream pathways (129). Mechanistically, it has been demonstrated that down-regulation of ARID1A in an immortalized endometriosis cell line did not markedly alter global chromatin accessibility or DNA methylation, but increased the active H3K27ac mark in promoter regions and decreased the H3K27ac at potential enhancers, suggesting a role of ARID1A loss in impacting the distribution of H3K27ac histone marks (128). In agreement with this observation, depletion of *ARID1A* displayed a dominant role in limiting chromatin accessibility at enhancers in HCT116 colon cancer cell line (130). Therefore, although the significance of these findings warrants further investigation, these studies suggest that ARID1A loss may reactivate hTERT activity, unleash cell cycle control and alter cell metabolism and cell-to-cell communication in their precursor cells through reducing the chromatin accessibility in their enhancer regions to allow malignant transformation.

Furthermore, to address whether ARID1A loss is sufficient for transformation of precursor cells, Guan *et al.* depleted ARID1A in non-transformed human ovarian surface epithelial cells using shRNAs and observed increased cellular proliferation and tumorigenicity, suggesting that ARID1A loss alone is sufficient for transformation of human ovarian surface epithelial cells (124). However, a subsequent study from the same group demonstrated that ARID1A loss alone was insufficient for transformation of mouse ovarian surface epithelium (131). Accordingly, simultaneous ARID1A depletion and PIK3CA activation or PTEN loss are required for transformation of both human and mice ovarian epithelial surface (131–133). Nevertheless, as both CCOC and ENOC are believed to have an endometrial cell origin, these studies did not address whether ARID1A loss is sufficient for transformation of endometrial cells. Recently, Lakshminarasimhan *et al.* knocked down ARID1A expression in an immortalized endometriosis cell line and observed signs of neoplastic transformation, such as higher efficiency of anchorage-independent growth, increased adhesion to collagen and increased invasion to basement membrane extract, leading the authors to conclude that ARID1A loss alone is sufficient for transformation of endometrial cells in endometriosis (128). However, the genomic background of this immortalized endometriosis cell line was not determined. Given the strong association of ARID1A loss and PIK3CA or PTEN mutations in endometriosis-associated ovarian cancer, it is plausible that such mutations may be present in this endometriosis cell line.

As no specific mutations have been found exclusively in either ENOC or CCOC, how a common premalignant lesion develop into two histologically distinct entities remains

unclear. Through proteomic analysis of epithelial carcinoma followed by IHC validation we have recently uncovered that ENOC shares many immunophenotypic features with secretory cells of normal endometrial epithelium, i.e. ER, whereas CCOC expresses some markers of ciliated cells of endometrial epithelium, i.e. cystathionine gamma-lyase (CTH) and EZRIN (134, 135). Since within the normal uterine environment, endometrial epithelial progenitor cells undergo terminal differentiation with a preference towards secretory cells, it is speculated that the local ovarian microenvironment of each patient, which holds distinct differentiation pressure, may determine the differentiation of ARID1A-deficient biopotential premalignant progenitor cells of endometriotic cysts and together with accumulated additional mutations or epigenetic changes to drive their malignant transformation towards either ENOC or CCOC, respectively (Figure 4). Thus, it will be crucial to identify such factors that alter the differentiation of biopotential endometrial progenitor cells. It will be also very interesting to determine whether introduction of mutations of *ARID1A* and *PIK3CA* simultaneously will drive malignant transformation of endometrial progenitor cells that have committed to differentiation into either secretory or ciliated cells.

5.3 Role of SWI/SNF mutations in DDEC

Although a worse outcome has been associated with SWI/SNF defects in DDEC, which establishes an unmet need for expanded understanding of DDEC biology and treatment paradigms, neither cell line nor genetic models of DDEC has been reported. Recently, we and others have demonstrated that TOV112D and OVK18, two ENOC cell lines, are likely DDEC cell lines derived from dedifferentiated carcinomas of the ovary based on their lack of expression of both SMARCA4 and SMARCA2 and histological reevaluation of original tumor material (119) (Karnezis *et al.*, manuscript in preparation). We and others have proven that both OVK18 and TOV112D cells behaved similarly to SCCOHT cells in their response to re-expression of SMARCA4 or EZH2 inhibitor treatment (115, 119), suggesting that SMARCA4/SMARCA2-dual deficient DDEC cells may largely resemble SCCOHT cells. As ARID1A/ARID1B-dual deficient DDEC has intact PBAF and GBAF complexes and SMARCB1-deficient DDEC has functional GBAF complex, whereas SMARCA4-deficient DDEC loses ATPase activity of all SWI/SNF complexes completely (Figure 5), it is plausible to propose that inactivation of the BAF complexes is sufficient to stall the differentiation of cancer initiating cells and drive histological dedifferentiation. Future development of DDEC cell lines and in vivo models, particularly the ARID1A/ARID1B-dual deficient models, will be essential for understanding the molecular pathogenesis of the disease.

6. Genetically engineered mouse models of SWI/SNF mutations in gynecologic cancers

GEMMs offer the opportunity to investigate the contribution of genetic mutations to cancer aetiology and to test novel therapeutics in immunocompetent organisms. Therefore, there has been great interests in developing SWI/SNF GEMMs of various human cancer types. Efforts from several teams have attempted to determine whether inactivation of *ARID1A* is sufficient to drive the development of ovarian cancer and whether co-existing mutations are required to synergize with ARID1A loss to promote tumorigenesis. Guan *et al.* reported that

adenoviral-mediated co-depletion of *Pten* and *Arid1a* in ovarian surface epithelium of the *Pten^{fl/fl};Arid1a^{fl/fl}* mice induces ovarian hyperplasia as early as 2 months after genetic depletion, which drives the development of undifferentiated or endometrioid carcinoma of the ovary in 6/13 mice examined at 6 months and 7/9 mice at 8–9 months (131). Noteworthy, inactivation of one or both alleles of *Arid1a* in ovarian surface epithelium prolonged the survival of tumor-bearing *Apc/Pten*-deficient mice and promoted cancer cell differentiation to more closely resemble the histology of human ovarian endometrioid cancer (136). Chandler *et al.* found that inactivation of *Arid1a* and expression of *Pik3ca* H1047R activating mutation in ovarian surface epithelium of the *Arid1a^{fl/fl}; (Gt)Rosa26Pik3ca*H1047R* mice rapidly develop primary ovarian tumor with a 7.5 week latency and clear cell carcinoma-like histopathology (11). In contrast, mice with deletion of *Pten* or *Arid1a* or activation of *Pik3ca.H1047R* alone did not develop ovarian lesions except that activation of *Pik3ca.H1047R* led to development of hyperplasia in ovarian surface epithelium. These studies support that ARID1A loss plays a critical role in driving the development of ovarian endometrioid and clear cell carcinoma. However, these models do not faithfully recapitulate the pathogenesis of ARID1A-deficient ovarian cancers in human patients.

Both ENOC and CCOC are highly associated with endometriosis (48). Recent genomic studies have demonstrated clonal relationships between these ovarian tumour types and the adjacent endometriosis (137, 138). In agreement with the robust protective effect of bilateral tubal ligation against endometriosis-associated cancer, these observations suggest that both ENOC and likely arise from endometrial cell lineages during endometriosis. Therefore, faithful GEMMs should be developed in the future to reflect the pathogenesis of these diseases. As *ARID1A* is also frequently mutated in endometrial carcinomas, inactivation of *Arid1a*, alone or in combination with genetic mutations of other genes (such as *Pten*, *Pik3ca*), in specific mouse cre strains in which the cre expression is driven by endometrial tissue specific promoters (i.e. *Pax8-cre*, *Ksp-cre*, etc.) will likely lead to the development of endometrial cancer that resembles human endometrial carcinoma with ARID1A loss. Injection of the untransformed menstrual endometrial tissues into the peritoneum of syngeneic recipient immunocompetent mice, which mimics human endometriosis (139), will likely drive the development of ovarian cancers that resembles ENOC or CCOC. These putative tissue-specific GEMMs will open the opportunity for better understanding how inactivation of ARID1A interacts with other genetic mutations as well as ovarian microenvironment to drive transformation of precursor cells through comparison of the gene expression profiles and epigenetic states of tumor cells to those of the precursor cells that can be identified by lineage tracking markers.

Although *SMARCA4* inactivation appears as the only driver event in SCCOHT, no SCCOHT GEMM has been developed so far. This is mainly due to the unknown origin of SCCOHT. Serber *et al.* reported that inactivation of *Smarca4* using a *Wap-cre* line, which activates cre expression in granulosa cells of mouse ovary and multiple lineages of mouse uterus, led to frequent development of ovarian cyst and a low incidence of endometrial cancer (140). The tumor incidence was not altered when *Smarca2* is simultaneously silenced (140). Therefore, inactivation of *Smarca4* cannot drive the transformation of ovarian granulosa cells, but has the ability to transform unknown lineage in uterus. The histology of

endometrial tumors developed in *Wap-cre:Smarca4^{fl/fl}* GEMM mice was not determined by Serber *et al.* However, as SMARCA4 loss can arise in undifferentiated endometrial stromal tumors, these tumors may resemble the undifferentiated endometrial stromal tumors. Therefore, specific and effective targeting *Smarca4* in the stromal lineages of uterus may provide a valuable GEMM of the undifferentiated endometrial stromal tumors. Furthermore, additional inactivation of *Smarca4* or the BAF complex through dual inactivation of *Arid1a/Arid1b* will likely promote the development of undifferentiated cancer resembling human DDEC in GEMMs of well differentiated endometrial cancer, such as *Pgr-Cre:Pten^{fl/fl}* GEMM mice (141). These models will offer great opportunities for better understanding the context-specific tumor suppressive roles of distinct SWI/SNF mutations in gynecologic cancers.

7. THERAPEUTIC IMPLICATIONS

Although SWI/SNF gene mutations occur in nearly 20% of all human cancers, most SWI/SNF gene mutations are loss of function mutations, including nonsense, frameshift and large deletions, that lead to concurrent loss of their protein expression. Therefore, these gene mutations are not targetable. Consequently, many efforts have been invested to identify synthetic lethal targets that are conferred by these SWI/SNF mutations on cancer cells, which has been summarized in details in several reviews (142–144). These putative therapeutic targets include two key hall markers of human cancer: sustained proliferative pathways, i.e. the PI3K/AKT/mTOR pathway and the YES1 SRC tyrosine kinase pathway in ARID1A-deficient CCOC (104, 132, 145, 146) or CDK4/6 and receptor tyrosine kinases in SCCOHT, and metabolic alterations, i.e. the glutathione biogenesis pathway in ARID1A-deficient CCOC (147, 148). Furthermore, as a consequence of loss of specific SWI/SNF subunit, tumor cells have adapted and evolved to rely on the residual complex and/or rewired epigenetic programming. Therefore, the residual complex member and certain epigenetic modifiers are attractive targets for therapeutic development of these cancers. For example, ARID1B has been reported to be a vulnerable target in ARID1A-deficient CCOC (96) and targeting epigenetic modifiers, such as EZH2, HDAC and BRD4 are feasible in SCCOHT (115, 118, 119, 149). Furthermore, ongoing clinical trials of EZH2 inhibitors, i.e. tazemetostat, for both SMARCB1-deficient epithelioid sarcoma and SCCOHT will demonstrate whether they can be utilized clinically in near future for clinical management of these diseases. Moreover, despite that SCCOHT has very low mutation burden, Jelinic *et al.* discovered that 8/11 SCCOHT expressed PD-L1 associated with strong T-cell infiltration and four SCCOHT patients responded to anti-PD1 immunotherapy (150). Although this study involved only a small number of cases and warrants validation, it provides a strong rationale for evaluation of immune checkpoint blockades in SCCOHT patients and potentially other SWI/SNF-deficient tumors with low mutation burden, such as the ARID1A-deficient CCOC and possibly SMARCA4-deficient uterine stromal sarcoma. The implication of PD1 blockade in CCOC is supported by a recent preclinical study using an ARID1A-depleted ID8 mouse ovarian cancer cell tumor model by Shen and colleagues (111). However, since the origin of this ARID1A-depleted mouse tumor model does not reflect the origin of CCOC, whether ARID1A-deficient CCOC will respond to immunotherapy requires further investigation.

8. CONCLUSIONS/PERSPECTIVES

Mutations of several SWI/SNF subunits have been discovered in multiple gynecologic cancers. The frequency and inactivating nature of these mutations supports that the SWI/SNF complexes are *bona fide* tumor suppressors in gynecologic tissues, which also define unique vulnerabilities that warrants further clinical investigations. These SWI/SNF mutations may function as either the sole driver event (SCCOHT), a malignant transformation-permitting early event (CCOC/ENOC/EEC) or a late progression event (DDEC) in distinct gynecologic cancers. Whether SMARCA4 loss or SMARCB1 loss functions as sole driver or early driver event of undifferentiated uterine sarcoma or vulvar cancers remains to be further studied. The SWI/SNF mutations appears to have a value in predicting the worse outcome of DDEC patients even though a large number of cases are required to validate its clinical utility. In contrast, there is unlikely a prognostic value for ARID1A loss in ENOC and CCOC, although it may hold a prognostic value in MSS endometrial cancers. Furthermore, the pathogenic roles of the SWI/SNF mutations are far beyond being fully understood in gynecologic cancers. The fact that specific subunits are mutated in specific gynecologic malignancies implies that the SWI/SNF complexes function in context-specific manners. Particularly, since ARID1A loss occurs predominantly in endometrial cancers and endometriosis-associated ovarian cancers, we believe that ARID1A loss promotes oncogenesis only in a permissive tissue and cell context, which is unlikely to be the ovarian surface epithelium or fallopian tube epithelium. Thus, the results from studies using the HGSOC cell lines or ovarian surface epithelium cells or tissues to determine the impact of ARID1A depletion on cellular processes should be cautiously interpreted. The development of *in vitro* and *in vivo* models that appropriately reflect the endometrial cell origin of these tumors will be essential to address the role of ARID1A loss in endometriosis-associated ovarian cancer. In addition, as ARID1A loss occurs as a gate event that permits the malignant transformation of pre-malignant endometrial cells in AH, the role of ARID1A loss should also be investigated on an appropriated genetic background. The understanding of SWI/SNF complex mutations and their cellular interactions will be pivotal to developing novel treatment strategies for these gynecologic malignancies, particularly those which portend poor prognoses and often only have conventional platinum-based chemotherapy as a therapeutic option.

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		BAF	PBAF	GBAF
ATPase cap	ATPase	SMARCA4/A2*	SMARCA4/A2*	SMARCA4/A2*
	others	ACTIN, ACTL6A, SS18 BCL7A/B/C*	ACTIN, ACTL6A, PBRM1 BCL7A/B/C*	ACTIN, ACTL6A, SS18 BCL7A/B/C*
Core subunits		SMARCC1/2* SMARCD1/2/3* SMARCE1, SMARCB1	SMARCC1/2* SMARCD1/2/3* SMARCE1, SMARCB1	SMARCC1/2*, SMARCD1/2/3*, GLTSCR1/1L*
		ARID1A/1B* DPF1/2/3*	ARID2, BRD7, PHF10	BRD9

Note: * mutually exclusive

Figure 1. Scheme of three classes of SWI/SNF complex.
For each class, there are distinct SWI/SNF complexes containing unique combination of mutually exclusive subunits of several components.

Figure 2. SWI/SNF mutations and protein loss in gynecologic cancers.

Specific mutations of the SWI/SNF complex were indicated for each gynecologic cancer described. Representative H&E and IHC staining of relevant SWI/SNF subunits were shown.

Figure 3. A hypothetical model of SCCOHT development.

SCCOHT may arise from progenitor cells of the ovary that hold the potential to undergo differentiation into neuronal lineages, in which SMARCA4 inactivation causes hyperactivation of polycomb repressive complex 2 (PRC2), reduces chromosomal accessibility of the promoters and/or enhancers of genes that promote differentiation, and drive the development of poorly differentiated cancer. Alternatively, SMARCA4 loss in sympathetic neurons of the ovary may alter the chromosomal structure, unleash the suppression of genes required for maintaining cell stemness (i.e. *EZH2*) and thereby drive cellular dedifferentiation and malignant transformation.

SCCOHT is characterized by SMARCA4/A2 dual deficiency

SCCOHT expresses abundant *EZH2* and neuroepithelium markers

SMARCA4 re-expression leads to growth suppression and differentiation into neuron-like cells

SMARCA4 re-expression increased chromatin accessibility and H3K27Ac at active promoter/enhancer regions

SCCOHT cells depend on the catalytic activity of PRC2 complex; *EZH2* inhibitors and HDAC inhibitors displayed robust pre-clinical activity in SCCOHT; combination of two inhibitors have great synergistic effects

SMARCA4 is genetic inactivated and SMARCA2 is epigenetically silenced in SCCOHT
The neuroepithelium in immature teratoma is a putative cell of origin of SCCOHT development

Re-expression of SMARCA4 increases the accessibility of nucleosome and promotes differentiation

EZH2 and HDAC inhibitors suppress the growth of SCCOHT cells in vitro and in vivo

Figure 4. A hypothetical model of ENOC and CCOC development.

Endometrial epithelial progenitor cells can differentiate into ciliated cells or secretory cells in normal endometrium or typical endometriosis. The local ovarian microenvironment of each patient, which holds distinct differentiation pressure, may determine the differentiation of ARID1A-deficient biopotential premalignant progenitor cells of endometriotic cysts and together with accumulated additional mutations to drive their malignant transformation towards either ENOC or CCOC. Such CCOC development pressure may include exposure to excessive hormones.

Figure 5. A hypothetical model of the development of the dedifferentiated carcinoma of endometrium and ovary.

Accumulation of genetic alternations, including ARID1A inactivating mutations, in endometrial epithelial progenitor cells drive their malignant transformation and development of either endometrioid or clear cell carcinoma. Subsequent loss of additional SWI/SNF components, such as ARID1B (in the presence of ARID1A loss), SMARCA4 or SMARCB1 in endometrioid carcinoma, but not clear cell carcinoma, leads to complete inactivation of SWI/SNF complexes and development of dedifferentiated carcinoma, possibly through stalling the differentiation of cancer initiating cells.