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Review Articles

SMARCA4 and SMARCA2 co-deficiency: An uncommon molecular signature defining a subset of rare, aggressive and undifferentiated malignancies associated with defective chromatin remodeling

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ABSTRACT

Genetic mutations and epigenetic modifications affecting multiple cancer-related genes occur synergistically to drive tumorigenesis. Across a wide spectrum of cancers, pathogenic changes have been identified in members of the SWItch/Sucrose Non-Fermentable complex including its two catalytic subunits, SMARCA4 and SMARCA2. During cancer development, it is not uncommon to lose the function of either SMARCA4 or SMARCA2, however, loss of both together has been reported to be synthetic lethal and therefore unexpected. Co-deficiency of SMARCA4 and SMARCA2 occurs as a pathognomonic feature of the early-onset ovarian cancer Small-cell carcinoma of the ovary, hypercalcemic type. The loss of both catalytic subunits is also described in other rare undifferentiated neoplasms including Thoracic *SMARCA4*-deficient undifferentiated tumors, Malignant rhabdoid tumors and dedifferentiated or undifferentiated carcinomas, predominantly of lung, gastrointestinal, and endometrial origin. This review provides the first extensive characterization of cancers with concurrent SMARCA4 and SMARCA2 loss through the discussion of shared clinical and molecular features. Further, we discuss the mechanisms triggering the loss of catalytic activity, the cellular processes that are dysfunctional as a consequence, and finally, current therapeutic candidates which may selectively target these cancers.

1. Background

Dysregulation of chromatin dynamics is a fundamental component in the onset and progression of malignant disease. For more than 20 % of human cancers, this is driven by aberrations in subunits of the SWItch/Sucrose Non-Fermentable (SWI/SNF) family of chromatin remodeling complexes, also referred to as BRG1/BRM associated factor (BAF) complexes [1–4]. There are three unique mammalian complexes with distinct subunit assemblies, specifically canonical BAF (cBAF), polybromo BAF (pBAF) and non-canonical BAF (ncBAF) (reviewed in Refs. [5,6]). All three complexes employ one of two mutually exclusive helicase subunits, SMARCA4 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4, also known as BRG1; BRM-related gene 1) or SMARCA2 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 2, also known as BRM; Brahma homologue) to catalyze ATP hydrolysis and remodel heterochromatin into an open, accessible state *via* nucleosome mobilization, eviction, or histone dimer exchange [7,8] (reviewed in Refs. [5,6]). Modulation of DNA accessibility by the SWI/SNF complex is critical for embryogenesis, stem cell pluripotency and lineage specification [9–14], oogenesis and spermatogenesis [15,16], DNA damage repair [17,18], and cell cycle control [19,20]. The catalytic activity of SMARCA4 underpins gene regulation associated with these biological processes, with specific links reported in stem cell maintenance and differentiation, neural and mesodermal development during embryogenesis, and modulation of folliculogenesis for oocyte developmental competence [14,15,21]. Somatic molecular aberrations in the coding region of *SMARCA4* have been reported in 5–7% of malignancies [2,22]. These are most frequent in cancer of unknown primary (15.6 %), skin (13.5 %), non-small cell lung cancer (NSCLC) (9.35 %), bladder (9.22 %) and endometrial (8.72 %) cancers [2]. Heterozygous germline *SMARCA4* missense mutations are found in ~11 % of patients with the rare neurodevelopmental disorder Coffin-Siris Syndrome (CSS, OMIM: #614609) [23,24].

Similar to SMARCA4, SMARCA2 also functions as an ATPase, sharing overlapping functions with SMARCA4 in development, stem cell regulation and differentiation. SMARCA2 exhibits distinct expression

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Abbreviations

AP-1	activator protein-1
ATRT	Atypical Teratoid/Rhabdoid tumors
BIS	Blepharophimosis-impaired intellectual development syndrome
cBAF	canonical BAF
ccRCC	clear cell renal cell carcinoma
CR	complete response
CSS	Coffin-Siris Syndrome
CUP	cancer of unknown primary
ECRT	Extracranial rhabdoid tumors
EMT	epithelial-mesenchymal transition
EZH2	Enhancer of Zeste 2 Polycomb Repressive Complex 2
GI	gastrointestinal
HDAC	histone deacetylase
ICB	immune checkpoint blockade
IHC	immunohistochemistry
MEF2	myocyte enhancer factor-2
MMR	mismatch repair
MRT	Malignant rhabdoid tumors
NCBRS	Nicolaides-Baraitser Syndrome
ncBAF	non-canonical BAF
NSCLC	Non-small cell lung cancer
OS	overall survival
pBAF	polybromo BAF
PR	partial response
PRC2	polycomb repressive complex 2
RTPS	Rhabdoid Tumor Predisposition Syndrome
SCCOHT	Small-cell carcinoma of the ovary, hypercalcemic type
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 2
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4
SWI/SNF	SWItch/Sucrose Non-Fermentable
TTF-1	Thyroid transcription factor-1
TSDUT	Thoracic SMARCA4-deficient undifferentiated tumor

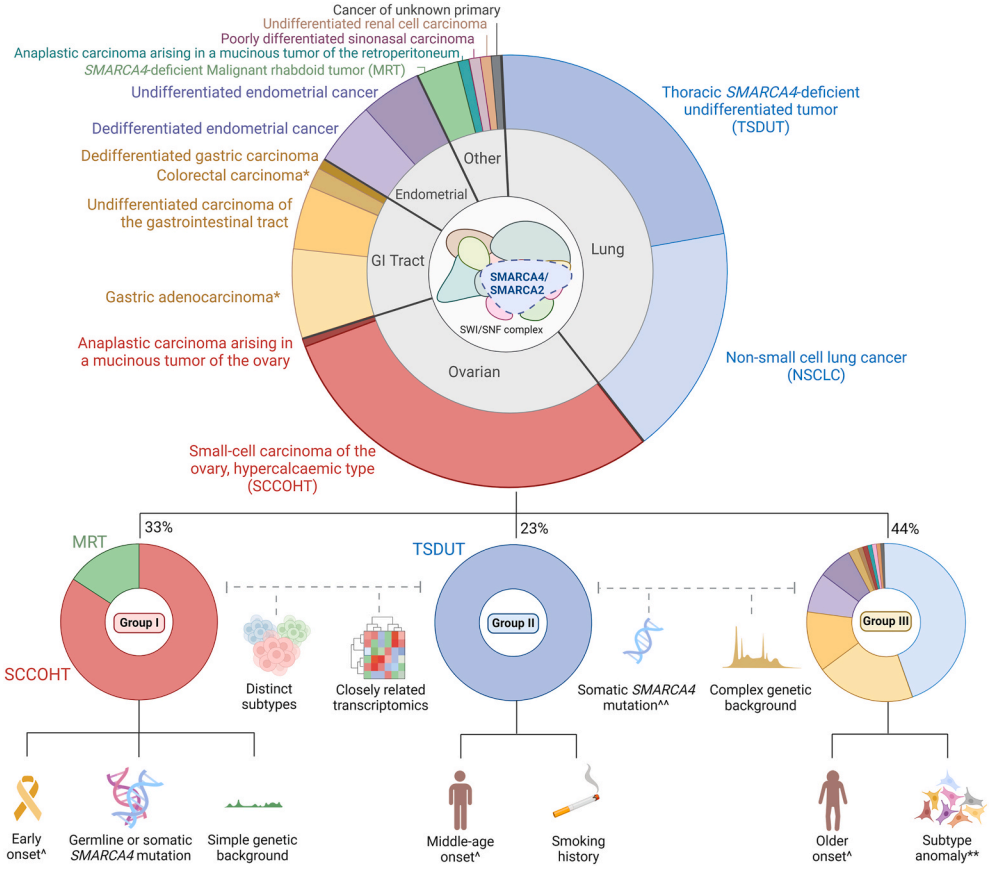

Fig. 1. Categorization of malignancies with simultaneous SMARCA2 and SMARCA4 loss (n = 292). In the large top circle SMARCA4/2-deficient cancers are categorized by their primary lineage (grey circle) then their subtype (colored circle). *Subtype breakdown for these malignancies beyond lineage was not available. GI: Gastrointestinal. Data is based on frequencies listed in Table 1, with size of the wedge proportional to the overall number of tumors reported. SMARCA4/2-deficient cancers were further broken down into three groups based on clinical and molecular characteristics: Group I is Small-cell carcinoma of the ovary, hypercalcemic type and Malignant rhabdoid tumor, Group II is Thoracic SMARCA4-deficient undifferentiated tumor and Group III consists of the remaining malignancies described in the top circle. Shared features between groups are indicated by a grey dotted line. Distinct traits of each group are indicated by a black solid line. ^Early-onset age range is defined as a median of 26 years (range 0–43 years), middle-age onset is a median of 55 years (range 27–82 years), older onset is a median of 63 years (range 39–81 years). ^^Current evidence suggests the mutations in these cancers are likely somatic, however extensive germline testing has not been reported. **The "subtype anomaly" category was defined as when co-loss of SMARCA4 and SMARCA2 is not a pathognomonic feature of the subtype but instead a rare molecular event. Created with BioRender.com.

patterns across different developmental stages [25,26]. Mutations in *SMARCA2* are implicated in several neurological congenital disorders: CSS, Nicolaides-Baraitser Syndrome (NCBRS, OMIM: #601358) and Blepharophimosis-impaired intellectual development syndrome (BIS, OMIM: #619293) [27,28]. *SMARCA2* is rarely mutated in cancer, although pathogenic variants have been reported in lymphoma [29], leukemia [30], clear cell renal cell carcinoma (ccRCC) [31], and gastric cancer [32]. SMARCA2 silencing, however, has been reported in ~15 % of solid tumors by reversible epigenetic suppression [33–35]. Given that loss of either SMARCA4 or SMARCA2 leads to the cell relying on its remaining ATPase paralog, selective ATPase inhibitors are an attractive potential therapeutic option for tumors with isolated functional abrogation of either SMARCA4 or SMARCA2 [36].

The simultaneous loss of SMARCA4 and SMARCA2 function (referred to as SMARCA4/2 for this review) is an exceptionally rare occurrence in human malignancy; nonetheless, SMARCA4/2-deficiency has been reported in Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), a lethal ovarian cancer subtype that predominantly impacts young women, with a median age of onset of 25 years [37–39]. When diagnosed at an early stage (FIGO 1), 5-year overall survival (OS) of SCCOHT is 51 %, however, non-specific symptoms to lead most patients being diagnosed with FIGO Stage II-IV, where the 5-year OS is 24 % [38]. SCCOHT is an incredibly rare disease, and as a result, limited reports on incidence are available. A recent publication assessing the Slovenian population over a 30-year period reported just 7 cases [40]. Further, an epidemiological study of pediatric (0–19 years) ovarian tumors from the Swedish National Cancer Register over a 44 year period identified only 2 SCCOHT patients [41]. Biallelic nonsense, frameshift, and splice-site *SMARCA4* variants define 69–100 % of SCCOHT patients and lead to subsequent loss of protein expression [42–48] (reviewed in Ref. [49]). SCCOHT has a remarkably uncomplicated genome, exhibiting less than 6 mutations/mb with no recurrent pathogenic genomic variants other than in *SMARCA4* [47,50]. However, epigenetic regulation is further abrogated by the hallmark loss of SMARCA2 protein expression in 86–100 % of SCCOHT cases [44,45,51–53] (reviewed in Ref. [49]). The absence of expected *SMARCA2* mutations in whole exome and deep sequencing has implicated this loss as epigenetic, albeit the exact mechanism of epigenetic regulation remains to be confirmed [44,50].

Aside from SCCOHT, SMARCA4/2-deficiency has also been observed in uncommon, poorly differentiated and aggressive tumors primarily of ovarian [53,54], lung [55–57], gastrointestinal (GI) [58,59], and endometrial [60,61] origin. Information on these variants are often scarce beyond the recognition of poor clinical outcomes and aberrant SMARCA4/2 immunohistochemical (IHC) staining [61–64]. These studies are indicative, however, of the existence of an exceedingly rare and distinct subgroup of tumors, where the concurrent loss of SMARCA4 and SMARCA2 drives a highly malignant phenotype. In this review, we draw parallels between the specific tumor conditions where this unusual phenomenon occurs and define three groups. The recognition of these groupings, which likely reflect differences in the timing and cellular context of SMARCA4/2 loss, may aid in clinical decision-making for diagnosis and, in the future, prospective therapy. Finally, we show that SMARCA4 and SMARCA2 are likely lost in these malignancies by genetic mutation and epigenetic silencing respectively and discuss therapeutic opportunities based on these molecular events.

2. The landscape of cancers with concurrent SMARCA4 and SMARCA2 loss

The existence of cancers with concurrent SMARCA4/2 loss was first recognized over two decades ago in a subset of NSCLC tumors [65]. Since then, less than 300 cases have been reported in the literature detailing malignancies with a clearly documented loss of SMARCA4/2 (Table 1). The number of cases driven by SMARCA4/2 loss is likely higher than reported as IHC staining for co-existent SWI/SNF helicase

Table 1
Summary of primary tumors which lack SMARCA4 and SMARCA2 protein expression.

Cancer lineage	Subtype	Targeted Cohort	Cases with negative SMARCA4 & SMARCA2[c]	Reference
Ovarian	Small-cell carcinoma of the ovary, hypercalcemic type	Yes[d]	100 % (43 of 43)	[53]
		Yes[d]	90 % (9 of 10)	[44]
		Yes[d]	80.5 % (29 of 36)	[54]
			5 of 5	[50]
			2 of 2	[45]
			1 of 1	[68]
			1 of 1	[69]
	Anaplastic carcinoma arising in mucinous tumor of the ovary	Yes[d]	4.5 % (1 of 22)	[70]
Lung	Thoracic SMARCA4-deficient undifferentiated tumor[a]	Yes[d]	100 % (15 of 15)	[45]
		Yes[d]	100 % (11 of 11)	[71]
		Yes[d]	81.8 % (18 of 22)	[55]
			9 of 9	[72]
			8 of 8	[73]
			2 of 2	[74]
			1 of 1	[75]
			1 of 1	[76]
			1 of 1	[77]
	Non-small cell lung cancer (NSCLC)	Yes[d]	10.5 % (14 of 133)	[57]
		Yes[d]	10 % (6 of 60)	[65]
		Yes[d]	6.7 % (1 of 15)	[45]
		Yes[d]	5.4 % (5 of 93)	[56]
		Yes[d]	1.3 % (4 of 316)	[62]
		Yes[d]	0.29 % (7 of 2390)	[63]
		Yes[e]	33.3 % (6 of 18)	[78]
		Yes[e]	8.3 % (1 of 12)	[71]
		Yes[f]	17.3 % (12 of 69)	[79]
Gastrointestinal Tract	Gastric adenocarcinoma[b]	No	2 % (26 of 1271)	[80]
	Colorectal carcinoma[b]	No	0.04 % (2 of 4508)	[64]
	Undifferentiated carcinoma of the gastrointestinal tract	Yes[d]	45.8 % (11 of 24)	[58]
			2 of 9	[59]
	Dedifferentiated gastric carcinoma	Yes[d]	8.3 % (1 of 12)	[59]
	Undifferentiated carcinomas of the esophagus		5 of 5	[81]
Endometrial	Dedifferentiated endometrial cancer	Yes[d]	36.6 % (11 of 30)	[60]
	Undifferentiated endometrial carcinoma	Yes[g]	0.46 % (1 of 216)	[82]
		Yes[d]	24.3 % (9 of 37)	[61]
Soft Tissue & renal	SMARCA4-deficient Malignant rhabdoid tumor	Yes[h]	7.7 % (1 of 13)	[71]
			5 of 5	[83]
			1 of 1	[45]
	Undifferentiated renal cell carcinoma	Yes[d]	3.3 % (1 of 30)	[84]

(*continued on next page*)

Table 1 (*continued*)

Cancer lineage	Subtype	Targeted Cohort	Cases with negative SMARCA4 & SMARCA2[c]	Reference
Head and Neck	Sinonasal undifferentiated carcinoma	Yes[d]	1.9 % (1 of 53)	[85]
Misc	Anaplastic carcinoma arising in mucinous tumor of the retroperitoneum		1 of 3	[70]
	SMARCA4-deficient cancer of unknown primary		1 of 1	[86]

+ positive, - negative, [a]previously known as SMARCA4-deficient thoracic sarcoma prior to reclassification by the World Health Organization in 2021. [b]Subtype breakdown was not available for these tumors. [c]Frequency and type of cohort has been reported when cohort n ≥ 10. [d]Cohort was respective subtype listed in column 2 only. [e]Cohort was SMARCA4-deficient NSCLC only. [f]Cohort was Pulmonary Sarcomatoid Carcinoma only. [g]Cohort was Uterine mesenchymal carcinoma only. [h]Cohort was SMARCB1-deficient and SMARCA4-deficient MRT only.

deficiency has only gained traction in recent years. These tumors are typically defined by negative nuclear staining following IHC evaluation with BRG1 and BRM antibodies [45,51,54,61,63]. Interestingly, recent discussions suggest weak/faint nuclear staining could still indicate underlying involvement of SMARCA4 [66,67]. To minimize diagnostic ambiguity, molecular profiling of the *SMARCA4* gene, to identify an underlying pathogenic variant, should be completed in combination with SMARCA4/2 IHC analysis.

When presented with an ambiguous, undifferentiated and aggressive malignancy, profiling of SWI/SNF subunit expression, including SMARCA4/2, may provide valuable insights. In the absence of molecular information, SMARCA4/2-deficient tumors appear as disparate malignancies which occur throughout the body as rare variants of ovarian, lung, endometrial, GI tract, head and neck, renal and soft tissue neoplasms (Table 1). After collation based on this rare molecular event, it is clear that there are undeniable similarities in clinical trajectory post-diagnosis, as well as tumor morphology, discussed in a subsequent section of this review. Recognition of other expected clinical (age, patient history, diagnosis) and molecular (germline status, genetic background, transcriptomics) factors may further assist in the diagnosis and consideration of future therapeutic interventions. Thus, a new way to consider these tumors is to stratify them based on the above properties. This has resulted in three distinct groupings which will be expanded upon throughout the review (Fig. 1).

I. The early onset distinct subtypes
II. The distinct subtype with middle-age onset
III. Later onset cancers of rare subtype anomalies

2.1. Group 1: the early onset distinct subtypes: SCCOHT and Malignant rhabdoid tumor (MRT)

SCCOHT and Malignant rhabdoid tumors (MRT), the tumor types of Group I, are classic examples of a cancer initiated by an epigenetic disorder as they are primarily driven from dysfunctional SWI/SNF components. SCCOHT represents an unusual primordial onset previously reported to make up less than 0.01 % of all ovarian cancer cases, an otherwise predominantly post-menopausal disease [87,88]. A recent retrospective cohort study of the United States Surveillance, Epidemiology and End Results (SEER) program reported a prevalence of 0.5 % across ovarian cancer [88]. Based on published literature, we have calculated a median age at diagnosis of 27 years (range; 14–43 years) for SCCOHT patients with documented SMARCA4/2 loss (Table S1) [44,45,50,54,68,69]. Across the literature, a broader age range of 1–56 years at diagnosis has been reported for patients with only confirmed SMARCA4 loss [89,90]. As raised by Witkowski and colleagues regarding SMARCA4 loss, cases in older patients diagnosed on clinical presentation alone may reflect a misdiagnosis [37]. There is potential this may extend to patients where dual SMARCA4/2 loss has not been examined. The histogenesis of SCCOHT has been a topic of controversy for the last three decades, theories postulating epithelial, sex-cord stromal or germ-cell origin have all been published yet none have been definitively proven [39,91,92]. The most widely endorsed argument supports SCCOHT as a primitive germ cell tumor, likely originating from an immature teratoma [91,93].

Both somatic and germline *SMARCA4* mutations cause SCCOHT, with the latter documented in up to 43 % of cases and linked to an accelerated onset and familial inheritance of the disease [37,90]. As stated earlier, the mutational loss of *SMARCA4* in SCCOHT is typically associated with loss of SMARCA2, the remaining ATPase of the SWI/SNF complex. Interestingly, in four SCCOHT patients, inactivation of SMARCB1 has been reported in lieu of conventional SMARCA4 deficiency, with SMARCA2 co-loss confirmed in three cases [53,94]. SMARCB1, also known as INI-1, BAF47 or SNF5, is a highly conserved core SWI/SNF subunit essential for maintaining complex integrity and transcriptional promoter/enhancer regulation [5,95]. Somatic or germline inactivation of *SMARCB1* is the monogenic driver for >95 % of MRT cases, a collection of pediatric brain and soft tissue tumors known as Atypical Teratoid/Rhabdoid tumors (ATRT) and Extracranial rhabdoid tumors (ECRT), respectively [96]. MRT is a lethal malignancy, diagnosed in young infants who rapidly succumb to the disease within months [83,96,97]. These rhabdoid tumors are thought to arise during embryogenesis from dysregulated and developmentally stunted progenitor cells that become unable to complete mesenchymal and/or ectodermal differentiation. The causative mechanisms are still an area of debate and likely to differ within ATRT and ECRT [98,99]. A small proportion of MRT cases are caused by complete inactivation of SMARCA4, most often in germline *SMARCA4* mutation carriers [83,96].

Mirroring SCCOHT as a low mutational burden tumor, no other recurrent pathogenic mutations are recorded in MRT beyond the mutually exclusive *SMARCA4* or *SMARCB1* mutations [83,100]. Primary rhabdoid tumors have also reported SMARCA2 downregulation or loss independent of the presence of a genetic mutation in this gene, including in uncommon SMARCA4 mutated MRT cases [34,45,83]. The close clinical, molecular, and morphological resemblance of SCCOHT to MRT has led some researchers to recommend the reclassification of SCCOHT as 'Malignant rhabdoid tumor of the ovary' [101]. Further, the causative role of germline mutations in both diseases has led to the recognition of Rhabdoid Tumor Predisposition Syndrome (RTPS), a cancer susceptibility syndrome defined by germline heterozygous variants in *SMARCB1* (Type 1; RTPS1, OMIM #609322) or *SMARCA4* (Type 2; RTPS2, OMIM #613325) and linked to heightened risk of aggressive early-onset rhabdoid tumors [102].

2.2. Group II: Thoracic SMARCA4-deficient undifferentiated tumor (TSDUT), a distinct subtype with middle-age onset

The second grouping consists entirely of Thoracic SMARCA4-deficient undifferentiated tumor (TSDUT), a newly described pulmonary subtype recognized by the World Health Organization (WHO) as a distinguishable disease in 2021 [103]. TSDUT is an adult acquired malignancy, nonetheless, it presents at a much younger age than the most frequent lung cancer, NSCLC, with the reported median age at diagnosis being respectively 48 and 70 years [72,104]. Although TSDUT is known to develop during the middle of adulthood, the typical reported age of occurrence in the literature does vary. The first study to define TSDUT described its presentation primarily in '30- to 35-year-old adults' [45].

From the cohort of cases with documented SMARCA4/2 loss, we have calculated a median age of 55 years (range; 27–82 years) (Table S1) [45,55,71,73–77]. Regardless, TSDUT is a highly aggressive malignancy occurring predominantly in males with a heavy smoking history, defined as ≥ 20 pack-years [55,71]. Approximately 91 % of patients present with stage IV disease with a median survival time of 6–7 months post diagnosis [45,55,72]. As of 2021, WHO classifies TSDUT under the 'other epithelial tumors of the lung' category but beyond this its cellular origin is not definitively known [55,103]. The identification of rare TSDUT composite tumors containing mature epithelial elements suggests that the malignancy may be emerging from impaired differentiation of an epithelial precursor cell [55].

Analogous to Group I, the concurrent loss of SMARCA4/2 in TSDUT is a pathognomonic molecular signature in almost all cases [45,55,71]. Further, closely related transcriptomic and methylation profiles have led to the postulation that SCCOHT, MRT and TSDUT may lose SMARCA4/2 in a similar cellular context or stage of tumorigenesis, triggering parallel epigenetic rewiring that contribute to a manifestation at a younger age, rapid disease progression and ultimately a primitive and aggressive rhabdoid or pseudo-rhabdoid tumor (Fig. 1) [45,72,83]. However, we have placed TSDUT into a distinct intermediate group (Group II) due to its closer association to Group III compared with Group I in terms of the genetic background of this tumor type. TSDUT reports exclusively somatic *SMARCA4* mutations against a complex molecular profile, defined by high tumor mutational burden of >14.2 mutations/mb, missense *TP53* variants, and a smoking associated genetic signature of *STK11, KEAP1* and/or *KRAS* mutations [55,71]. The impact of SMARCA2 loss on survival has not yet been reported, however, the loss of SMARCA4 in TSDUT would appear to associate with a more aggressive phenotype when compared to SMARCA4-retained thoracic sarcomas, with 2-year survival rates of 12.5 % and 64.4 % respectively [73].

2.3. Group III: Later onset cancers of rare subtype anomalies stemming from abnormal differentiation

Adult cancer is generally accepted as an age-related disease initiated by an accumulation of oncogenic events over time [105]. The remaining SMARCA4/2-deficient malignancies appear to fit this model of age-dependent development, wherein the added loss of SWI/SNF catalytic activity during cancer initiation and/or progression leads to a poorly differentiated tumor variant. Patients we have classified into this group are predominantly older than those in Group I and II, with a median age of 63 years (range; 39–81 years) (Table S1) [45,57,59,60,62,78,81,82,85,86], and can display primary tumors from a range of anatomical sites across lung, gastrointestinal (GI) tract, endometrial, ovarian, renal, retroperitoneal and sinonasal tissue (Fig. 1). Irrespective of origin, Group III malignancies typically appear in one of two forms.

A. A poorly or undifferentiated carcinoma, which may be a *de novo* malignancy, arising when the terminal differentiation of a precursor cell is blocked, or alternatively, the complete overgrowth of undifferentiated cells from an initial low-grade tumor [58,61,81,82,86,106,107].
B. A dedifferentiated carcinoma, which is defined as a well-differentiated tumor accompanied by a primitive high-grade neoplasm [55,59–61,70,106].

In contrast to the previous groups, the loss of SMARCA4/2 in Group III tumors does not define them under distinct diseases, but rather they represent exceedingly rare and independent malignancies or rare molecular subtypes of a more frequently diagnosed cancer. As an example, within NSCLC, the most frequent subtype of lung cancer, approximately 10 % of cases have SMARCA4 or SMARCA2 deficiency yet less than 1 % display loss of both subunits [62,63,104]. In terms of survival, where data is available and Group III malignancies are compared to their respective subtypes across different tissue types, including those with single loss of either SMARCA4 or SMARCA2, SMARCA4/2-deficient tumors are consistently associated with a worse prognosis [56,60,62,64,78,80].

In distinction to Group I, the malignancies we have defined as Groups II and III frequently report pathogenic mutations in addition to *SMARCA4* mutations that are reflective of their respective tumor lineages. Parallel to TSDUT (Group II), NSCLC (Group III) cases often possess missense *TP53* and/or other lung cancer associated mutations in genes including *KRAS, KEAP1* and *STK11* in addition to SMARCA4/2 deficiency, however, as previously reported for NSCLC, *EGFR* mutations do not coexist with *SMARCA4* mutations [76,78,108]. Endometrial cancer mutations in *ARID1A*, *PTEN*, *KRAS* and *PIK3CA* in conjunction with a mismatch repair (MMR) deficient phenotype, most often from loss of PMS2 expression, were documented in SMARCA4/2-negative dedifferentiated or undifferentiated endometrial carcinomas (Group III) [60,61]. MMR deficiency and mutant p53 staining was frequently observed in tumors originating from the GI tract that lack SMARCA4/2 [64,80]. Further breakdown of Group III tumors is challenging given the current state of the literature, as information beyond morphology and SMARCA4 and SMARCA2 IHC staining is not always reported. Based on the available data, shared features such as later-onset, poor survival, complex genetic composition, and SMARCA4/2 loss define this grouping.

3. The shared traits of SMARCA4/2-negative tumors

3.1. Inactivating SMARCA4 mutations lead to loss of protein expression in SMARCA4/2-deficient tumors

Cancer-associated *SMARCA4* mutations are usually either truncating (nonsense, frameshift, splice-site) or missense variants [22]. For cancers with documented SMARCA4/2 loss, *SMARCA4* mutation data was reported for a selection of SCCOHT, MRT, TSDUT, NSCLC and endometrial cancer cases (Table S2) [42,44,45,50,53,55,60,68,69,71,76,83]. Most reported cases were from Groups I and II, with Group I harboring both germline and somatic mutations (Table 2). Regardless of group or tumor type, *SMARCA4* mutations were scattered throughout the gene and were predominantly of nonsense, frameshift, or splice-site type (Fig. 2).

3.2. Epigenetic mechanisms of SMARCA2 loss which may apply to SMARCA4/2-deficient tumors

In the last two decades, emerging evidence has begun to elucidate the molecular processes which may trigger the transcriptional shutdown of *SMARCA2* in cancer. For SMARCA4/2-deficient SCCOHT, MRT and TSDUT, the absence of *SMARCA2* genetic variants after whole exome sequencing implicates that this loss, as is the case for most SMARCA2-negative malignancies, stems from epigenetic modulation [44,45,53,55,76,83,109]. In SCCOHT, expression of exogenous SMARCA4 does not alter SMARCA2 protein levels, inferring that mutant *SMARCA4* is not the driving force behind the absence of SMARCA2 in these dual loss tumors [44,53]. Instead, there is evidence, detailed in this section, suggesting that impaired histone deacetylase (HDAC) and polycomb repressive complex 2 (PRC2) activity are key factors in maintaining the absence of *SMARCA2* transcription in SCCOHT. Given the low tumor mutational burden, it is not clear whether additional molecular processes are involved in the development and progression of SCCOHT, or further, what mechanisms may be accountable for the non-SCCOHT SMARCA4/2-deficient cancers. Fig. 3 outlines the known pathways resulting in SMARCA2-negative malignancies and highlights potential mechanisms which may be contributing to SMARCA4/2-deficient tumors. A summary of which of these epigenetic processes have already been examined in specific cancers is provided in Table 2.

Table 2
Summary of potential mechanisms driving SMARCA4/2-deficient cancers.

Group	Subtype	Mechanism of SMARCA4 silencing[a]		Mechanism of SMARCA2 silencing				
		Mutation	Germline or Somatic	Mutation	PRC2 involvement	HDAC involvement	Homozygous Promoter polymorphisms	Promoter methylation
I	SCCOHT	+	Both	- [44,53]	+[b] [111,112]	+[b] [53]	- [50]	NT
I	MRT	+	Both	- [83]	NT	NT	NT	NT
II	TSDUT	+	Somatic	- [45,55,76]	NT	NT	NT	NT
III	NSCLC	+	Somatic	NT	+[b] [111]	+[b] [35]	NT	NT
III	DDEC	+	Somatic	NT	NT	NT	NT	NT
III	Gastric adenocarcinoma	NT	NT	NT	+[b] [111]	NT	NT	NT

[a] Reference for mutation data reported in Table S2.
[b] Tested only in pre-clinical cell line model(s). NT: Not yet tested. SCCOHT: Small-cell carcinoma of the ovary, hypercalcemic type, MRT: Malignant rhabdoid tumor, TSDUT: Thoracic SMARCA4-deficient undifferentiated tumor, NSCLC: Non-small cell lung cancer, DDEC: Dedifferentiated endometrial carcinoma, PRC2: Polycomb repressive complex 2, HDAC: Histone deacetylase.

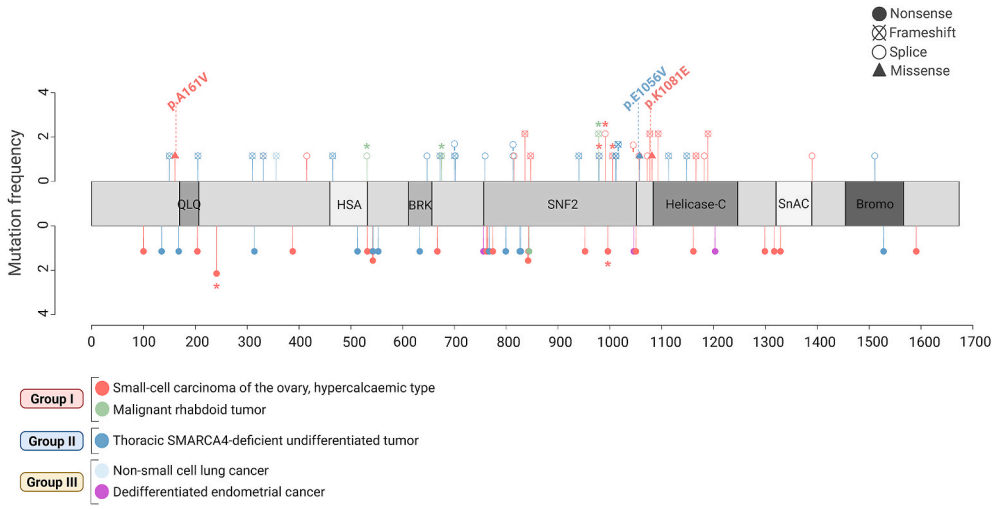

Fig. 2. Schematic of *SMARCA4* showing the location of mutations in SMARCA4/2-deficient cancer (n = 83). The x-axis corresponds to the amino acid number and the y-axis corresponds to the frequency of occurrence of the corresponding mutations. Name and location of functional SMARCA4 domains taken from UniProtKB (P1532). HSA = Helicase/SANT-associated domain, SnAC = SNF2 ATP coupling domain, Bromo = Bromodomain. Floating symbol above a lollipop represents a distinct mutation occurring at the same amino acid as another mutation. All missense mutations have corresponding protein nomenclature above the mutation. *Indicates a proven germline variant. In all cases, where the asterisk is above a mutation with a frequency of 2, only one mutation is germline. Group I is defined as the early onset distinct subtypes. Group II is defined as the distinct middle-age onset subtype. Group III is defined as later age of onset rare subtype anomalies. Full variant and reference list reported in Table S2. Created with R Version 4.4.0.

3.2.1. The PRC2 complex silences SMARCA2 by enriching H3K27me3 at the SMARCA2 promoter

In cells with mutant SWI/SNF complexes, it is not uncommon to see upregulation of histone-modifying enzyme complexes such as PRC2 and its associated repressive chromatin mark H3K27me3 as a consequence of failed SWI/SNF-mediated PRC2 eviction, ultimately leading to increased silencing of PRC2 target genes (Fig. 3A) [110,111]. In pre-clinical ovarian, gastric and lung cancer models with SMARCA4/2 deficiency, *SMARCA2* is postulated to be one of the genes under PRC2 mediated suppression due to the strong enrichment of H3K27me3 at the *SMARCA2* promoter compared to cells with only SMARCA4 deficiency. Two studies have shown that inhibition of the PRC2 catalytic unit EZH2 (Enhancer of Zeste 2 Polycomb Repressive Complex 2) in SMARCA4/2-negative cells has the capacity to induce *SMARCA2* transcription, likely as the result of suppressing H3K27me3 at the *SMARCA2* promoter region [111,112].

3.2.2. Inhibition of HDACs 3, 4 and 9 induces functional SMARCA2 expression

The inhibition of HDACs, a class of post-translational histone modifiers known to increase the proportion of transcriptionally silent heterochromatin, have been shown to induce *SMARCA2* transcription in several SMARCA2-negative cancers including SCCOHT, MRT, NSCLC and ccRCC (Fig. 3C) [35,53,113]. Although pan-HDAC inhibitors lead to re-expression of SMARCA2, they also simultaneously induce acetylation of its c-terminus rendering the resultant protein functionally inactive [35]. It is now understood that only specific HDACs, namely HDAC3, HDAC4 and HDAC9 suppress SMARCA2 transcription and that HDAC2 is predominantly responsible for its acetylation [34,35,113].

3.2.3. Homozygous SMARCA2 promoter polymorphisms can disrupt SMARCA2 expression through recruitment of MEF2D and HDAC9

Homozygous indel (insertion-deletion) polymorphisms in the *SMARCA2* promoter −741bp (reference SNP ID rs3448094; TATTTTT) and −1321bp (rs3832613/rs5925917; TTTTAA) upstream of the transcription start site are strongly associated with cancer susceptibility across lung, esophageal, head and neck, hepatocellular and pancreatic cancers [114]. Furthermore, the presence of either variant correlated with a significantly worse clinical outcome when compared to the wild-type genotype [115–118]. Homozygous variants present in at least

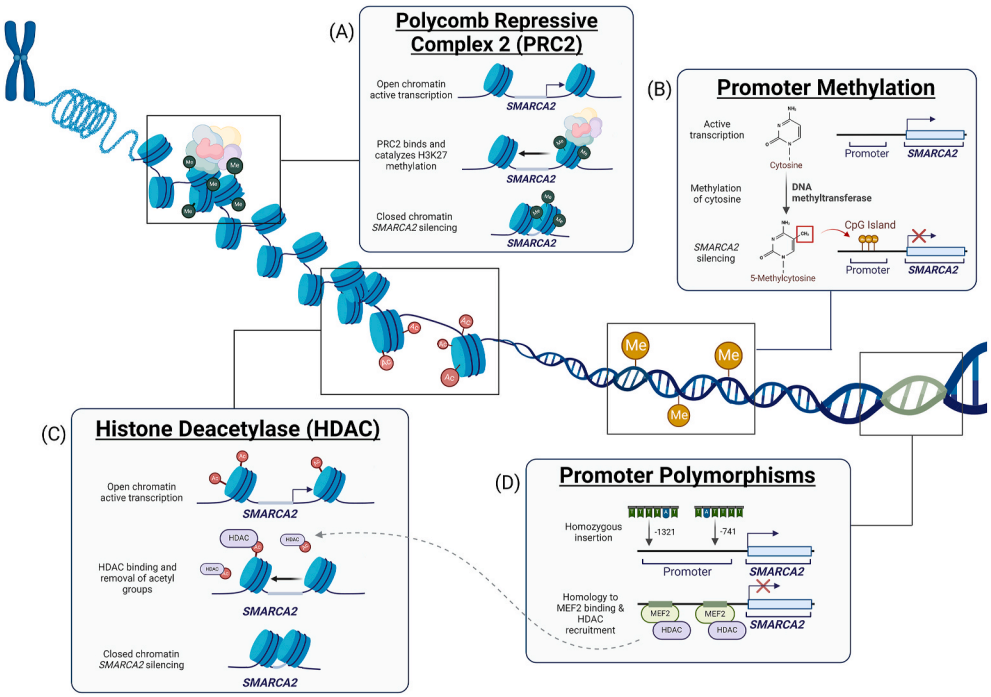

Fig. 3. Four epigenetic mechanisms linked to SMARCA2 silencing in cancer. (A) Polycomb Repressive Complex 2 (PRC2), an epigenetic modulator, has been found to deposit the repressive mark of Histone H3 lysine 27 (H3K27) methylation at the *SMARCA2* promoter region, leading to SMARCA2 silencing. Methyl groups bound to histones are indicated by a green circle. (B) Hypermethylation of the SMARCA2 promoter region is led by the addition of methyl groups to a cytosine base of DNA at cytosine-guanine (CpG) dinucleotides by DNA methyltransferases. Methylation of CpG islands located within the *SMARCA2* gene promoter has been linked to downstream transcription suppression. Methyl groups bound to DNA are indicated by a yellow circle. (C) Histone deacetylases (HDACs) are histone modifiers which bind to open portions of acetylated chromatin. HDACs remove acetyl groups from the lysine residue of histone proteins, causing, transcriptionally inactive chromatin. Acetyl groups bound to histones are indicated by a red circle. (D) Two polymorphisms (−1321bp, TTTTAT; −741bp, TATTTT) in the SMARCA2 promoter region create a DNA sequence that is homologous to the binding site of the transcription factor MEF2 (myocyte enhancer factor-2). This has been linked to recruitment of HDACs leading to downstream loss of SMARCA2 expression (see C) as indicated by the dotted grey line. Created with BioRender.com.

one of these polymorphic sites correlated with loss of SMARCA2 expression in lung and esophageal tumors [34,115,116]. In rhabdoid and hepatocellular neoplasms, studies reported that only presence of the −1321bp indel was statistically significant in relation to SMARCA2 loss [34,117]. The resulting mutant *SMARCA2* promoter sequences have >90 % homology to the binding sites of the transcription factor myocyte enhancer factor-2 (MEF2). MEF2 binding then triggers a cascade of HDAC recruitment, predominantly HDAC9, which ultimately provokes the suppression of *SMARCA2* transcription (Fig. 3D) [34,35,115]. In SCCOHT, the polymorphic sites have been sequenced in eight primary tumors and two SCCOHT cell lines (SCCOHT-1 and BIN-67). The results from this study identified at least one heterozygous indel in every case, but failed to find homozygous variants in every patient, leading the authors to conclude that these homozygous polymorphisms are not a mechanism of *SMARCA2* silencing in SCCOHT [50]. It remains to be determined whether heterozygous polymorphisms at these SNPs are capable of silencing SMARCA2 [50]. Interestingly, in a separate study of the SMARCA2-deficient rhabdoid cell line KP-MRT-NS, it was confirmed that a heterozygous indel at just one of the polymorphic sites may be enough to recruit MEF2D and HDAC9 binding to the *SMARCA2* promoter [34].

3.2.4. *Promoter hypermethylation is linked to SMARCA2 silencing in renal and lung cancer*

Hypermethylation of the *SMARCA2* gene promoter has been identified in 42.8 % (6 of 14) of primary SMARCA2-deficient RCCC (Fig. 3B) [31]. Two of these cases were composite tumors, containing low grade and poorly differentiated components. It was only in the poorly differentiated areas of these tumors that CpG methylation was detected, suggesting that *SMARCA2* promoter methylation may play a role in the reversion of differentiated cells to a progenitor-like state. Similarly, in the case of lung adenocarcinoma, *in silico* and *in vitro* data is showed a strong negative correlation between *SMARCA2* expression and corresponding promoter methylation and was associated with poorer survival [119].

3.2.5. *Additional epigenetic regulatory mechanisms linked to drive SMARCA2 silencing*

Other processes that have been linked to *SMARCA2* regulation, albeit with currently less available evidence. The transcription factor GATA3, a key regulator of tissue specific cellular differentiation, has been found to bind at the *SMARCA2* promoter region and recruit HDACs, which modulate *SMARCA2* transcription as previously described (Fig. 3C) [25,34]. Interestingly, in cancer cell lines with SMARCA4/2 loss, a double-negative feedback loop has been proposed where high levels of the transcription factor EGR1 promotes expression of mature non-coding RNAs (miR-199a-5p and miR-199a-3p) which in turn silence *SMARCA2* expression [120].

3.3. *Loss of ATPase activity may drive phenotypic plasticity in SMARCA4/2-deficient tumors*

3.3.1. *SMARCA4/2-deficient tumors have non-specialized and primitive morphology*

The loss of SMARCA4/2-driven SWI/SNF signaling during cancer pathogenesis appears to foster a highly malignant phenotype in part by evading terminal differentiation. As implied by their subtype nomenclature, the disruption of normal cell differentiation is evident in the morphology of the SMARCA4/2-deficient cancers (Table 1). Regardless of grouping, consistent observations of tumor morphology range from

brief notes of an 'undifferentiated' or 'rhabdoid' phenotype to extensive accounts describing diffuse sheets of poorly differentiated, densely packed cells with rapid mitotic activity [39,56,60,63,70,74,80,83,86,91]. A subset of SCCOHT, TSDUT, endometrial, ovarian, and GI malignancies also report rhabdoid features including high-grade eccentric nuclei, an eosinophilic cytoplasm and paranuclear inclusions [45,60,70,81]. Composite tumors identified in the lung, endometrium, and GI tract have demonstrated the loss of epithelial features and SMARCA4/2 only in the undifferentiated components [55,59,60]. Interestingly, while EZH2 or HDAC inhibitors are known to re-express *SMARCA2*, SCCOHT cells have been reported to also undergo a 'neuronal-like' differentiation following treatment [121,122].

3.3.2. *Alterations to chromatin architecture following SMARCA4/2 loss in undifferentiated cells*

After dual ATPase loss, the residual cBAF and pBAF complexes contain key subunits (ARID1A, ARID2, SMARCB1, SMARCC1/2, SMARCD1/2/3, SMARCE1, DPF2, GLTSCR1/L and BRD7/9) but are deficient in members that require SMARCA4/2 for binding (ACTL6A, BCL7A/B/C, PBRM1 and SS18). The resulting compromised SWI/SNF complex may still bind to chromatin but cannot form into specific cBAF/pBAF conformations [123]. This loss of catalytic activity is associated with a global upregulation of heterochromatin, triggering transcriptional shifts found to disrupt normal regulation of epithelial-mesenchymal transition (EMT), cell differentiation, cell cycle control and adhesion [83,92,123,124]. The proportion and severity of these changes is likely influenced by the cellular context and timing of SMARCA4/2 loss during cancer pathogenesis, a paradigm initially proposed by Rekhtman and colleagues (Fig. 4) [55].

In the case of NSCLC, it has been suggested that the loss of SMARCA4/2 may upregulate the epithelial-mesenchymal transition (EMT) and result in a highly malignant 'mesenchymal-like' phenotype [56]. Following on, the re-expression of functional *SMARCA4* in SCCOHT and SMARCA4/2-deficient NSCLC cell lines promoted an epithelial morphology and gene signature through SMARCA4-mediated enrichment of Activator Protein 1 (AP-1) transcription factor motifs on epithelial gene promoters [92]. Across SMARCA4/2-deficient tumors, mixed staining for epithelial markers (claudin-4, cytokeratin, E-cadherin, Epithelial membrane antigen (EMA) and Thyroid transcription factor-1 (TTF-1)) alongside positive staining for the mesenchymal marker vimentin has been reported, potentially supporting the presence of EMT in these cells (Fig. 4, Table S3) [39,45,50,56,84,91].

Stem cell fate determination, another cellular process marked by the transition of cell states, may also be dysregulated, and contributing to the acquisition of phenotypic plasticity in SMARCA4/2-deficient cells. In lung adenocarcinoma, *SMARCA4* inactivation appears to enrich an embryonic stem cell-like transcription factor program, effectively displacing lung lineage motifs [125]. Furthermore, across 27 solid tumor cohorts, significantly low levels of *SMARCA2* were associated with high cancer stemness as defined by the transcriptome-based stemness index (mRNA-SI) and its prevalence in dedifferentiated tumor variants [126]. Albeit not frequently tested, positive staining for stem cell markers SOX2, SALL4, or CD34 has been reported in SMARCA4/2-deficient SCCOHT, TSDUT and undifferentiated gastric carcinoma (Table S3) [45,50,55,59,71,91]. These specific markers are rarely positive in SMARCA4/2-deficient NSCLC, indicating the mechanisms and existence of cancer stemness in SMARCA4/2-deficient tumors may be subtype specific and not a universal trait (Fig. 4) [55].

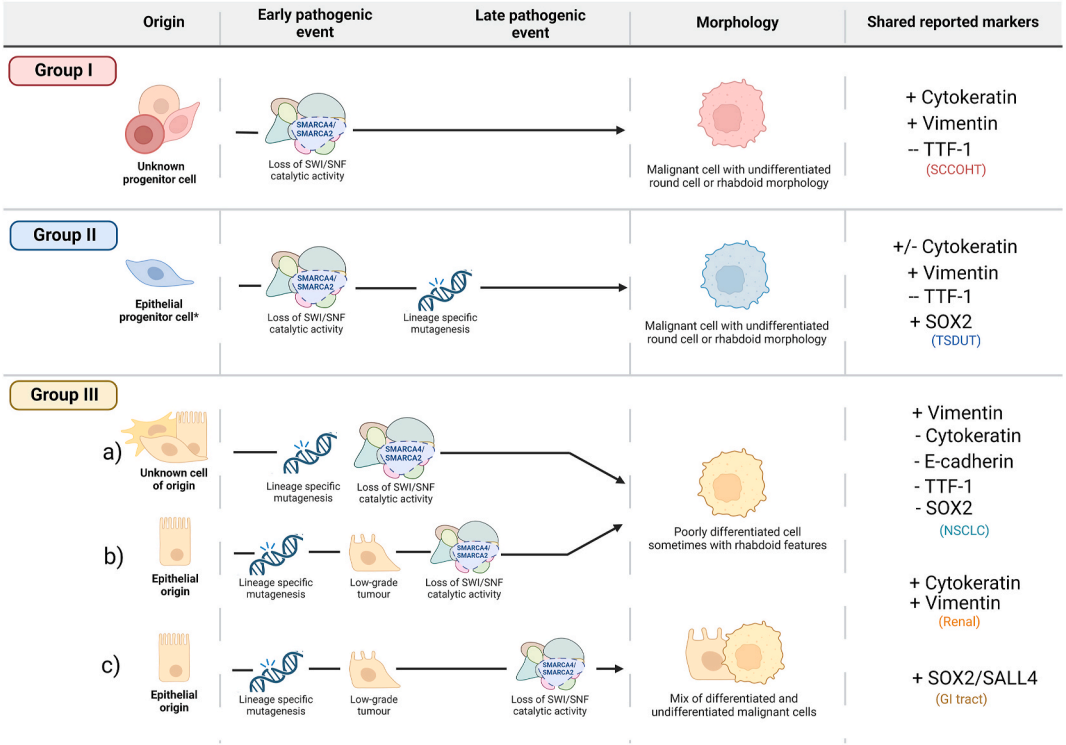

Fig. 4. Potential timelines of SMARCA4/2 loss during tumorigenesis of SMARCA4/2-deficient malignancies. Group I is defined as the early onset distinct subtypes. Group II is defined as the distinct middle-age onset subtype. Group III is defined as the later age onset of rare subtype anomalies. *The cell of origin for group II is not yet known but postulated to be an epithelial progenitor cell. Group III represents a diverse cluster of malignancies thus timing of SMARCA4/2 loss may vary. Three hypothetical timelines are presented based on (a) De Novo undifferentiated tumor, (b) An undifferentiated tumor originating from dedifferentiation of an epithelial cell (c) A dedifferentiated tumor originating from an epithelial cell and containing mixed differentiated and undifferentiated elements. SCCOHT: Small-cell carcinoma of the ovary, hypercalcemic type, TSDUT: Thoracic SMARCA4-deficient undifferentiated tumor, NSCLC: Non-small cell lung cancer, GI: Gastrointestinal. Renal: Undifferentiated renal carcinoma. TTF-1: Thyroid transcription factor-1 +: positive expression, - low expression, – negative expression. ± mixed expression. References for commonly reported markers are reported in Table S3. Created with BioRender.com.

In summary, amongst the genome-wide transcriptional changes following SMARCA4/2 loss, there is emerging evidence implicating EMT and abnormal stem cell differentiation as potential mechanisms behind the hallmark absence of well-differentiated cells in SMARCA4/2-deficient tumors. Both processes, which may have overlapping features, have been linked to provide increased proliferative, migratory, and invasive properties in cancer [106,127].

4. Targeting SMARCA4/2-deficient malignancies with molecular therapeutics

The strong resistance of SMARCA4/2-deficient tumors to standard platinum-based chemotherapy is likely driven by changes in gene expression following loss of SWI/SNF catalytic activity. In SCCOHT and NSCLC cells, the loss of SMARCA4/2 leads to inaccessibility of the *ITPR3* (Inositol 1,4,5-Trisphosphate Receptor Type 3) gene, inhibiting downstream expression and ultimately preventing the required intracellular mitochondrial Ca^{2+} flux for cisplatin-induced apoptosis [128,129]. In an effort to overcome the extensively rewired cellular signaling network, researchers have begun identifying targetable weak points exclusive to SMARCA4/2-deficient cells, predominantly in SCCOHT, which have been reviewed in detail by Tischkowitz et al. and Wens et al. [38,130]. Below, we have highlighted key investigative candidates alongside more recent findings which may be relevant to the application of molecular targeted therapy in SCCOHT and broader SMARCA4/2-negative malignancies.

4.1. Targeting the dysregulated epigenome: EZH2 and HDAC inhibitors

Chromatin remodeling factors lacking SMARCA4/2 are unable to evict polycomb occupancy, leading to the critical dependency of SMARCA4/2-deficient cells on PRC-mediated gene repression [112,130]. As a result, suppression of the H3K27 histone methyltransferase EZH2 is a well-established molecular target for SCCOHT, with EZH2 inhibitors eliciting a strong selective response in pre-clinical SCCOHT and other SMARCA4/2-deficient cell lines when compared to wild-type or cell lines with single ATPase subunit loss [111,112,130]. SCCOHT patients have been enlisted in phase I/II clinical trials for the EZH2 inhibitor tazmetostat (EPZ-6438), specifically NCT01897571 and NCT02601950. The latter study (NCT02601950) also investigated TSDUT and MRT, enrolling 11 SCCOHT, 10 TSDUT and 11 SMARCB1-deficient MRT patients. Notably, this trial failed stage 2 futility, which required confirmed partial response (PR) or complete response (CR) in $\geq$5 patients based on RECIST 1.1 criteria to assess tumor burden [131]. Two patients did report a PR, one TSDUT patient exhibited an ongoing response at 8 weeks, and a stage IV SCCOHT patient remained progression-free for 8 months [50,131]. In efforts to improve the efficacy of EZH2 inhibitors, researchers have proposed combination therapy with HDAC inhibitors based on pre-clinical evidence in SCCOHT and SMARCA4/2-deficient dedifferentiated ovarian cancer cells [121]. Further, the addition of HDAC inhibitors to platinum-based chemotherapy regimens may also be advantageous as they hold the capacity to restore *ITPR3* transcription in SCCOHT and SMARCA4/2-deficient NSCLC, subsequently enhancing cisplatin response [128].

4.2. Targeting vulnerabilities caused by changes in transcription: OXPHOS and CDK4/6 inhibitors

Concurrent SMARCA4/2 loss was recently shown to trigger significant downregulation of *SLC2A1* (Solute Carrier Family 2 Member 1), a gene coding for the key glucose transporter GLUT1, in SMARCA4/2-deficient SCCOHT, NSCLC and dedifferentiated ovarian cancer cell lines. The resulting cells underwent a metabolic shift and became highly reliant on oxidative phosphorylation (OXPHOS) and glutamine metabolism for energy production. This study proposed that the dietary supplementation of alanine, at doses within the approved range for diabetes treatment, may assist the metabolic starvation of SMARCA4/2-deficient cancers as alanine is the preferred target over glutamine for the critical alanine/glutamine transporter SLC38A2 (Solute Carrier Family 38 Member 2) [132]. In SCCOHT and NSCLC cells with SMARCA4 and/or SMARCA2 loss, cell cycle dysregulation has been identified from the suppression of the key regulator cyclin D1 (*CCND1*) to critically low levels as a consequence of impaired chromatin accessibility at the *CCND1* locus and downregulation of the transcription factor c-Jun [133,134]. This is a targetable vulnerability by CDK4/6 inhibition that is currently being assessed in the phase II Canadian Profiling and Targeted Agent Utilization Trial (NCT03297606).

4.3. Anecdotal evidence supports the use of immunotherapy in SCCOHT and TSDUT

Based on published case studies, immunotherapy, specifically the use of immune checkpoint blockade (ICB), appears to be the most promising available targeted therapy for SCCOHT and TSDUT [130,135–139]. In consequence, there are several clinical trials either ongoing (NCT04602377, NCT02834013, NCT05368207) or recently concluded (NCT03012620) with results not yet published that investigate pembrolizumab or a combination of nivolumab and ipilimumab in SCCOHT patients. Despite exhibiting low tumor mutational burden, SCCOHT tumors appear relatively responsive to ICB due to strong PD-L1 expression and T-cell infiltration, likely due to transcriptional changes [139]. It is unclear whether this may be a universal consequence of SMARCA4/2 loss or specific to SCCOHT, as the rationale for the effect seen in TSDUT is its high tumor mutational burden and PD-L1 expression [138]. There are reports supporting potential survival benefit in related cancers such as SMARCB1-deficient MRT and SMARCA4-deficient NSCLC, however, corresponding SMARCA2 expression status is not evaluated [108,140]. Interestingly, two patients with SCCOHT have reported significant survival benefit from the combined use of CDK4/6 inhibition with ICB, remaining stable at the time of publication 3- and 5-years post diagnosis with extensive disease [136,137]. Inhibition of CDK4 and CDK6 may increase tumor immunogenicity, thus eliciting strong synergy when paired with ICB, providing favorable evidence for the use of this combined targeted therapy [137].

5. Concluding remarks

The concurrent absence of SMARCA4/2 represents a distinctive molecular hallmark that is primarily reported in rare and aggressive tumors with poor differentiation, the most common being SCCOHT. We have categorized SMARCA4/2-deficient malignancies into three groups based on clinical and molecular features, including the recognition of SMARCA4/2 loss as a pathognomonic feature in a defined subtype, age of onset and genetic background. The distinct presentations of these groups likely reflect differences in cell of origin and timing of SMARCA4/2 loss during cancer development, however, this is currently an area of ambiguity. Irrespective of grouping, SMARCA4/2-negative tumors appear to lose *SMARCA4 via* mutations that lead to a premature protein truncation, with germline mutations present in a subset of SCCOHT/MRT cases. The mechanisms driving the loss of *SMARCA2* transcription in these tumors are less clear. Overexpression of PRC2 has been linked to modulation of *SMARCA2* expression in SMARCA4/2-deficient ovarian, lung and gastric tumors. Further, HDAC dysfunction has been identified in SCCOHT and several SMARCA2-negative cancers, whereas *SMARCA2* promoter hypermethylation and polymorphisms have only been investigated in the latter. The loss of SMARCA4/2, whether as an initial driver event or at a later stage in disease progression, yields an undifferentiated phenotype, with early evidence suggesting this may be driven by EMT and/or impaired stem cell differentiation in some tumors. From the perspective of precision oncology, it is likely that there are mutual vulnerabilities amongst

SMARCA4/2-deficient cancers driven by a shared dysfunctional epigenome. Current key investigative compounds, predominantly reported for SCCOHT and including, epigenetic inhibitors (EZH2 and HDAC inhibitors), and additional targeted therapies (OXPHOS metabolic pathways, CDK4/6 inhibitors, and immunotherapy), may have broader application for other SMARCA4/2-deficient cancers. Despite these advances, prognosis remains poor for these rare and aggressive malignancies and further investigation into their underlying mechanisms and potential novel vulnerabilities is warranted.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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