Review

SMARCB1 Deficiency as a Driver of the Hallmarks of Cancer in Rhabdoid Tumours: Novel Insights into Dysregulated Energy Metabolism, Emerging Targets, and Ongoing Clinical Trials

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Review

SMARCB1 Deficiency as a Driver of the Hallmarks of Cancer in Rhabdoid Tumours: Novel Insights into Dysregulated Energy Metabolism, Emerging Targets, and Ongoing Clinical Trials

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Abstract: Rhabdoid tumours (RTs) are aggressive neoplasms most often characterised by biallelic loss of the SMARCB1 gene, which encodes a core subunit of the SWI/SNF chromatin remodelling complex. Despite their relative genetic stability, RTs exhibit a highly malignant phenotype and poor prognosis. This review aims to explore the mechanisms underlying SMARCB1 aberrations, their role in driving hallmarks of cancer, and emerging therapeutic strategies for RTs. The loss of SMARCB1 drives multiple cancer hallmarks by disrupting key regulatory pathways. It promotes unchecked cell proliferation through alterations in p16INK4a and Myc signalling. SMARCB1-deficient tumours possess immune evading capabilities via PD-L1 overexpression and immune checkpoint activation. SMARCB1 deficiency also alters cellular energetics by various mechanisms. The nucleotide biosynthesis pathway has been demonstrated to be upregulated in RT organoids, as shown by increased levels of pathway metabolites. Enzymes of the mevalonate pathway such as HMG-CoA reductase and mevalonate kinase are also dysregulated. Targeting glutathione metabolism with eprenetapopt may result in oxidative stress and induce apoptosis in RTs. Widespread epigenetic aberrations, including increased EZH2 activity, are being targeted with inhibitors such as tazemetostat. Future horizons in RT treatment include immunotherapies, epigenetic modifiers, and gene therapies. The synergy and optimal timing of targeted therapy with conventional treatment needs to be better characterised in order to proceed to later stage clinical trials and clinical practice.

Keywords: rhabdoid tumours; SMARCB1 deficiency; hallmarks of cancer; energy metabolism; targeted therapy

Introduction

The SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) gene is located on chromosome 22q11.2 and encodes a core subunit of the ATP-dependent SWI/SNF complex [1]. It is involved in chromatin remodelling and regulation of gene expression. Loss of the SMARCB1 has been linked to various neoplasms, including rhabdoid tumours (RT), epithelioid sarcoma, and renal medullary carcinoma [2]. RTs are rare neoplasms which typically present in the paediatric population before the age of 3 [3]. They have been described in nearly all anatomical locations, and are divided into those located intracranially, most commonly in the cerebellum [4], or extracranially in organs such as the kidney, gastrointestinal track, or liver [5]. Apart from the frequent biallelic loss of SMARCB1, RTs are considered relatively genetically stable, despite their highly aggressive phenotype [6]. Germline mutations also predispose patients to various malignancies in a condition known as rhabdoid tumour predisposition syndrome [7]. Loss of SMARCB1 promotes cancer through various pathways (Figure 1), which will be described in more detail in this review. This article will also serve to discuss the mechanisms by which aberrations of the SMARCB1 gene occur, their implications in driving the various hallmarks of cancer, and provide an overview of the novel therapeutic approaches in clinical trials for treatment of RT.

The SMARCB1 gene extends over 50 kilobases and its peptide sequence is encoded by nine exons [8]. The encoded protein has a molecular weight of 47kDa with a length of 385 amino acids. It is composed of 4 domains, including 2

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highly conserved tandem repeat 1 and 2 domains (RPT1/2), flanked by the N-terminal Winged Helix DNA binding domain and the C-terminal coiled-coil domain (CTD). Data derived from COSMIC v95 revealed 815 alterations in the SMARCB1 gene, largely clustered at the CTD. The majority of mutations (49.33%) were missense, followed by frameshift mutations (20.12%) and nonsense mutations (19.88%). Silent and inframe mutations accounted for approximately 10% of genetic aberrations [2].

Confirmation of the role of SMARCB1 as a tumour suppressor gene (TSG) arose when conditional gene knockout in adult mice resulted in CD8+ mature lymphoma and fully penetrant cancer formation [9]. Later studies were also able to produce RTs by inducing SMARCB1 deletion in earlier stages of embryonic development [10]. While complete loss-of-function of SMARCB1 is the best characterised genetic mutation in RT, some cases are associated with cytoplasmic localisation of the C-terminal truncated version of the gene, compromising its ability to exert its biological functions in the nucleus. Exportin 1 is thought to be responsible for this abnormal localisation through its interaction with the RPT2 domain of SMARCB1. As a result, nuclear export inhibitors such as leptomycin B and selinexor may be effective in these cases [11]. However, clinical efficacy is yet to be established [12].

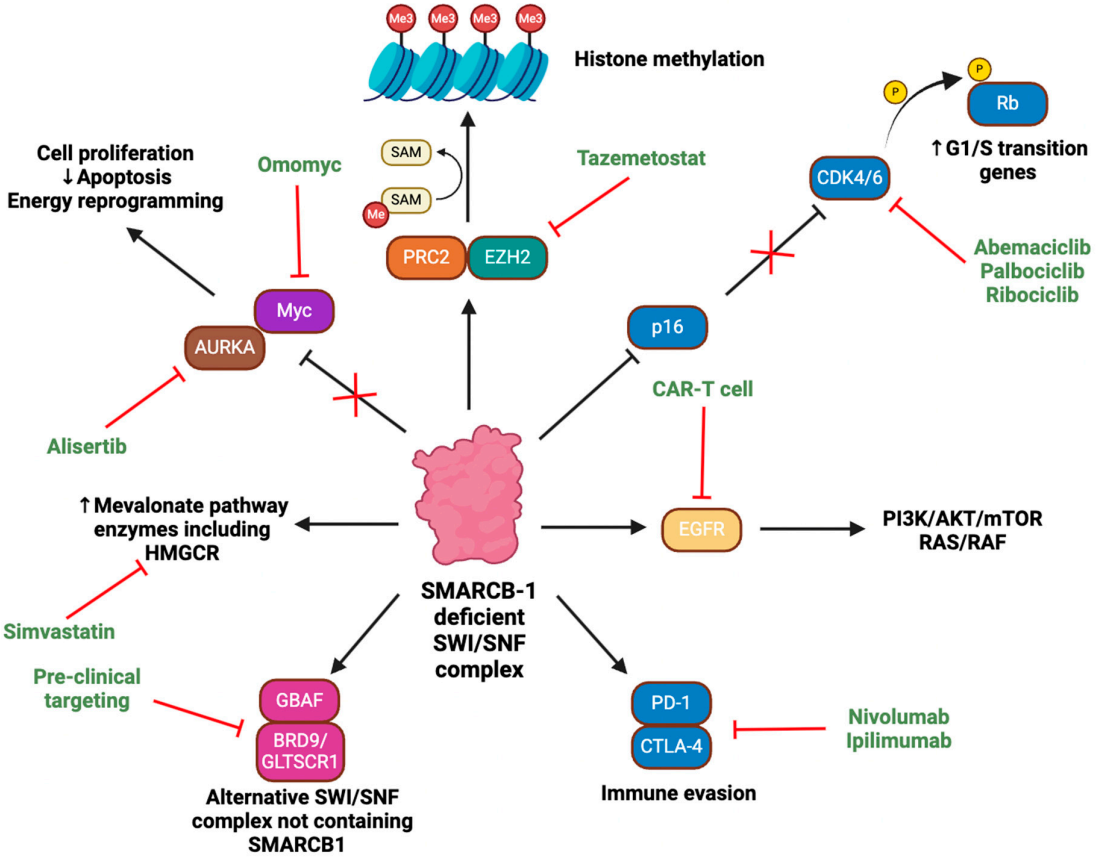

Figure 1. Aberrant pathways induced by SMARCB1 deficiency and corresponding therapeutic targets. 'PRC2' denotes polycomb repressive complex 2, 'AURKA' Aurora Kinase A, 'EGFR' epidermal growth factor receptor, 'BRD9' bromodomain-containing protein 9, 'GLTSCR1' glioma tumour suppressor candidate region gene 1, 'Rb' retinoblastoma, 'CDK4/6' cyclin-dependent kinase 4/6, 'HMGCR' HMG-CoA reductase. Figure created using BioRender.

Driver of the Hallmarks of Cancer

The hallmarks of cancer were introduced by Hanahan and Weinberg in 2000, and were later expanded in 2011 and 2022 [13–15]. They describe a set of capabilities acquired by human cells during the carcinogenic process, and provide a systematic structure for studying cancer, designing therapeutic targets, and guiding experimental models. Figure 2 summarises the role of SMARCB1 loss as a driver of the hallmarks of cancer in RTs.

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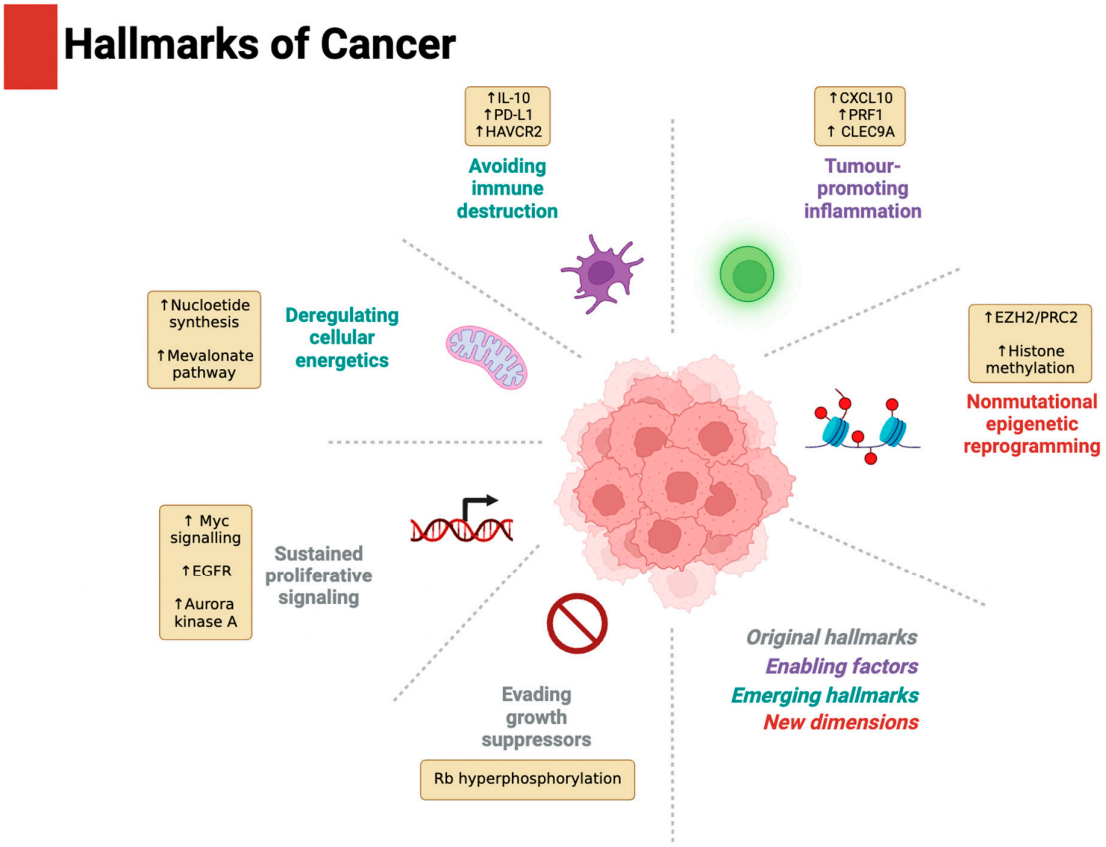

Figure 2. A summary of the role of SMARCB1 deficiency as a driver of the hallmarks of cancer in RT. The upregulation of nucleotide synthesis has yet to be confirmed as a causal outcome of SMARCB1 deficiency. Figure created using BioRender.

Evading Growth Suppressors and Sustaining Proliferative Signalling

SMARCB1 has been shown to regulate the $p16^{INK4a}$ cyclin-dependent kinase (CDK) inhibitor which prevents the activation of the CDK4/6-cyclin D1 complex, responsible for Rb protein phosphorylation and hence the transcription of genes associated with G1/S phase progression [16]. Weissmiller and colleagues found that SNF5 encoded by SMARCB1 inhibits the DNA-binding ability of Myc, impeding its ability to recognise target genes. Further-supporting these findings, the reintroduction of SNF5 into SMARCB1-null cells mimicked the primary transcriptional effects of MYC inhibition [17]. Myc is a helix-loop-helix transcription factor that is one of the best-described drivers of cell proliferation [18]. As a heterodimer with MAX, it regulates the expression of various genes involved in cell-cycle regulation, apoptosis, angiogenesis and cell metabolism [19–21]. OmoMYC (OMO-103) is a drug that targets Myc signalling by binding to c- and n-Myc, Max, and Miz1 and was shown to reduce RT cell viability in in-vitro studies [17].

Another implicated oncogene is the epidermal growth factor receptor (EGFR), where a phosphoproteomic study highlighted its abnormal expression in RT and that its inhibition hinders cell proliferation [22]. Overexpression of Aurora kinase A (AURKA) has been described as a result of SMARCB1 deficiency, which plays a key role in mitotic division and cell survival. Its targeting is also being investigated in clinical trials [23]. CAR-T cell targeting of glypican 3 (GPC3), an over-expressed membrane-bound proteoglycan which regulates cell growth and apoptosis [24], is subject to various ongoing clinical trials (NCT05103631, NCT04715191, NCT04377932) [25–27].

The use of small molecules aimed at recovering the lost function of TSGs in malignancy poses significant challenges, and many tumour suppressors are considered "undruggable" for this reason [28]. Synthetic lethal relationships therefore provide a promising approach for the targeting of such genetic abnormalities [29]. *Radko-Juettner et al* in 2024 showed through a genome-wide CRISPR screen that the DDB1-CUL4-associated factor 5 (DCAF5) gene, which functions as substrate receptor for E3-ubiquitin ligase, is required for the survival of SMARCB1-mutated RTs. In

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addition, depletion of DCAF5 allowed SWI/SNF to reaccumulate and restored histone marks such as H3K27ac and H3K4me1 at active enhancers, normalising cellular differentiation and reversing the cancer phenotype. These results suggest that SMARCB1 mutation leads to the destabilisation of the SWI/SNF complexes, which are subsequently cleared by the ubiquitin quality control pathway, in order to keep malignant cells viable [30]. As such, targeting of DCAF5 may serve as a potential novel therapeutic approach in the treatment of RTs [31].

Tumour-Promoting Inflammation and Avoiding Immune Destruction

The microenvironment of certain subsets of RTs has been shown to be highly inflammatory and to express a high level of genes involved in CD8+ T cell activation, homing, and tumour infiltration such as CXCL10, PRF1, and CLEC9A. Yet, RTs deploy various survival mechanisms that allow them to thrive in such a hostile environment. Immunohistochemistry of RT revealed overexpression of IL-10, programmed death ligand 1 (PD-L1), PD-L1-expressing CD68+ myeloid cells, as well as other immune checkpoint proteins such as HAVCR2 [32]. One study found that in samples of 30 paediatric RTs, 47% stained positive for PD-L1 expression, and therefore may benefit from immune checkpoint inhibitors [33]. It is therefore no surprise that various clinical trials are currently examining the efficacy of a multitude of immune checkpoint inhibitors in the treatment of RTs (Table 1).

Deregulating Cellular Energetics

An emerging metabolic target in SMARCB1-deficient tumours is the cholesterol biosynthetic pathway (Figure 3). Cholesterol plays a key role in the tumoural immune response by regulating the function of various immune cells, including dendritic cells, $CD8^+$ T lymphocytes, NK cells, and γδ T cells [34]. One metabolite in the cholesterol biosynthetic pathway, isopentenyl pyrophosphate (IPP), regulates the activity of glutathione peroxidase 4 (GPX4), which inhibits ferroptosis to promote cancer cell survival [35]. In addition, cholesterol contributes to the maintenance of cancer stem cells by activating downstream of several developmental signalling pathways, including Hedgehog and Notch [36]. In a newly established RT cell line it was found that restoration of SMARCB1 significantly downregulated the expression of enzymes such as HMG-CoA reductase (HMGCR) and mevalonate kinase, and that the frequently prescribed cholesterol-lowering drug simvastatin induced apoptosis in RT cells [37]. A phase I study (NCT02390843) of simvastatin in combination with topotecan and cyclophosphamide in relapsed and/or refractory paediatric patients with solid and central nervous system (CNS) tumours including RTs has since been carried out, and found that the combination was well-tolerated [38].

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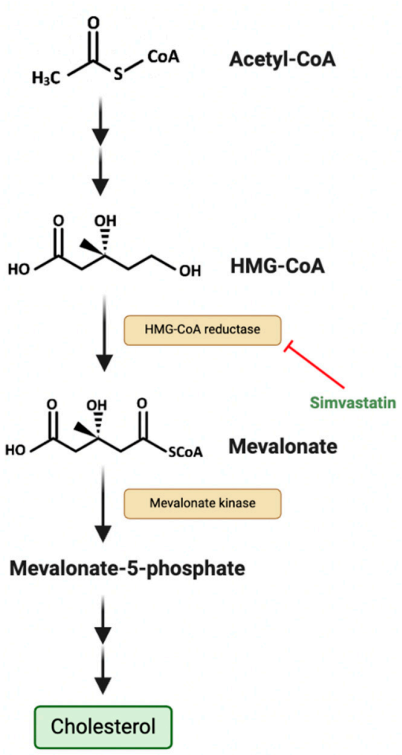

Figure 3. The mevalonate pathway, highlighting the inhibition of HMG-CoA reductase using simvastatin. 'HMG-CoA' denotes β-Hydroxy β-methylglutaryl-CoA. Figure created using BioRender.

A recent study by Kes and colleagues used patient-derived organoids to investigate the metabolic vulnerabilities of RT [39]. Gene expression analysis and liquid chromatography-mass spectrometry revealed that de novo nucleotide biosynthesis is significantly upregulated in RT, as demonstrated by the increased levels of metabolites such as uridine monophosphate (UMP) and inosine monophosphate (IMP). Pharmacological inhibition (Figure 4) using methotrexate and BAY-2402234, targeting purine and pyrimidine synthesis pathways respectively, resulted in significant cytotoxic effects in RT tumoroids while sparing normal kidney organoids. Further in vivo validation in RT xenograft mouse models demonstrated that methotrexate treatment delayed tumour progression [39]. While the direct link between these metabolic aberrations and SMARCB1 loss has not been confirmed, SMARCB1 loss is likely to be indirectly or directly causal given that it is the defining driver of RTs. Further research into the precise role of SMARCB1 deficiency as a driver of nucleotide synthesis may yield novel therapeutic targets and enhance the understanding of the pathogenesis of the disease.

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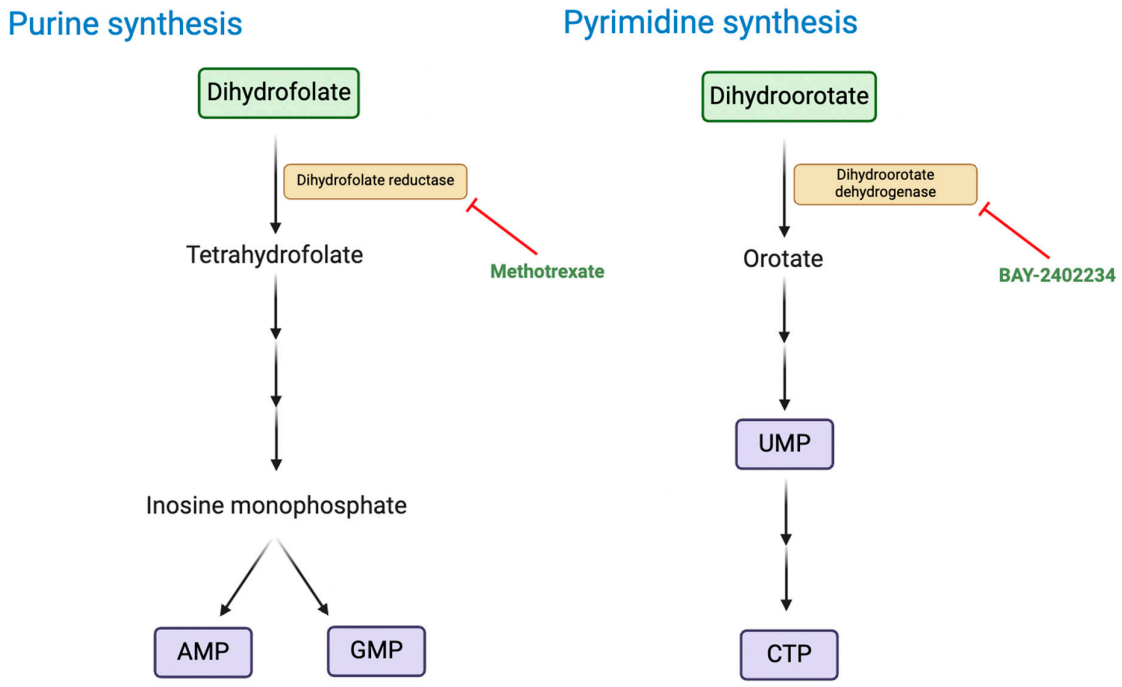

Figure 4. The nucleotide biosynthetic pathway as a potential metabolic vulnerability in RT. 'AMP' denotes adenosine monophosphate, 'GMP' guanine monophosphate, 'UMP' uridine monophosphate, 'CTP' cytidine triphosphate. Figure created using BioRender.

Non-Mutational Epigenetic Reprogramming

Widespread transcriptional dysregulation and aberrant chromatin-remodelling is known to occur as a result of SMARCB1 loss in RT [40]. In mouse embryonic fibroblasts, SMARCB1 deletion resulted in decreased levels of active histone markers H3K27ac and H3Kme1 at enhancers [41]. The action of the polycomb repressive complex 2 (PRC2), whose catalytic subunit EZH2 contains histone methyltransferase activity, is opposed by the SWI/SNF complex. As a result, SMARCB1 mutation is associated with uncontrolled PRC2-mediated inhibition of BAF target genes. Tazemetostat, an inhibitor of EZH2, has received FDA approval for treatment of SMARCB1-deficient epithelioid sarcoma [42], and trials for other malignancies including RT are ongoing. In the absence of SMARCB1, RT cells upregulate GBAF expression, a SWI/SNF subcomplex which does not contain the SMARCB1 subunit. GBAF's subunits BRD9 and GLTSCR1 are proposed drug targets, and their degradation or inhibition has been shown to reduce viability of RT cell lines [43]. SMARCB1-deficiency also prevents the recruitment of cBAF and PBAF to the promoter and enhancer regions of SLC7A11, which plays a crucial role in glutathione metabolism by supplying cysteine for glutathione synthesis. Treatment with eprenetapopt has been shown to further-decrease glutathione levels, resulting in oxidative stress and apoptosis [44].

It has recently been demonstrated that in SMARCB1-deficient cells, CBP/p300-mediated H3K27 acetylation promotes the expression of Kringle containing transmembrane protein 2 (*KREMEN2)* [45], encoding a protein which complexes with KREMEN1 to regulate the Wnt/β catenin pathway [46] and inhibit apoptosis [47]. SMARCB1-deficient cells subsequently become dependent on KREMEN2 for survival. Dual inhibitors of CBP/p300 have been shown to suppress growth and induce apoptosis in cell lines and xenograft models of SMARCB1-deficient cells but not SMARCB1-expressing cells [45]. This serves as another example of synthetic lethal vulnerabilities in SMARCB-1 deficient RTs, which are highlighted in Figure 5.

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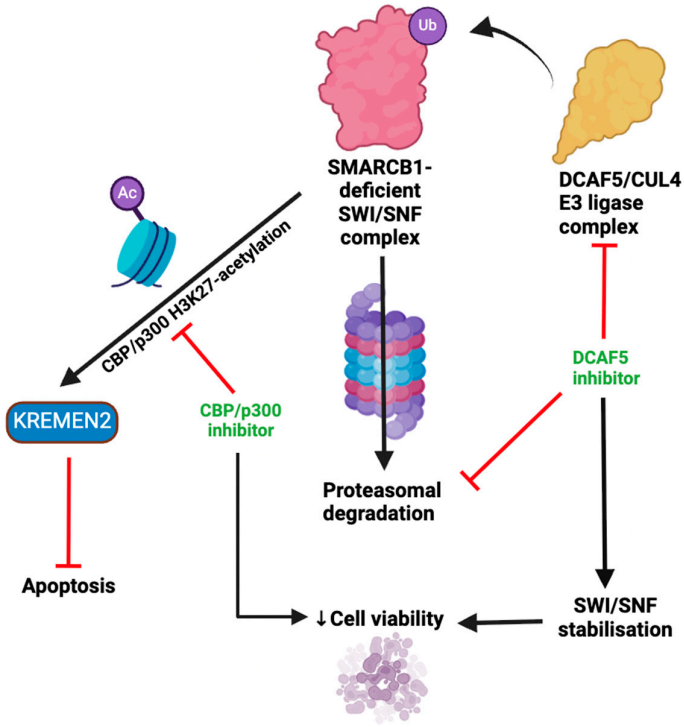

Figure 5. Synthetic lethal vulnerabilities in RTs. In SMARCB1-deficient cells, SMARCB1-deficient SWI/SNF complexes are targeted for ubiquitination and proteasomal degradation by the DCAF5/CUL4 E3 ligase complex. Inhibition of DCAF5 stabilises these defective SWI/SNF complexes, leading to toxic accumulation and loss of cell viability. In addition, CBP/p300-mediated H3K27 acetylation upregulates KREMEN2 expression, which suppresses apoptosis and promotes cell survival. Inhibition of CBP/p300 reduces KREMEN2 levels, promoting apoptosis. Figure created using BioRender.

Ongoing Trials and Future Direction

Immunotherapies

Immune checkpoint proteins (ICPs) are molecules which control the activation of T lymphocytes, a mechanism employed by the body in order to limit the indiscriminate killing of healthy tissues [48]. Various ICPs have been discovered to date, the most notable being PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). PD-1 on T cells binds to PD-L1 expressed on tumour cells and antigen-presenting cells to suppress T-cell proliferation, activity, and cytokine production [49]. CTLA-4 competes with CD28 for the binding of co-stimulatory molecules CD80/86 [50]. A more recently discovered ICP is T cell immunoreceptor with Ig and ITIM domains (TIGIT) which inhibits T and NK cell activation through interaction with CD155 [51].

Immune checkpoint inhibitors (ICIs) have been hailed as exciting anti-cancer therapeutics in the last few decades. Single-agent inhibition of PD-1 or PD-L1 in adults has demonstrated promising activity in various solid tumours. However, in the paediatric population, efficacy with mono-blockade has been limited to just a few tumours, particularly lymphomas [52]. Various ongoing clinical trials are therefore investigating the efficacy of combinations of ICIs in the treatment of SMARCB-1 deficient RTs. A phase II trial (NCT04416568) is currently recruiting patients to investigate the combination of nivolumab (anti-PD1) with ipilimumab (anti-CTLA4) in children and young adults with SMARCB1-deficient tumours, including RTs, epithelioid sarcomas, and chordomas [53]. In mouse models of solid tumours, co-blockade of both PD-L1 and TIGIT has been shown to promote the clonal expansion of multipotent anti-tumoural T lymphocytes [54]. Inhibition of PD-L1 and TIGIT through atezolizumab and tiragolumab respectively is subject to a phase I/II clinical trial for the treatment of relapsed or refractory SMARCB1- or SMARCA4-deficient tumours [55]. Another proposed mechanism of enhancing ICI efficacy is through simultaneous inhibition of EZH2, a histone methyltransferase which has been shown to suppress MHC-I presentation and upregulate PD-L1 [56]. TAZNI

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(NCT05407441) is a phase I/II study recruiting to evaluate the combination of an EZH2 inhibitor, tazemetostat, with nivolumab and ipilimumab for SMARCA4/SMARCB-1 deficient paediatric malignancies [57].

Chimeric antigen receptor T (CAR-T) cells are genetically engineered T lymphocytes that express synthetic receptors designed to specifically recognise and bind target antigens on tumour cells [58]. This results in the activation of intracellular signalling domains such as CD3ζ, 4-1BB, or CD28 to elicit cancer cytotoxicity [59]. Multiple CAR-T cell strategies are being investigated for RTs (Table 2). CAR-T cells are often targeted against over-expressed tumour antigens, such as GPC3 in the case of solid tumours including RTs. These trials (NCT05103631, NCT04715191, NCT04377932) are investigating the use of IL-15/21 to enhance CAR-T cell efficacy and persistence [25–27]. CAR-T cells may also serve as ICIs. For example, several trials (NCT05835687, NCT04897321) are exploring the targeting of B7-H3, a transmembrane immunoregulatory protein, by CAR-T cells for the treatment of solid.

Table 1. Active clinical trials utilising immune checkpoint inhibitors to target RTs. At the top of the list are the latest trials to be entered to clinicaltrials.gov..

Trial number	Phase	SMARCB-1 targeting therapies	Disorder	Target	Status	Sites	Primary outcome measures
NCT06622941 [60]	II	Nivolumab (ONO-4538)	RT	PD-1	Not yet recruiting	Osaka and Tokyo, Japan.	Objective response rate
NCT05407441 [57]	I/II	Tazemetostat, nivolumab, ipilimumab.	SMARCB1 negative or SMARCA4-deficient tumours including RT	EZH2, PD-1, CTLA-4	Recruiting	Boston, USA.	Toxicity and dosing parameters
NCT05286801 [55]	I/II	Tiragolumab and Atezolizumab	SMARCB1 or SMARCA4 deficient tumours including RT	TIGIT, PD-L1	Recruiting	USA, Canada, and Australia.	Objective response rate and dose-limiting toxicities
NCT04416568 [53]	II	Nivolumab and Ipilimumab	SMARCB1-negative tumours	PD-1, CTLA-4	Recruiting	Texas, USA.	Objective overall response rate

Table 2. Active clinical trials utilising CAR-T cells and cytotoxic lymphocytes against RTs..

Trial number	Phase	SMARCB-1 targeting therapies	Disorder	Target	Status	Sites	Primary outcome measures
NCT06193759 [61]	I	Cytotoxic T lymphocytes directed against proteogenomically determined tumour-specific antigens	Paediatric brain tumours, including RT.	Various tumour-specific antigens	Recruiting	Washington, USA.	Various adverse event and toxicity parameters
NCT05835687 [62]	I	Locoregional autologous B7-H3-CAR T cells	Primary CNS neoplasms including RT	B7-H3-positive tumours	Recruiting	Tennessee, USA.	Maximum tolerated dose
NCT05103631 [25]	I	GPC3-CART cells and IL-15	Solid tumours including RT	GPC3-positive tumours	Recruiting	Texas, USA.	Dose-limiting toxicities
NCT04897321 [63]	I	Autologous B7-H3-CAR T cells	Solid tumours including RT	B7-H3-positive tumours	Recruiting	Tennessee, USA.	Maximum tolerated dose
NCT04715191 [26]	I	GPC3-CART cells and IL-15/21	Paediatric solid tumours including RT	GPC3-positive tumours	Recruiting	Texas, USA.	Dose-limiting toxicities
NCT04377932 [27]	I	GPC3-CART cells and IL-15	Paediatric solid tumours including RT	GPC3-positive tumours	Recruiting	Texas, USA.	Dose-limiting toxicities
NCT04185038 [64]	I	Locoregional autologous B7-H3-CAR T cells	Paediatric CNS tumours including RTs	B7-H3-positive tumours	Recruiting	Washington, USA.	Feasibility and adverse event parameters
NCT03618381 [65]	I	EGFR806 CAR T Cell Immunotherapy	Recurrent/refractory solid tumours in children and young adults including RT	EGFR	Recruiting	Washington, USA.	Maximum tolerated dose, feasibility, and adverse event parameters.
NCT04483778 [66]	I	B7-H3-CAR T cells	Recurrent/refractory solid tumours in children and young adults including RT	B7-H3-positive tumours	Active, not recruiting	Washington, USA.	Various safety, tolerability, toxicity, and feasibility parameters

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Targeting Epigenetic Aberrations

The role of epigenetics in cancer development and progression has been spotlighted as a key area of interest in recent years. In 2024, an article by Esteller and colleagues proposed the concept of six potentially targetable epigenetic hallmarks of cancer [67]. Epigenetic therapies in cancer aim to modify aberrant epigenetic patterns, such as DNA methylation, histone modifications, and chromatin remodelling [68]. The phase I study of tazemetostat, which targets the PRC2 catalytic subunit EZH2, (NCT02601937) included paediatric patients with relapsed or refractory RTs, other SMARCB1-deficient tumours, and synovial sarcoma [69]. Objective responses were seen in 14% of the dose expansion cohort population, with a 24% response in intracerebral RT patients [70].

Vorinostat is an agent which inhibits the activity of histone deacetylases [71]. A phase I trial (NCT01076530) investigated the combination of vorinostat with temozolomide for the treatment of relapsed/refractory paediatric CNS tumours [72]. 19 patients were recruited including two with rhabdoid tumours. Clinical efficacy was modest, with only three patients exhibiting stable disease and one having a partial response. Nevertheless, the combination was well-tolerated and myelosuppression was identified as the dose-limiting toxicity. It was also noted that accumulation of acetylated H3 histone in peripheral blood mononuclear cells occurred following administration of vorinostat [73]. While clinical utility with epigenetic targeting appears limited thus far, it remains a relatively novel field of cancer research. Future studies focused on identifying predictive biomarkers and exploring synergistic combinations may improve outcomes.

Targeting Auxiliary Oncogenic Aberrations

AURKA plays a pivotal role in mitotic spindle formation and its overexpression has implicated in various malignancies including RTs [74,75]. A phase II clinical trial evaluated alisertib, an AURKA inhibitor, as monotherapy in patients under 22 years with recurrent or progressive atypical teratoid rhabdoid tumours (ATRTs). The study did not meet its primary efficacy endpoint of ≥10 patients progression-free at 12 weeks. However, alisertib was found to be well-tolerated with a 6-month progression-free survival (PFS) of 31%±8.2%. A third of patients also demonstrated disease stabilisation beyond 6 months [76]. Mutations leading to truncated SMARCB1 can result in its exportin-1-mediated mislocalisation in the cytoplasm and hence loss of tumour suppressive capacity. A Phase I trial for paediatric patients with recurrent/refractory solid and CNS tumours established the maximal tolerated dose and recommended a phase II (NCT05985161) starting dose of 35 mg/m² for patients with recurrent/progressive ATRTs [76,77]. The proteins CDK4/6 are crucial for cell cycle progression. A phase I trial of CDK4/6 inhibitor ribociclib in paediatric patients with RTs, neuroblastoma, and other solid tumours showed acceptable safety and prolonged stable disease in a subset of patients [78]. A phase II study is currently recruiting to assess the efficacy of ribociclib with topotecan and temozolomide in paediatric patients with relapsed or refractory neuroblastoma and solid tumours including RTs [79]. Table 3 provides an overview of the active clinical trials targeting aberrations in the cell cycle (CDK4/6) and the dysregulated nuclear export of SMARCB1 (exportin-1). Future efforts should attempt to identify predictive biomarkers to stratify patients most likely to benefit from inhibitors of these auxiliary oncogenic aberrations.

Table 3. Clinical trials targeting the cell cycle checkpoint control, the dysregulated nuclear export of SMARCB1, and Aurora kinase A.

Trial number	Phase	SMARCB-1 targeting therapies	Disorder	Target	Status	Sites	Primary outcome measures
NCT05985161 [80]	II	Selinexor	Solid tumours including RT	Exportin-1	Recruiting	Various USA sites.	Complete and partial response
NCT05429502 [79]	I/II	Ribociclib	Solid tumours including RT	CDK4/6	Recruiting	USA, UK, Spain, Singapore, Italy, Germany, France, and Australia.	Overall response rate and dose-limiting toxicities
NCT03709680 [81]	I/II	Palbociclib	Recurrent/refractory solid tumours including RT	CDK4/6	Active, not recruiting	> 10 countries including USA, UK, Brazil, and Korea.	Event-free survival, first cycle dose-limiting toxicities, frequency of adverse events, complete response or partial response

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Gene therapy holds promise as a potential approach to treating cancers through the modification or restoration of gene expression [82]. A study published by Kim et al in 2024 explored the use of scL-SMARCB1, a nanomedicine used to deliver wild type SMARCB1 into ATRT cells via transferrin receptor-mediated endocytosis [83]. scL-SMARCB1 therapy was found to upregulate the expression of MYC-repressed genes such as CDKN1C and CDKN2A, while down-regulating MYC-activated genes. AURKA expression was also significantly suppressed. It was also found that transfection with SMARCB1 potentiated cytotoxicity induced by cisplatin and radiation therapy [83]. This highlights how genetic therapy may not only restore biological markers in rhabdoid tumours, but can also enhance their sensitivity to conventional chemoradiation. This may have potential to increase therapeutic efficacy and limit toxicity to healthy tissue.

Artificial intelligence (AI) may serve as a powerful tool for analysing complex genomic data in order to identify new therapeutic indications for drugs. One study has described the application of the Response Algorithm for Drug Positioning and Rescue (RADR®) AI platform, combined with the CellMiner Cross Database, in uncovering novel therapeutic insights for the acylfulvene derivative anti-cancer drugs LP-100 and LP-184 [84]. Gene set enrichment analysis (GSEA) revealed a significant negative correlation between LP-184 sensitivity and SMARCB1 expression. These computational findings were then validated in SMARCB1-deficient ATRT cell lines and through in vivo experiments [84]. This demonstrates the utility of AI-driven platforms in rapidly identifying novel therapeutic indications for drugs. Such approach may especially be useful for rarer cancers such as SMARCB1-deficient rhabdoid malignancies, which tend to have relatively limited specific research focus.

The discussed trials and future innovations highlight how personalised therapies based on genomic, metabolomic, and immunological profiling have the potential to be the mainstay of RT treatment and disease monitoring. Emerging evidence also highlights the importance of metabolic reprogramming in RTs, with pathways such as cholesterol biosynthesis and nucleotide metabolism presenting novel therapeutic vulnerabilities. Integrating metabolomic profiling into future studies may uncover additional biomarkers and enable the development of metabolism-targeted therapies in SMARCB1-deficient tumours. Identifying subsets of patients who are most likely to respond to the various treatments will be crucial. The effects, optimal timing, and integration of combination of SMARCB1 targeted treatments with conventional therapies must be better characterised in order to enhance patient outcomes and allow incorporation into later phase clinical trials and clinical practice. Additional research and genomic analysis is required to further-elucidate the role of SMARCB1 in tumour-suppression and to identify additional molecular targets.

Conflicts of interest: The authors declare that they have no conflicts of interest regarding the publication of this review.

Author Contributions: Abdul L Shakerdi: writing original draft, figure design. Graham P Pidgeon: conceptualisation, writing original draft, correcting drafts.

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