SMARCB1 in the Pathobiology of Epithelioid Sarcoma

Subjects: Pathology

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SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1) is a key component of the SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeling complexes. Functional inactivation of SMARCB1 is the only recurrent genetic alteration reported in so far in Epithelioid Sarcoma (ES), a very rare and aggressive mesenchymal tumor of unclear origin and uncertain lineage characterized by a prevalent epithelioid morphology.

SMARCB1 soft tissue sarcoma epithelioid sarcoma SWI/SNF PRC2 tazemetostat

1. Introduction

Epithelioid sarcoma (ES) is a very rare (incidence ~0.02–0.05/100,000) mesenchymal tumor characterized by a prevalent epithelioid morphology [1]. It primarily affects adolescents and young adults, accounting for less than 1% of all sarcomas in adults and 4–8% of pediatric non-rhabdomyosarcomatous sarcomas [2][3]. ES is an aggressive tumor, with a high rate of recurrences (from 15% to 60% in different series) and 30–50% of the cases metastasizing at distal sites [4][5][6][7][8][9][10][11][12][13]. A molecular hallmark of ES is the loss of SMARCB1 protein expression.

2. SMARCB1 inactivation in the pathogenesis of Epithelioid Sarcoma

SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1), a.k.a. INI1 (Integrase Interactor 1), is a subunit of the mammalian SWI/SNF (SWItch/Sucrose Non-Fermentable) ATP-dependent chromatin remodeling complexes, also known as BAF (BRG1/BRM-associated factor) complexes. These complexes are central regulators of nucleosome remodeling and are implicated in different biological processes, including cell cycle control and maintenance of genomic stability [14][15][16]. Mammalian SWI/SNF complexes are classified into three subgroups: canonical BAF (cBAF), polybromo-associated BAF (PBAF), and non-canonical BAF (ncBAF), also called GLTSCR1 or GLTSCR1L-containing and BRD9-containing (GBAF) complexes [17][18] (**Figure 1**). SMARCB1 participates only into cBAF and PBAF complexes [19][20]. Notably, SWI/SNF subunits are mutated in over 20% of all human cancers [16][21]. In particular, SMARCB1 inactivation is implicated in the pathobiology of ES, malignant rhabdoid tumors (MRT), atypical teratoid/rhabdoid tumors (AT/RT)

of the central nervous system, malignant peripheral nerve sheath tumors (MPNST), myoepithelial neoplasms and renal medullary carcinomas (RMC) [22][23][24][25].

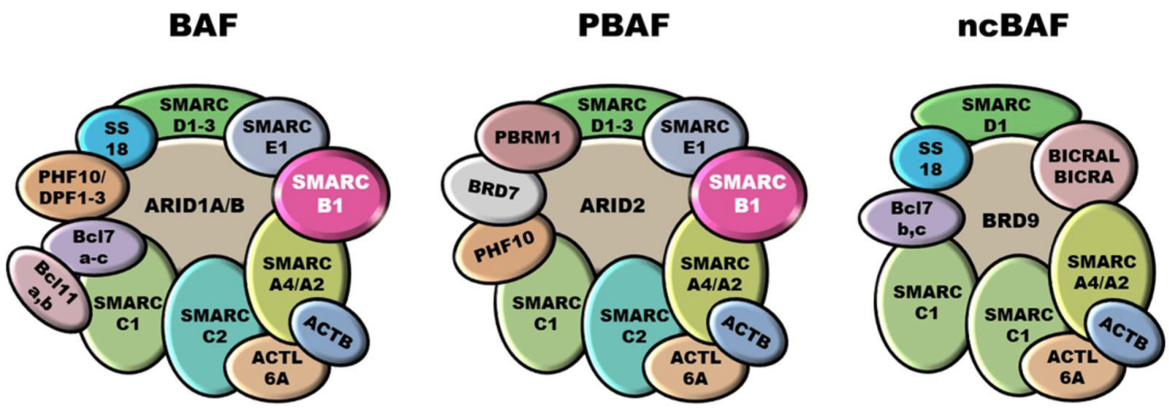

Figure 1. SWI/SNF chromatin remodeling complexes. SWI/SNF complexes are classified into three subgroups: canonical BAF (cBAF), polybromo-associated BAF (PBAF), and non-canonical BAF (ncBAF). SMARCB1 participates into cBAF and PBAF complexes whilst is not included into the ncBAF ones.

Over 90% of ES harbor biallelic SMARCB1 deletions or, more rarely, nonsense frameshift and splice site mutations [26][27][28]. In the ES samples lacking obvious SMARCB1 genetic defects, i.e. SMARCB1-intact ES, epigenetic mechanisms have been proposed to account for SMARCB1 functional inactivation. However, no promoter methylation was detected [29][30], and decitabine treatment failed to restore SMARCB1 expression in these tumors [30]. microRNAs have been also implicated in SMARCB1 silencing, namely miR-193a-5p, miR-206, miR-381, and miR-671-5p [31][32][33], although the actual capacity of these microRNAs to inhibit SMARCB1 in the context of ES cells was not confirmed by independent studies [30]. Therefore, the mechanism underlying the loss of SMARCB1 expression in SMARCB1-intact ES remains to be elucidated.

In SMARCB1-deleted ES cell models, such as the VA-ES-BJ cell line, restoration of SMARCB1 expression induces cell cycle arrest and impairs anchorage-independent growth and cell migration, substantiating its tumor suppressive role [34]. The mechanism of action of SMARCB1 as a tumor suppressor relies on the intersection with several pathways, including cell proliferation and survival [35] (**Figure 2**).

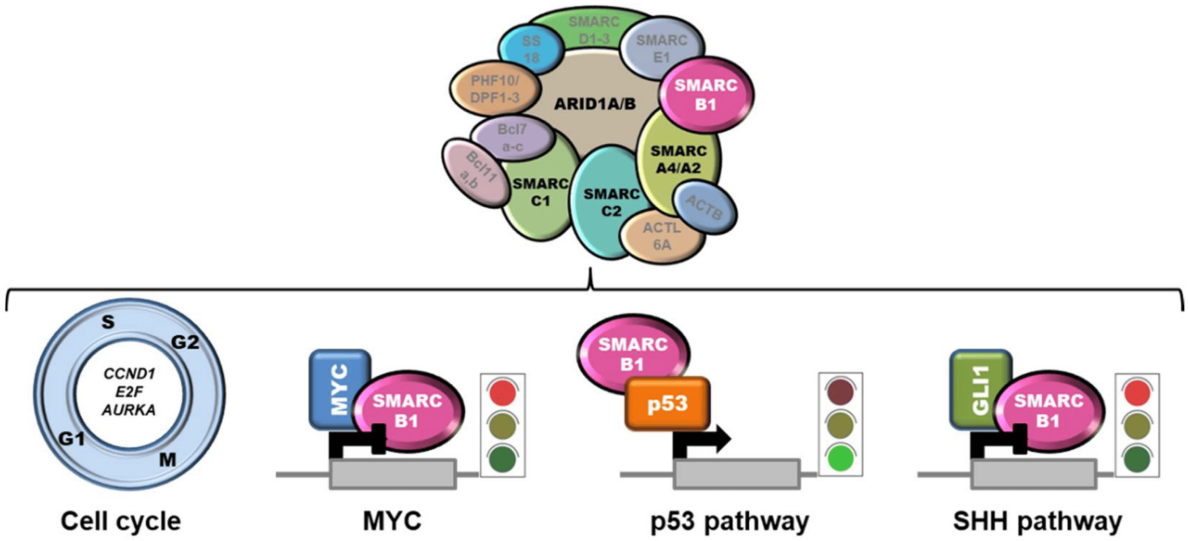

Figure 2. SMARCB1 intersection with relevant pathways. SMARCB1 negatively controls the expression of several cell cycle-related genes. Moreover, by interacting with MYC or GLI1, it hampers their transactivation activity. Conversely, the binding to p53 potentiates p53 tumor suppressive activity. The loss of the SWI/SNF subunits ARID1A, SMARCC1, SMARCC2, and SMARCA4 (in black) has been claimed to play a pathogenic role in the small fraction of SMARCB1-proficient ES.

SMARCB1 negatively regulates the expression of cyclin D1, E2F, and AURKA and, accordingly, SMARCB1-deleted tumors show up-regulation of these targets and cell cycle perturbation [36][37][38][39]. SMARCB1 was also demonstrated to directly bind MYC and to interfere with MYC-mediated transcriptional regulation [40][41]. Indeed, in SMARCB1-negative cell lines, SMARCB1 loss associates with enhanced MYC activity and increased DNA replication [42]. SMARCB1 also binds and potentiates p53 transactivation activity [43], and favors nucleotide excision repair by interacting with several components of this machinery, including BRCA1, BARD1 and XPC [44][45]. This suggests that SMARCB1 loss may result in impaired control over genome stability. Furthermore, SMARCB1 plays a role in Wnt/β-catenin and sonic hedgehog (SHH) signaling pathways [46][47]. In particular, SMARCB1 has been reported to bind GLI1, a SHH effector, thereby inhibiting the SHH signaling [46]. Finally, a role for SMARCB1 in regulating the expression of IL6 has been recently proposed [48].

Notably, SMARCB1 was documented to repress EZH2 and, accordingly, high levels of EZH2 have been shown in SMARCB1-deficient tumors, including ES [29], AT/RT [49], MRT [50] and chordomas [51]. EZH2 is a core component of PRC2 complexes (Polycomb Repressive Complex 2) and catalyzes the methylation of histone H3 on lysine 27 (H3K27) mediating the transcriptional repression of target genes [50]. PRC2 complexes are functional antagonists of the SWI/SNF complexes, and the balance between the two is key for cellular homeostasis [50][52][53][54] (**Figure 3**).

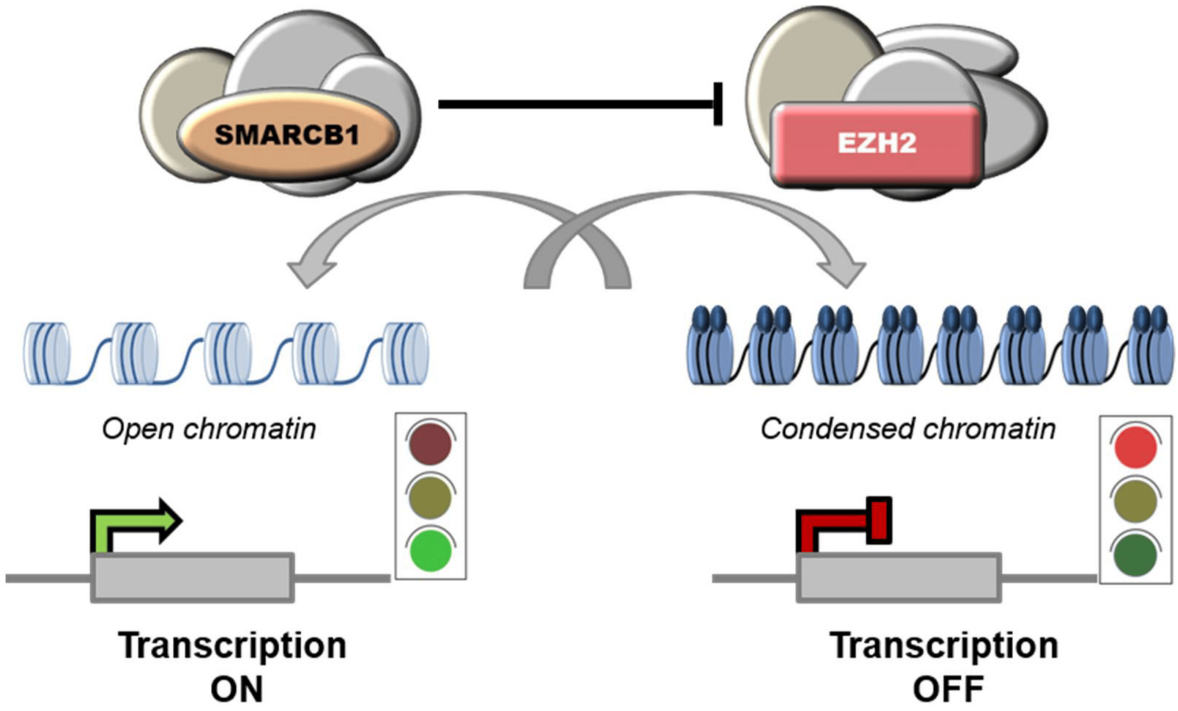

Figure 3. Functional antagonism between SWI/SNF and PRC2 complexes. SWI/SNF complexes regulate nucleosome remodeling by promoting sliding or ejection of nucleosomes, thus facilitating gene expression. Instead, PRC2 complexes induce chromatin compaction and transcriptional repression by catalyzing methylation of histone H3 on lysine 27 (H3K27).

Concomitant inactivation of EZH2 and SMARCB1 is synthetic lethal. *In vitro* and *in vivo* experiments demonstrated that EZH2 silencing in SMARCB1-deficient MRT cells significantly impaired cell proliferation and triggered cell senescence, and prevented the formation of tumors driven by SMARCB1 loss in mouse models [50]. Also the pharmacological inhibition of EZH2 induced strong anti-proliferative effects in SMARCB1-deleted cells and determined a complete regression of xenografts in mouse [55][56]. Based on these findings, EZH2-inhibitors have been proposed as a potential therapeutic strategy in SMARCB1-deficient tumors. In 2013, an open-label, multicenter, phase I/II trial demonstrated that the EZH2 inhibitor tazemetostat showed antitumor activity in ES [57]. The study was followed by a phase II, multicenter study (NCT02601950) in 2015: of the 62 ES patients enrolled in this trial, 15% (9/62) showed durable objective response after 32 weeks of treatment, and 21% (13/62) remained progression-free at 1 year [28]. These encouraging results led to the accelerated approval by the USA Food and Drug Administration (FDA) of tazemetostat for the treatment of adults and adolescents over 16 years of age with locally advanced or metastatic ES not eligible to complete surgical resection. Based on these promising results, other PRC2 components are currently considered for therapeutic targeting.

References

1. Frezza, A.M.; Botta, L.; Pasquali, S.; Stacchiotti, S.; Gronchi, A.; Casali, P.G.; Trama, A.; Rarecarenet, W.G. An Epidemiological Insight into Epithelioid Sarcoma (ES): The Open Issue of Distal-Type (DES) versus Proximal-Type (PES). Ann. Oncol. 2017, 28, v525.
2. Casanova, M.; Ferrari, A.; Collini, P.; Bisogno, G.; Alaggio, R.; Cecchetto, G.; Gronchi, A.; Meazza, C.; Garaventa, A.; Di Cataldo, A.; et al. Epithelioid Sarcoma in Children and Adolescents: A Report from the Italian Soft Tissue Sarcoma Committee. Cancer 2006, 106, 708–717.
3. Jawad, M.U.; Extein, J.; Min, E.S.; Scully, S.P. Prognostic Factors for Survival in Patients with Epithelioid Sarcoma: 441 Cases from the SEER Database. Clin. Orthop. 2009, 467, 2939–2948.
4. Chase, D.R.; Enzinger, F.M. Epithelioid Sarcoma. Diagnosis, Prognostic Indicators, and Treatment. Am. J. Surg. Pathol. 1985, 9, 241–263.
5. Ross, H.M.; Lewis, J.J.; Woodruff, J.M.; Brennan, M.F. Epithelioid Sarcoma: Clinical Behavior and Prognostic Factors of Survival. Ann. Surg. Oncol. 1997, 4, 491–495.
6. Callister, M.D.; Ballo, M.T.; Pisters, P.W.; Patel, S.R.; Feig, B.W.; Pollock, R.E.; Benjamin, R.S.; Zagars, G.K. Epithelioid Sarcoma: Results of Conservative Surgery and Radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 2001, 51, 384–391.
7. Baratti, D.; Pennacchioli, E.; Casali, P.G.; Bertulli, R.; Lozza, L.; Olmi, P.; Collini, P.; Radaelli, S.; Fiore, M.; Gronchi, A. Epithelioid Sarcoma: Prognostic Factors and Survival in a Series of Patients Treated at a Single Institution. Ann. Surg. Oncol. 2007, 14, 3542–3551.
8. Wolf, P.S.; Flum, D.R.; Tanas, M.R.; Rubin, B.P.; Mann, G.N. Epithelioid Sarcoma: The University of Washington Experience. Am. J. Surg. 2008, 196, 407–412.
9. Guzzetta, A.A.; Montgomery, E.A.; Lyu, H.; Hooker, C.M.; Meyer, C.F.; Loeb, D.M.; Frassica, D.; Weber, K.L.; Ahuja, N. Epithelioid Sarcoma: One Institution’s Experience with a Rare Sarcoma. J. Surg. Res. 2012, 177, 116–122.
10. Levy, A.; Le Péchoux, C.; Terrier, P.; Bouaita, R.; Domont, J.; Mir, O.; Coppola, S.; Honoré, C.; Le Cesne, A.; Bonvalot, S. Epithelioid Sarcoma: Need for a Multimodal Approach to Maximize the Chances of Curative Conservative Treatment. Ann. Surg. Oncol. 2014, 21, 269–276.
11. Pradhan, A.; Grimer, R.J.; Abudu, A.; Tillman, R.M.; Carter, S.R.; Jeys, L.; Ferguson, P.C.; Griffin, A.M.; Wunder, J.S. Epithelioid Sarcomas: How Important Is Loco-Regional Control? Eur. J. Surg. Oncol. 2017, 43, 1746–1752.
12. Elsamna, S.T.; Amer, K.; Elkattawy, O.; Beebe, K.S. Epithelioid Sarcoma: Half a Century Later. Acta Oncol. 2020, 59, 48–54.
13. Frezza, A.M.; Sbaraglia, M.; Lo Vullo, S.; Baldi, G.G.; Simeone, N.; Frenos, F.; Campanacci, D.; Stacchiotti, S.; Pasquali, S.; Callegaro, D.; et al. The Natural History of Epithelioid Sarcoma. A

Retrospective Multicentre Case-Series within the Italian Sarcoma Group. Eur. J. Surg. Oncol. 2020, 46, 1320–1326.

14. Medjkane, S.; Novikov, E.; Versteege, I.; Delattre, O. The Tumor Suppressor HSNF5/INI1 Modulates Cell Growth and Actin Cytoskeleton Organization. Cancer Res. 2004, 64, 3406–3413.
15. Vries, R.G.J. Cancer-Associated Mutations in Chromatin Remodeler HSNF5 Promote Chromosomal Instability by Compromising the Mitotic Checkpoint. Genes Dev. 2005, 19, 665–670.
16. Wang, X.; Haswell, J.R.; Roberts, C.W.M. Molecular Pathways: SWI/SNF (BAF) Complexes Are Frequently Mutated in Cancer-Mechanisms and Potential Therapeutic Insights. Clin. Cancer Res. 2014, 20, 21–27.
17. Raab, J.R.; Resnick, S.; Magnuson, T. Genome-Wide Transcriptional Regulation Mediated by Biochemically Distinct SWI/SNF Complexes. PLoS Genet. 2015, 11, e1005748.
18. Alpsoy, A.; Dykhuizen, E.C. Glioma Tumor Suppressor Candidate Region Gene 1 (GLTSCR1) and Its Paralog GLTSCR1-like Form SWI/SNF Chromatin Remodeling Subcomplexes. J. Biol. Chem. 2018, 293, 3892–3903.
19. Michel, B.C.; D'Avino, A.R.; Cassel, S.H.; Mashtalir, N.; McKenzie, Z.M.; McBride, M.J.; Valencia, A.M.; Zhou, Q.; Bocker, M.; Soares, L.M.M.; et al. A Non-Canonical SWI/SNF Complex Is a Synthetic Lethal Target in Cancers Driven by BAF Complex Perturbation. Nat. Cell Biol. 2018, 20, 1410–1420.
20. Centore, R.C.; Sandoval, G.J.; Soares, L.M.M.; Kadoch, C.; Chan, H.M. Mammalian SWI/SNF Chromatin Remodeling Complexes: Emerging Mechanisms and Therapeutic Strategies. Trends Genet. TIG 2020, 36, 936–950.
21. Kadoch, C.; Hargreaves, D.C.; Hodges, C.; Elias, L.; Ho, L.; Ranish, J.; Crabtree, G.R. Proteomic and Bioinformatic Analysis of Mammalian SWI/SNF Complexes Identifies Extensive Roles in Human Malignancy. Nat. Genet. 2013, 45, 592–601.
22. Thway, K.; Jones, R.L.; Noujaim, J.; Fisher, C. Epithelioid Sarcoma: Diagnostic Features and Genetics. Adv. Anat. Pathol. 2016, 23, 41–49.
23. Hollmann, T.J.; Hornick, J.L. INI1-Deficient Tumors: Diagnostic Features and Molecular Genetics. Am. J. Surg. Pathol. 2011, 35, e47–e63.
24. Agaimy, A. The Expanding Family of SMARCB1(INI1)-Deficient Neoplasia: Implications of Phenotypic, Biological, and Molecular Heterogeneity. Adv. Anat. Pathol. 2014, 21, 394–410.
25. Margol, A.S.; Judkins, A.R. Pathology and Diagnosis of SMARCB1-Deficient Tumors. Cancer Genet. 2014, 207, 358–364.

26. Sullivan, L.M.; Folpe, A.L.; Pawel, B.R.; Judkins, A.R.; Biegel, J.A. Epithelioid Sarcoma Is Associated with a High Percentage of SMARCB1 Deletions. Mod. Pathol. 2013, 26, 385–392.
27. Le Loarer, F.; Zhang, L.; Fletcher, C.D.; Ribeiro, A.; Singer, S.; Italiano, A.; Neuville, A.; Houlier, A.; Chibon, F.; Coindre, J.-M.; et al. Consistent SMARCB1 Homozygous Deletions in Epithelioid Sarcoma and in a Subset of Myoepithelial Carcinomas Can Be Reliably Detected by FISH in Archival Material. Genes Chromosomes Cancer 2014, 53, 475–486.
28. Gounder, M.; Schöffski, P.; Jones, R.L.; Agulnik, M.; Cote, G.M.; Villalobos, V.M.; Attia, S.; Chugh, R.; Chen, T.W.-W.; Jahan, T.; et al. Tazemetostat in Advanced Epithelioid Sarcoma with Loss of INI1/SMARCB1: An International, Open-Label, Phase 2 Basket Study. Lancet Oncol. 2020, 21, 1423–1432.
29. Papp, G.; Changchien, Y.-C.; Péterfia, B.; Pecsenka, L.; Krausz, T.; Stricker, T.P.; Khoor, A.; Donner, L.; Sápi, Z. SMARCB1 Protein and MRNA Loss Is Not Caused by Promoter and Histone Hypermethylation in Epithelioid Sarcoma. Mod. Pathol. 2013, 26, 393–403.
30. Jamshidi, F.; Bashashati, A.; Shumansky, K.; Dickson, B.; Gokgoz, N.; Wunder, J.S.; Andrulis, I.L.; Lazar, A.J.; Shah, S.P.; Huntsman, D.G.; et al. The Genomic Landscape of Epithelioid Sarcoma Cell Lines and Tumours. J. Pathol. 2016, 238, 63–73.
31. Kohashi, K.; Yamamoto, H.; Kumagai, R.; Yamada, Y.; Hotokebuchi, Y.; Taguchi, T.; Iwamoto, Y.; Oda, Y. Differential MicroRNA Expression Profiles between Malignant Rhabdoid Tumor and Epithelioid Sarcoma: MiR193a-5p Is Suggested to Downregulate SMARCB1 MRNA Expression. Mod. Pathol. 2014, 27, 832–839.
32. Papp, G.; Krausz, T.; Stricker, T.P.; Szendrői, M.; Sápi, Z. SMARCB1 Expression in Epithelioid Sarcoma Is Regulated by MiR-206, MiR-381, and MiR-671-5p on Both MRNA and Protein Levels: Smarcb1 Regulation By Mirnas In Epithelioid Sarcoma. Genes Chromosomes Cancer 2014, 53, 168–176.
33. Sápi, Z.; Papp, G.; Szendrői, M.; Pápai, Z.; Plótár, V.; Krausz, T.; Fletcher, C.D.M. Epigenetic Regulation of SMARCB1 By MiR-206, -381 and -671-5p Is Evident in a Variety of SMARCB1 Immunonegative Soft Tissue Sarcomas, While MiR-765 Appears Specific for Epithelioid Sarcoma. A MiRNA Study of 223 Soft Tissue Sarcomas. Genes Chromosomes Cancer 2016, 55, 786–802.
34. Brenca, M.; Rossi, S.; Lorenzetto, E.; Piccinin, E.; Piccinin, S.; Rossi, F.M.; Giuliano, A.; Dei Tos, A.P.; Maestro, R.; Modena, P. SMARCB1/INI1 Genetic Inactivation Is Responsible for Tumorigenic Properties of Epithelioid Sarcoma Cell Line VAESBJ. Mol. Cancer Ther. 2013, 12, 1060–1072.
35. Cooper, G.W.; Hong, A.L. SMARCB1-Deficient Cancers: Novel Molecular Insights and Therapeutic Vulnerabilities. Cancers 2022, 14, 3645.

36. Versteege, I.; Medjkane, S.; Rouillard, D.; Delattre, O. A Key Role of the HSNF5/INI1 Tumour Suppressor in the Control of the G1-S Transition of the Cell Cycle. Oncogene 2002, 21, 6403–6412.

37. Lee, S.; Cimica, V.; Ramachandra, N.; Zagzag, D.; Kalpana, G.V. Aurora A Is a Repressed Effector Target of the Chromatin Remodeling Protein INI1/HSNF5 Required for Rhabdoid Tumor Cell Survival. Cancer Res. 2011, 71, 3225–3235.

38. Lin, L.; Hicks, D.; Xu, B.; Sigel, J.E.; Bergfeld, W.F.; Montgomery, E.; Fisher, C.; Hartke, M.; Tubbs, R.; Goldblum, J.R. Expression Profile and Molecular Genetic Regulation of Cyclin D1 Expression in Epithelioid Sarcoma. Mod. Pathol. 2005, 18, 705–709.

39. Isakoff, M.S.; Sansam, C.G.; Tamayo, P.; Subramanian, A.; Evans, J.A.; Fillmore, C.M.; Wang, X.; Biegel, J.A.; Pomeroy, S.L.; Mesirov, J.P.; et al. Inactivation of the Snf5 Tumor Suppressor Stimulates Cell Cycle Progression and Cooperates with P53 Loss in Oncogenic Transformation. Proc. Natl. Acad. Sci. USA 2005, 102, 17745–17750.

40. Stojanova, A.; Tu, W.B.; Ponzielli, R.; Kotlyar, M.; Chan, P.-K.; Boutros, P.C.; Khosravi, F.; Jurisica, I.; Raught, B.; Penn, L.Z. MYC Interaction with the Tumor Suppressive SWI/SNF Complex Member INI1 Regulates Transcription and Cellular Transformation. Cell Cycle 2016, 15, 1693–1705.

41. Weissmiller, A.M.; Wang, J.; Lorey, S.L.; Howard, G.C.; Martinez, E.; Liu, Q.; Tansey, W.P. Inhibition of MYC by the SMARCB1 Tumor Suppressor. Nat. Commun. 2019, 10, 2014.

42. Msaouel, P.; Malouf, G.G.; Su, X.; Yao, H.; Tripathi, D.N.; Soeung, M.; Gao, J.; Rao, P.; Coarfa, C.; Creighton, C.J.; et al. Comprehensive Molecular Characterization Identifies Distinct Genomic and Immune Hallmarks of Renal Medullary Carcinoma. Cancer Cell 2020, 37, 720–734.e13.

43. Lee, D.; Kim, J.W.; Seo, T.; Hwang, S.G.; Choi, E.-J.; Choe, J. SWI/SNF Complex Interacts with Tumor Suppressor P53 and Is Necessary for the Activation of P53-Mediated Transcription. J. Biol. Chem. 2002, 277, 22330–22337.

44. Ray, A.; Mir, S.N.; Wani, G.; Zhao, Q.; Battu, A.; Zhu, Q.; Wang, Q.-E.; Wani, A.A. Human SNF5/INI1, a Component of the Human SWI/SNF Chromatin Remodeling Complex, Promotes Nucleotide Excision Repair by Influencing ATM Recruitment and Downstream H2AX Phosphorylation. Mol. Cell. Biol. 2009, 29, 6206–6219.

45. Fontana, G.A.; Rigamonti, A.; Lenzken, S.C.; Filosa, G.; Alvarez, R.; Calogero, R.; Bianchi, M.E.; Barabino, S.M.L. Oxidative Stress Controls the Choice of Alternative Last Exons via a Brahma-BRCA1-CstF Pathway. Nucleic Acids Res. 2017, 45, 902–914.

46. Jagani, Z.; Mora-Blanco, E.L.; Sansam, C.G.; McKenna, E.S.; Wilson, B.; Chen, D.; Klekota, J.; Tamayo, P.; Nguyen, P.T.L.; Tolstorukov, M.; et al. Loss of the Tumor Suppressor Snf5 Leads to Aberrant Activation of the Hedgehog-Gli Pathway. Nat. Med. 2010, 16, 1429–1433.

47. Mora-Blanco, E.L.; Mishina, Y.; Tillman, E.J.; Cho, Y.-J.; Thom, C.S.; Pomeroy, S.L.; Shao, W.; Roberts, C.W.M. Activation of β-Catenin/TCF Targets Following Loss of the Tumor Suppressor SNF5. Oncogene 2014, 33, 933–938.
48. Choi, S.K.; Kim, M.J.; You, J.S. SMARCB1 Acts as a Quiescent Gatekeeper for Cell Cycle and Immune Response in Human Cells. Int. J. Mol. Sci. 2020, 21, 3969.
49. Alimova, I.; Birks, D.K.; Harris, P.S.; Knipstein, J.A.; Venkataraman, S.; Marquez, V.E.; Foreman, N.K.; Vibhakar, R. Inhibition of EZH2 Suppresses Self-Renewal and Induces Radiation Sensitivity in Atypical Rhabdoid Teratoid Tumor Cells. Neuro-Oncology 2013, 15, 149–160.
50. Wilson, B.G.; Wang, X.; Shen, X.; McKenna, E.S.; Lemieux, M.E.; Cho, Y.-J.; Koellhoffer, E.C.; Pomeroy, S.L.; Orkin, S.H.; Roberts, C.W.M. Epigenetic Antagonism between Polycomb and SWI/SNF Complexes during Oncogenic Transformation. Cancer Cell 2010, 18, 316–328.
51. Joldoshova, A.; Elzamly, S.; Brown, R.; Buryanek, J. Prometastatic CXCR4 and Histone Methyltransferase EZH2 Are Upregulated in SMARCB1/INI1-Deficient and TP53-Mutated Poorly Differentiated Chordoma. J. Mol. Pathol. 2022, 3, 7.
52. Kadoch, C.; Copeland, R.A.; Keilhack, H. PRC2 and SWI/SNF Chromatin Remodeling Complexes in Health and Disease. Biochemistry 2016, 55, 1600–1614.
53. Kadoch, C.; Crabtree, G.R. Mammalian SWI/SNF Chromatin Remodeling Complexes and Cancer: Mechanistic Insights Gained from Human Genomics. Sci. Adv. 2015, 1, e1500447.
54. Völkel, P.; Dupret, B.; Le Bourhis, X.; Angrand, P.-O. Diverse Involvement of EZH2 in Cancer Epigenetics. Am. J. Transl. Res. 2015, 7, 175–193.
55. Knutson, S.K.; Warholic, N.M.; Wigle, T.J.; Klaus, C.R.; Allain, C.J.; Raimondi, A.; Porter Scott, M.; Chesworth, R.; Moyer, M.P.; Copeland, R.A.; et al. Durable Tumor Regression in Genetically Altered Malignant Rhabdoid Tumors by Inhibition of Methyltransferase EZH2. Proc. Natl. Acad. Sci. USA 2013, 110, 7922–7927.
56. Stacchiotti, S.; Zuco, V.; Tortoreto, M.; Cominetti, D.; Frezza, A.M.; Percio, S.; Indio, V.; Barisella, M.; Monti, V.; Brich, S.; et al. Comparative Assessment of Antitumor Effects and Autophagy Induction as a Resistance Mechanism by Cytotoxics and EZH2 Inhibition in INI1-Negative Epithelioid Sarcoma Patient-Derived Xenograft. Cancers 2019, 11, 1015.
57. Italiano, A.; Soria, J.-C.; Toulmonde, M.; Michot, J.-M.; Lucchesi, C.; Varga, A.; Coindre, J.-M.; Blakemore, S.J.; Clawson, A.; Suttle, B.; et al. Tazemetostat, an EZH2 Inhibitor, in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma and Advanced Solid Tumours: A First-in-Human, Open-Label, Phase 1 Study. Lancet Oncol. 2018, 19, 649–659.