Review

Epigenetics of Cutaneous Sarcoma

Emi Mashima and Yu Sawada *

Department of Dermatology, University of Occupational and Environmental Health, 1-1, Iseigaoka, Yahatanishi-Ku, Kitakyushu 807-8555, Japan; e-mashima@med.uoeh-u.ac.jp
* Correspondence: long-ago@med.uoeh-u.ac.jp

Abstract: Epigenetic changes influence various physiological and pathological conditions in the human body. Recent advances in epigenetic studies of the skin have led to an appreciation of the importance of epigenetic modifications in skin diseases. Cutaneous sarcomas are intractable skin cancers, and there are no curative therapeutic options for the advanced forms of cutaneous sarcomas. In this review, we discuss the detailed molecular effects of epigenetic modifications on skin sarcomas, such as dermatofibrosarcoma protuberans, angiosarcoma, Kaposi's sarcoma, leiomyosarcoma, and liposarcoma. We also discuss the application of epigenetic-targeted therapy for skin sarcomas.

Keywords: skin sarcoma; epigenetics; dermatofibrosarcoma protuberans; angiosarcoma; Kaposi's sarcoma; leiomyosarcoma; liposarcoma

1. Introduction

1.1. The Skin as an Exposure Site to Environmental Stimuli

Various environmental stimuli have their most direct effect on the skin, the outermost organ that covers the human body (reviewed in [1]). The skin is the most susceptible organ to various external factors, and continuous skin reactions to environmental factors augment tissue damage caused by inflammatory reactions [2]. In recent studies, skin physiology has been found to involve many epigenetic mechanisms that regulate gene expression without changing genetic information [3] (reviewed in [4,5]). In addition to playing a role in adaptation to environmental conditions, epigenetics also contributes to carcinogenesis in skin cancers (reviewed in [6,7]). Thus, it has been hypothesized that cutaneous malignancies may acquire a selective advantage within the body via an epigenetic mechanism.

1.2. The Skin Structure and Functions

The skin is a three-layered structure consisting of the epidermis, dermis, and adipose tissue, each with unique cells, and its importance has been investigated in various studies [8,9]. It plays essential roles in maintaining homeostasis in the human body, such as having barrier, sensory, thermoregulatory, immune, and secretory functions (reviewed in [10]). Keratinocytes produce moisturizing factors to increase the water retention capacity of the stratum corneum, thus contributing to skin barrier function [11]. Keratinocytes, dendritic cells, and lymphocytes in the skin play a vital role in immunity [12]. These cells carry Toll-like receptors, which recognize the specific molecular pattern of invading pathogens and activate innate immunity to promote the production of various cytokines and antimicrobial peptides. Skin also plays an important role as a sensory organ (reviewed in [13]). Itch exists only in the skin, and the scratching action that accompanies itching is greatly involved in the exacerbation of skin diseases [14]. In addition, proper thermoregulation of the skin surface, which involves the dilation of capillary vessels and sweating, is essential for maintaining homeostasis. Hair follicles, sebaceous glands, and sweat glands are mini-appendages that produce sebum and sweat, which can lead to skin diseases (reviewed in [15]). Various types of soft tissue tumors are known to develop in the skin. As the skin is susceptible to epigenetic modification by environmental factors, it has been inferred that these skin-derived, soft-tissue tumors might be affected by these mechanisms.

1.3. Epigenetic Changes in the Skin

Epigenetic chemical modifications of deoxyribonucleic acid (DNA) or DNA-binding histones regulate gene transcription without changing the DNA sequence (reviewed in [16]). DNA binds histones via electrostatic interactions. DNA transcription is affected by histone binding; for example, transcription is activated when histone–DNA bonds are disrupted, which is considered an epigenetic mechanism. Environmental stimuli have been hypothesized to promote oncogenesis in the skin via epigenetic mechanisms. Therefore, elucidating the detailed molecular mechanism of epigenetic changes in cutaneous malignancies may be critical for our understanding of skin cancers.

In this review, we focus on soft-tissue sarcomas affected by epigenetic regulation mechanisms and clarify the relationship between their initiation and epigenetics. Furthermore, we discuss the future direction of epigenetic-targeted therapy for cutaneous soft-tissue sarcomas. We highlight the molecular mechanisms of epigenetic modification in cutaneous sarcomas, such as dermatofibrosarcoma protuberans (DFSP), angiosarcoma, Kaposi's sarcoma, leiomyosarcoma, and liposarcoma.

2. Dermatofibrosarcoma Protuberans (DFSP)

DFSP is a rare cutaneous sarcoma derived from fibroblasts and is mainly located in the dermis [17]. It has an indolent clinical course. Although surgical resection is the gold standard treatment, there is no effective therapeutic option to prevent local aggressive invasion (although distant metastasis rarely occurs) [18]. Therefore, various studies are currently exploring therapeutic candidates for DFSP. COL1A1–PDGFB fusion has been identified in DFSP cases [19]. COL1A1–PDGFB fusion variants frequently involve exons 25, 32, and 47, suggesting possible pathogenesis of DFSP [19]. The incidence of DFSP is 4.2 cases per one million persons per year [20]. It accounts for 4.5% of all cutaneous soft tissue sarcomas [21] and approximately 1.8% of all soft tissue sarcomas (reviewed in [22]).

A possible contribution of histone methylation to DFSP has been previously reported. One of the inducers of histone methylation, polycomb repressive complex 2 (PRC2), primarily tri-methylates histone H3 on lysine 27 to form H3K27me3, and it is required for the initial silencing of targeted genes [23]. The core complex of PRC2, consisting of enhancer of zest homolog (EZH) 1 and EZH2, the zinc-finger protein SUZ12, and the WD40 protein EED [24–28], is necessary for its catalytic function. EZH2 is the major catalytic subunit of PRC2 and the histone methyltransferase that catalyzes H3K27 trimethylation (reviewed in [29]). Whole-transcriptome sequencing analysis showed a strong upregulation of EZH2 in DFSP, possibly associated with the epithelial–mesenchymal transition [30]. EZH2 enhances cell proliferation and is widely found in cancers, including renal cancer [31], breast cancer [32], prostate cancer [33], and lymphoma [34]. Therefore, EZH2-mediated histone methylation might cause transcriptional repression of key tumor suppressor genes, such as p53 [35], and contribute to the development of DFSP.

3. Angiosarcoma

Angiosarcoma is a malignancy of endothelial cells in the blood or lymphatic vessels (reviewed in [36]). High frequencies of local recurrence and distant organ metastases have been reported. Current therapeutic options for high-grade malignancies are not satisfactory. The incidence of angiosarcoma is 1.5 cases per one million persons per year (reviewed in [37]). It accounts for 0.4% of all cutaneous soft tissue sarcomas [21], and approximately 2.0% of all soft tissue sarcomas [38].

The oncogenesis of angiosarcoma is shown in Figure 1. The p53/mouse double minute 2 homolog (MDM2) pathway has been postulated to be central to the development of angiosarcoma [39,40]. MDM2 suppresses p53 activity and vascular endothelial growth factor (VEGF) [39]. Intact p53 acts as a negative driver of the VEGF gene, thus inhibiting angiogenesis [39]. The suppression of p53 by MDM2 enhances angiogenesis in angiosarcoma cells, suggesting that p53 suppresses MDM2-induced angiosarcoma growth [41]. A high incidence of angiosarcoma has been observed in p53-deficient mice [42]. MYC is a

multifunctional nuclear protein that is related to the cell cycle, apoptosis, angiogenesis, and metastasis of angiosarcoma (reviewed in [43]). MYC upregulation was observed in secondary angiosarcoma and to a lesser extent in primary angiosarcoma. The mammalian target of the rapamycin (mTOR) pathway is involved in angiosarcoma onset [44]. mTOR enhances cancer cell growth and proliferation, and mTOR inhibitors inhibit growth in a dose-dependent manner [45].
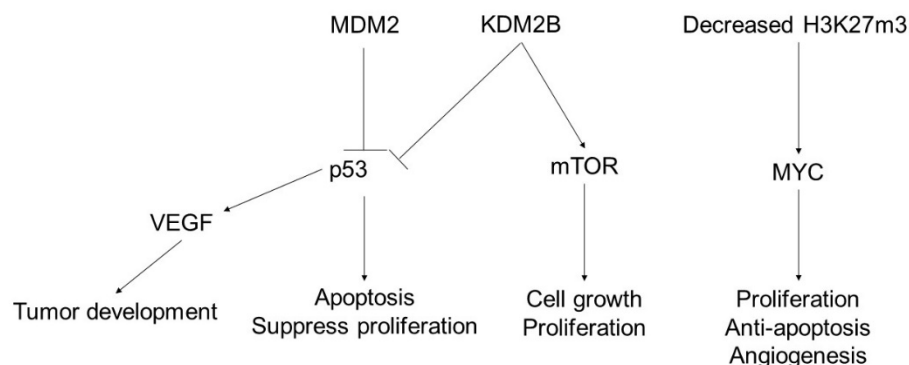
Figure 1. The pathogenesis of angiosarcoma and the influence of epigenetics.

　　Histone demethylation is involved in the development of angiosarcoma. H3K27me3 deficiency is observed in radiation-associated angiosarcoma [46]. As histone methylation causes downregulation of targeted genes [47,48], it has been speculated that epigenetic modulators are involved in histone methylation. Lysine-specific demethylase 2b (KDM2B) is a Jumonji domain histone demethylase [49] and is a component of PRC1 [50]. PRC1 is part of a polycomb repressive complex that inhibits the activated form of the RNA polymerase II preinitiation complex assembly by using immobilized H3K27-methylated chromatin [51]. KDM2B regulates various physiological and pathological processes, such as proliferation and oncogenesis [52]. KDM2B is upregulated in angiosarcomas [53], where it suppresses p53 and activates mTOR signaling (reviewed in [54]). KDM2B silencing in angiosarcoma cells enhances cell death via inactivation of DNA repair. The histone demethylase inhibitor GSK-14 induces apoptosis and cell death and reduces tumor size [53]. MYC upregulation is closely associated with radiation-related angiosarcoma due to H3K27me3 deficiency [46].

　　In angiosarcoma, p53 is a tumor suppressor that enhances apoptosis and suppresses tumor cell proliferation. The impairment of p53 function enhances VEGF function and causes tumor development. In addition, mTOR and MYC positively drive cell growth and angiogenesis. In these tumorigenesis mechanisms, KDM2B is upregulated in angiosarcoma, suppresses p53, and activates mTOR signaling. This leads to the suppression of apoptosis and enhancement of cell growth and proliferation. MYC upregulation is closely associated with radiation-related angiosarcoma due to H3K27me3 deficiency.

4. Kaposi's Sarcoma

　　Human herpesvirus-8, also known as Kaposi's sarcoma-associated herpesvirus (KSHV), is an opportunistic pathogen infecting vascular endothelial cells in immunocompromised people, such as those on immunosuppressive agents (e.g., after organ transplantation) and AIDS patients (reviewed in [55]). KSHV is a double-stranded DNA virus that causes either latent or lytic infections and infects a range of cells, including endothelial and immune cells. Patients with Kaposi's sarcoma develop purpura or dark brown macules or plaques, which are prone to bleeding and ulceration. Kaposi's sarcoma in patients with untreated acquired immunodeficiency syndrome (AIDS) can spread to the rest of the body within a few months. Locally limited Kaposi's sarcoma of the skin can be removed by surgical resection [56]. However, patients who must continue to receive immunosuppressive drugs, chemotherapy, and radiation therapy are particularly susceptible to progression to advanced Kaposi's sarcoma. The incidence of Kaposi's sarcoma is approximately 0.2 cases per 100,000 per-

sons per year [57]. It accounts for 17.1% of all cutaneous soft tissue sarcomas [21], and approximately 3.3% of all soft tissue sarcomas [57].

KSHV-associated LANA inactivates p53 and pRb [58], which blocks cell cycle arrest and causes uncontrolled proliferation [59] (Figure 2). LANA also binds to glycogen synthase kinase 3b (GSK-3b) [60,61], which increases the level of β-catenin (reviewed in [62]), facilitating tumor progression through the induction of angiogenesis [63]. LANA acts via methylation of the TbetaRII promoter and deacetylation of histones, which leads to inhibition of TGF-β signaling [64]. LANA also cooperates with DNA methyltransferase 3a (DNMT3a), which is a representative driver for DNA methylation in CpG-enriched DNA sites, especially targeted gene promoter regions (reviewed in [65]) and facilitates promoter methylation of cadherin 13 [66]. Cadherin 13 is a member of the cadherin family that is often downregulated in various tumors and is associated with an unfavorable prognosis [67]. Cadherin 13 inhibits cell proliferation and tumor invasion and increases apoptosis (reviewed in [68]). Therefore, LANA-mediated cadherin 13 downregulation contributes to the development of Kaposi's sarcoma.
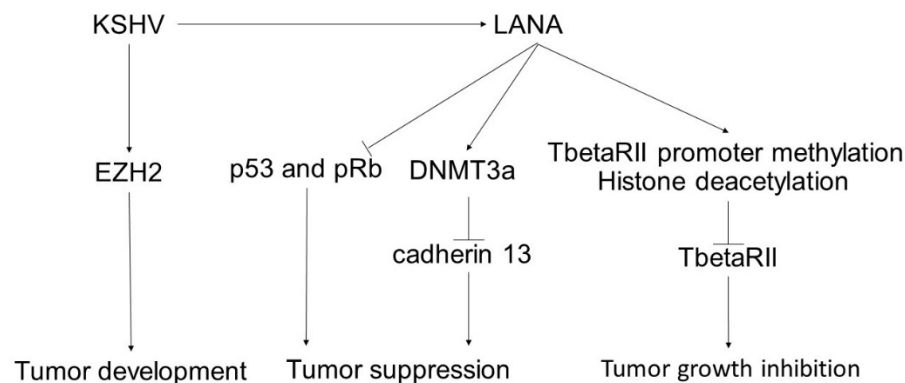
Figure 2. The pathogenesis of Kaposi's sarcoma and the influence of epigenetics.

KSHV also encodes viral interleukin-6, which contributes to the development of Kaposi's sarcoma [69,70]. Viral interleukin-6 promotes cell proliferation, tumor invasion, and angiogenesis by suppressing caveolin 1, which plays a role in tumor development mediated by DNA methyltransferase 1 (DNMT1)-targeted STAT3 acetylation [69].

EZH2 upregulation is related to epigenetic changes in KSHV and contributes to the development of KSHV-induced oncogenesis and angiogenesis [71].

KSHV-associated LANA inactivates p53 and pRb, enhances cell cycle arrest, and causes tumor cell proliferation. LANA acts via methylation of the TbetaRII promoter and deacetylation of histones, which leads to the inhibition of TGF-β signaling. LANA cooperates with DNMT3a and facilitates promoter methylation of cadherin 13 to cause its downregulation in various tumors, leading to cell proliferation, tumor invasion, and suppression of apoptosis. Therefore, LANA-mediated cadherin 13 downregulation contributes to the development of Kaposi's sarcoma. KSHV promotes tumor development mediated by EZH2 activation.

5. Leiomyosarcoma

Leiomyosarcoma is a form of malignant smooth muscle tumor and is one of the most common types of soft-tissue sarcomas (reviewed in [72]). Dermal leiomyosarcoma develops from the pilar follicle erector muscles or smooth muscles surrounding the sweat glands, and subcutaneous leiomyosarcoma develops from the smooth muscle of arteries and veins [73]. The incidence of leiomyosarcoma is between 0.7 cases per 100,000 persons per year [57]. It accounts for 0.6% of all cutaneous soft tissue sarcomas [21] and approximately 11.4% of all soft tissue sarcomas [57].

DNA methylation of DAXX and receptor-type tyrosine-protein phosphatase N2 (PT-PRN2) has been found in patients with leiomyosarcoma [74]. Hypermethylation-mediated

downregulation of soft tissue leiomyosarcoma-related genes, such as potassium voltage-gated channel subfamily A regulatory beta subunit 3 (KCNAB3), have been observed [75]. The actual role of KCNAB3 hypermethylation remains unclear, and a genome-wide analysis revealed hypermethylation in KCNAB3 in pre-cancer (reviewed in [76]), suggesting that this alteration is a positive driver for oncogenesis.

Hypermethylation in the potassium voltage-gated channel, Isk-related family, member 3 (KCNE3), TSPY-like 5 (TSPYL5), Homeobox A11 (HOXA11), HOXA11 antisense RNA (HOXA11AS), HOX9, and LOC100130872, was observed in leiomyosarcoma [75]. These genes are related to epigenetic regulation mediated by epigenetic modulators such as EZH2, histone 3 lysine methyltransferase 2A (KMT2A), BRD4, and histone deacetylase 4 (HDAC4) [75]. KMT2A has a SET domain that is responsible for its histone H3 lysine 4 (H3K4) methyltransferase activity in cancers (reviewed in [77,78]). BRD4 is an epigenetic regulator and has two tandem bromodomains (BD1 and BD2), which bind acetylated lysine residues on histones and regulate gene transcription (reviewed in [79]). Leiomyosarcoma growth is suppressed by treatment with DNA methyltransferase inhibitors [80].

HDAC9 can influence H3K27 acetylation in leiomyosarcoma and enhance cell survival by repressing Fas cell surface death receptor (FAS) transcription [81]. The addition of valproic acid (VPA), a weak histone deacetylase inhibitor, combined with gemcitabine and docetaxel, has cytotoxic effects [82]. Patients with extrauterine leiomyosarcomas showed a partial response after VPA treatment.
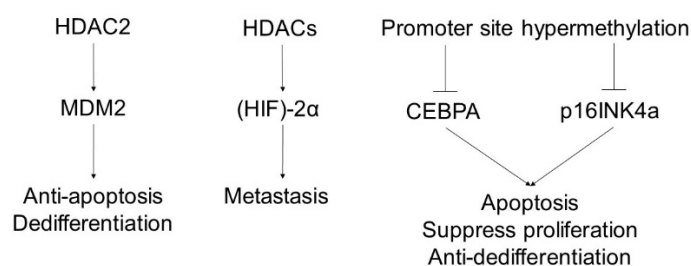
6. Liposarcoma

Liposarcoma is a malignant soft tissue tumor located in the deep soft tissues of the extremities [83]. Epigenetic effects have been reported in several types of liposarcomas, such as atypical lipomatous tumor (ALT)/well-differentiated liposarcoma, myxoid/round-cell liposarcoma (MRCL), and dedifferentiated liposarcoma. The incidence of liposarcoma is approximately 0.7 cases per 100,000 persons per year [57]. It accounts for 0.1% of all cutaneous soft tissue sarcomas [21] and less than 20% of all soft tissue sarcomas (reviewed in [84]).

Evans et al. reported that well-differentiated liposarcomas—namely, ALT, located in a subcutaneous site or within a muscle layer have high frequencies of local recurrence and distant metastasis [85]. ALT is associated with gene amplification in the 12q12-21 and 10p11-14 regions and of *MDM2* and cyclin-dependent kinase 4 (*CDK4*) [86]. Well-differentiated liposarcomas rarely metastasize and are often associated with p16INK4a deficiency. Gene silencing by methylation of the *p16INK4a* gene promoter has been reported in the progression and dedifferentiation of well-differentiated liposarcoma [87].

MRCL is a subtype of liposarcoma that usually occurs in the extremities and often spreads throughout the body (reviewed in [88]). Typical myxoid liposarcomas exhibit nonpleomorphic ovoid mesenchymal cells with a myxoid matrix. Round-cell liposarcoma is a high-grade form of round mesenchymal cell liposarcoma without a myxoid matrix. The most common cytogenetic feature of MRCL, in 95% of cases, is chromosomal translocation t(12;16)(q13;p11) producing FUS RNA-binding protein (FUS)–DNA damage-inducible transcript 3 (DDIT3) fusion proteins [89]. The remaining 5% cases of MRCL involved a t(12;22)(q13;q12) chromosomal translocation, producing EWS RNA-binding protein 1 (EWSR1)–DDIT3 fusion proteins [90]. These translocations can be used as diagnostic indicators (reviewed in [91]). The FUS–DDIT3 fusion gene enhances MRCL infiltration by inhibiting the expression of miR-486, which plays an inhibitory role in MRCL cell growth. Tumors with a methylated adenomatous polyposis coli (APC) promoter showed downregulation of APC, which acts as a scaffolding protein for the regulation of oncoprotein beta-catenin [92].

Many genetic mutations have been reported in dedifferentiated liposarcomas, including mutations in *MDM2, CDK4*, high mobility group AT-hook 2 (*HMGA2*), fibroblast growth factor receptor substrate 2 (*FRS2*), and neuron navigator 3 (*NAV3*), all located in 12q13-15 [93] (Figure 3). The p16INK4a gene promoter is also hypermethylated in

50% of dedifferentiated liposarcomas [94]. Somatic mutation of *HDAC1* was identified in 8.3% of patients with dedifferentiated liposarcoma [95]. HDAC2 was highly co-expressed with MDM2, and pharmacological HDAC2 inhibition decreased MDM2 expression and enhanced tumor cell apoptosis [96]. CCAAT/enhancer-binding protein alpha (CEBPA) methylation was observed in 24% of patients with dedifferentiated liposarcomas. Pharmacological demethylation restored CEBPA expression in DLPS cells, suppressing proliferation and enhancing apoptosis [95]. Hypoxia-inducible factor (HIF)-2α activates gene transcription under hypoxic conditions and promotes metastasis of soft-tissue sarcomas. The HDAC inhibitor vorinostat inhibits tumor growth mediated by HIF-2α [97]. H3K9me3 is enhanced in dedifferentiated liposarcoma [98].

Figure 3. The pathogenesis of liposarcoma and the influence of epigenetics.

MDM2 is responsible for the development of dedifferentiated liposarcomas that cause antiapoptotic effects and the dedifferentiation of tumors. HDAC2 is co-expressed with MDM2, and HDAC2 inhibition results in decreased MDM2 expression and enhanced tumor cell apoptosis. CEBPA and p16INK4a act as suppressors of liposarcoma to induce apoptosis and suppress proliferation and dedifferentiation. Hypermethylation of CEBPA and p16INK4a is observed in liposarcoma and causes downregulation and enhances tumor development. HIF-2α activates gene transcription under hypoxic conditions and promotes metastasis in liposarcomas. Therefore, HDAC inhibitors inhibit tumor growth mediated by HIF-2α.

7. Radiotherapy-Induced Epigenetics Alteration

Radiation therapy is a representative treatment for soft tissue sarcomas [99]. Recent studies have identified alterations in epigenetics following radiotherapy. Changes in DNA methylation indicated a potential epigenetic response to ionizing radiation in MDA-MB-231 cells, and methylated genes were enriched in gene ontology categories related to cell cycle, DNA repair, and apoptosis pathways [100]. These actions are expected to improve the therapeutic efficacy of radiotherapy against cutaneous sarcomas. Radiation also alters histone H3 methylation profiles [101]. The decreased expression of H3K27me3 is observed in almost all cases of radiation-related angiosarcoma, suggesting that histone methylation might contribute to the development of angiosarcoma following radiation [46]. This indicates that radiation might have bi-directional effects on the development and regulation of cutaneous sarcoma.

8. Summary of Epigenetic Modification in Cutaneous Sarcoma and Therapeutic Application

Finally, we summarize the roles of epigenetic targets and epigenetic-modifying enzymes in Table 1. Table 2 shows the possible therapeutic options for skin sarcomas. Various epigenetic enzyme inhibitors are currently being tested in clinical trials for the treatment of malignancies and inflammatory diseases. As there are several epigenetic-modifying enzymes involved in skin cancers, we discuss the clinical application of these inhibitors in cutaneous sarcomas.

Table 1. Epigenetic modifications in skin cancers.

Cutaneous Sarcomas	Epigenetic Modulator	Histone Modification	DNA Modification
DFSP	EZH2↑ [30]		
Angiosarcoma	KDM2B↑ [53]	H3K27me3↓ [46]	
Kaposi's sarcoma	DNMT1↑ [69] DNMT3A↑ [66] EZH2↑ [71]		Methylation TbetaRII↑ [64]
Leiomyosarcoma	EZH2↑ [75]. KMT2A-AFDN↑ [75] BRD4↑ [75] HDAC4↑ [75] HDAC9↑ [81] DNMT↑ [80]		Methylation DAXX↑ [74] PTPRN2↑ [74]
Liposarcoma	miR-486↑ [92] HDAC2↑ [96]	H3K9me3↑ [98]	Methylation p16INK4a↑ [94] APC↑ [92] C/EBPα↑ [95].

EZH2 activation is involved in DFSP, MPNST, angiosarcoma, Kaposi's sarcoma, leiomyosarcoma, epithelioid sarcoma, and synovial sarcoma. Tazemetostat is a selective, reversible, small-molecule inhibitor of EZH2 that has been used in clinical trials for refractory non-Hodgkin's B-cell lymphoma [102–104], diffuse large B-cell lymphoma [105], follicular lymphoma [106], and advanced epithelioid sarcoma [107]. Due to the role of EZH2 in skin sarcomas, tazemetostat may be effective against these cancers.

DNA methyltransferases (DNMTs) are a family of enzymes that catalyze the transfer of methyl groups to DNA (reviewed in [108]) and play a role in a wide range of biological functions. DNMT1 and DNMT3B are involved in Kaposi's sarcoma, and DNMTs are upregulated in leiomyosarcoma. MG98, which inhibits DNMT1 production, has antitumor effects in advanced renal cell carcinoma [109]. Another DNMT1 inhibitor, decitabine, has antitumor effects in patients with myelodysplastic syndrome [110]. SGI-1027 is another DNMT1 inhibitor that showed synergistic antitumor effects in combination with a JAK1/2 inhibitor [111].

Histones contain many basic amino acids, such as lysine and arginine, which are positively charged and can bind to negatively charged DNA (reviewed in [112]). Histone acetylation by histone acetyltransferase converts the amino group (-NH2) of a specific lysine residue in histone to amide (-NHCOCH3), neutralizing the charge (reviewed in [113]). Partial weakening of the bonds between DNA and histones makes it easier for transcription factors and RNA polymerases to bind to the DNA strand and activate gene transcription (reviewed in [114,115]). In contrast, histone deacetylation by HDAC has the opposite effect, causing the DNA to condense around histones, suppressing transcription (reviewed in [116]). HDAC4 and HDAC9 are upregulated in leiomyosarcoma, and HDAC2 is activated in liposarcomas. A variety of HDAC inhibitors that inhibit multiple HDACs are currently available. As pan-HDAC inhibitors show antitumor effects in cutaneous sarcoma, current specific HDAC inhibitors may be used against skin sarcomas. HDAC4 is upregulated in leiomyosarcoma, and LMK235, a specific HDAC4 inhibitor, dose-dependently suppressed MKK7 transcription and JNK/c-Jun activity in early brain injury following subarachnoid hemorrhage and impaired neuronal apoptosis [117]. HDAC2 is enhanced in liposarcoma, and Ohio State University HDAC42 (OSU-HDAC42) is a selective HDAC2 inhibitor that has been examined in colon cancer [118]. The HDAC2 inhibitor CAY10683 ameliorates LPS-induced inflammation in neurons [119] and acute liver dysfunction [120]. Pan-HDAC inhibitors are known to have therapeutic efficacy against cutaneous sarcomas. The HDAC inhibitors romidepsin and quisinostat can suppress tumor growth in synovial sarcoma [121,122]. Vorinostat is currently available in clinics [123]. Other HDAC inhibitors are also expected to be useful in treating cutaneous sarcomas.

Table 2. The potent therapeutic efficacy against skin sarcomas.

Candidates	Action Mechanism
Tazemetostat	EZH2 inhibitor [102–107]
MG98	DNMT1 inhibitor [109]
Decitabine	DNMT1 inhibitor [110]
SGI-1027	DNMT1 inhibitor [111]
Quisinostat and romidepsin	Pan-HDAC inhibitor [121,122]
OSU-HDAC42	HDAC2 inhibitor [118]
CAY10683	HDAC2 inhibitor [120]
LMK235	HDAC4 inhibitor [117]

Current advancements in immunotherapy against malignancies have improved the clinical outcomes for the treatment of advanced or metastasis-form cancers. Sarcomas are also expected to be treatable using immunotherapy. Specifically, PD-1-targeted therapy has been highlighted in sarcomas [124]. Class I HDAC is associated with an unfavorable prognosis in patients with sarcomas, and its inhibition by chidamide, in combination with anti-PD-1 antibody treatment, improved survival in mice [125].

Although these epigenetic-targeted treatments have been explored to a modest degree for cutaneous sarcoma, further clinical trials are needed to clarify their impact and future utility.

9. Conclusions

Herein, we reported the effects of epigenetic modifications on skin soft-tissue malignancies and ways to target such modifications for future therapeutic applications. Epigenetics comprehensively affects soft tissue malignant tumors. As oncogenesis depends on the characteristics of each originating cell type, the influence of specific epigenetic modifications must be studied in each tumor type. Based on the promising antitumor effects of epigenetics-targeted therapy on cutaneous sarcomas in previous studies, clinical studies are needed to further explore this option. As curative treatment for soft-tissue sarcomas is still difficult to achieve, the development of epigenetic-targeted treatment for this tumor type could hold great potential.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kabashima, K.; Honda, T.; Ginhoux, F.; Egawa, G. The immunological anatomy of the skin. *Nat. Rev. Immunol.* **2019**, *19*, 19–30. [CrossRef]
2. Kim, S.; Park, J.W.; Yeon, Y.; Han, J.Y.; Kim, E. Influence of exposure to summer environments on skin properties. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 2192–2196. [CrossRef]
3. Sawada, Y.; Nakatsuji, T.; Dokoshi, T.; Kulkarni, N.N.; Liggins, M.C.; Sen, G.; Gallo, R.L. Cutaneous innate immune tolerance is mediated by epigenetic control of MAP2K3 by HDAC8/9. *Sci. Immunol.* **2021**, *6*, 59. [CrossRef]
4. Mervis, J.S.; McGee, J.S. DNA methylation and inflammatory skin diseases. *Arch. Dermatol. Res.* **2020**, *312*, 461–466. [CrossRef]
5. Pastar, I.; Marjanovic, J.; Stone, R.C.; Chen, V.; Burgess, J.L.; Mervis, J.S.; Tomic-Canic, M. Epigenetic regulation of cellular functions in wound healing. *Exp. Dermatol.* **2021**, *30*, 1073–1089. [CrossRef]
6. Giunta, E.F.; Arrichiello, G.; Curvietto, M.; Pappalardo, A.; Bosso, D.; Rosanova, M.; Diana, A.; Giordano, P.; Petrillo, A.; Federico, P.; et al. Epigenetic Regulation in Melanoma: Facts and Hopes. *Cells* **2021**, *10*, 8. [CrossRef]

7.   Kashyap, M.P.; Sinha, R.; Mukhtar, M.S.; Athar, M. Epigenetic regulation in the pathogenesis of non-melanoma skin cancer. *Semin. Cancer Biol.* **2020**. [CrossRef]

8.   Soboleva, A.G.; Mezentsev, A.; Zolotorenko, A.; Bruskin, S.; Pirusian, E. Three-dimensional skin models of psoriasis. *Cells Tissues Organs* **2014**, *199*, 301–310. [CrossRef]

9.   Sawada, Y.; Tong, Y.; Barangi, M.; Hata, T.; Williams, M.R.; Nakatsuji, T.; Gallo, R.L. Dilute bleach baths used for treatment of atopic dermatitis are not antimicrobial in vitro. *J. Allergy Clin. Immunol.* **2019**, *143*, 1946–1948. [CrossRef]

10.   Fuchs, E. Epithelial Skin Biology: Three Decades of Developmental Biology, a Hundred Questions Answered and a Thousand New Ones to Address. *Curr. Top. Dev. Biol.* **2016**, *116*, 357–374.

11.   Sakabe, J.; Kamiya, K.; Yamaguchi, H.; Ikeya, S.; Suzuki, T.; Aoshima, M.; Tatsuno, K.; Fujiyama, T.; Suzuki, M.; Yatagai, T.; et al. Proteome analysis of stratum corneum from atopic dermatitis patients by hybrid quadrupole-orbitrap mass spectrometer. *J. Allergy Clin. Immunol.* **2014**, *134*, 957–960. [CrossRef] [PubMed]

12.   Sawada, Y.; Honda, T.; Nakamizo, S.; Nakajima, S.; Nonomura, Y.; Otsuka, A.; Egawa, G.; Yoshimoto, T.; Nakamura, M.; Narumiya, S.; et al. Prostaglandin E(2) (PGE(2))-EP2 signaling negatively regulates murine atopic dermatitis-like skin inflammation by suppressing thymic stromal lymphopoietin expression. *J. Allergy Clin. Immunol.* **2019**, *144*, 1265–1273. [CrossRef]

13.   Slominski, A.T.; Zmijewski, M.A.; Plonka, P.M.; Szaflarski, J.P.; Paus, R. How UV Light Touches the Brain and Endocrine System Through Skin, and Why. *Endocrinology* **2018**, *159*, 1992–2007. [CrossRef] [PubMed]

14.   Kabashima, K.; Matsumura, T.; Komazaki, H.; Kawashima, M. Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. *N. Engl. J. Med.* **2020**, *383*, 141–150. [CrossRef]

15.   Eichenfield, D.Z.; Sprague, J.; Eichenfield, L.F. Management of Acne Vulgaris: A Review. *JAMA* **2021**, *326*, 2055–2067. [CrossRef]

16.   Sawada, Y.; Gallo, R.L. Role of Epigenetics in the Regulation of Immune Functions of the Skin. *J. Investig. Dermatol.* **2021**, *141*, 1157–1166. [CrossRef]

17.   Beaziz, J.; Battistella, M.; Delyon, J.; Farges, C.; Marco, O.; Pages, C.; Le Maignan, C.; Da Meda, L.; Basset-Seguin, N.; Resche-Rigon, M.; et al. Long-Term Outcome of Neoadjuvant Tyrosine Kinase Inhibitors Followed by Complete Surgery in Locally Advanced Dermatofibrosarcoma Protuberans. *Cancers* **2021**, *13*, 9. [CrossRef]

18.   Cai, H.J.; Fang, J.H.; Cao, N.; Wang, W.; Kong, F.L.; Sun, X.X.; Huang, B. Dermatofibrosarcoma metastases to the pancreas: A case report. *World J. Clin. Cases* **2019**, *7*, 3316–3321. [CrossRef] [PubMed]

19.   Giacchero, D.; Maire, G.; Nuin, P.A.; Berthier, F.; Ebran, N.; Carlotti, A.; Celerier, P.; Coindre, J.M.; Esteve, E.; Fraitag, S.; et al. No correlation between the molecular subtype of COL1A1-PDGFB fusion gene and the clinico-histopathological features of dermatofibrosarcoma protuberans. *J. Investig. Dermatol.* **2010**, *130*, 904–907. [CrossRef]

20.   Criscione, V.D.; Weinstock, M.A. Descriptive epidemiology of dermatofibrosarcoma protuberans in the United States, 1973 to 2002. *J. Am. Acad. Dermatol.* **2007**, *56*, 968–973. [CrossRef]

21.   Rouhani, P.; Fletcher, C.D.; Devesa, S.S.; Toro, J.R. Cutaneous soft tissue sarcoma incidence patterns in the U.S.: An analysis of 12,114 cases. *Cancer* **2008**, *113*, 616–627. [CrossRef]

22.   Protein CellMendenhall, W.M.; Zlotecki, R.A.; Scarborough, M.T. Dermatofibrosarcoma protuberans. *Cancer* **2004**, *101*, 2503–2508.

23.   Corvetta, D.; Chayka, O.; Gherardi, S.; D'Acunto, C.W.; Cantilena, S.; Valli, E.; Piotrowska, I.; Perini, G.; Sala, A. Physical interaction between MYCN oncogene and polycomb repressive complex 2 (PRC2) in neuroblastoma: Functional and therapeutic implications. *J. Biol. Chem.* **2013**, *288*, 8332–8341. [CrossRef]

24.   Cao, R.; Wang, L.; Wang, H.; Xia, L.; Erdjument-Bromage, H.; Tempst, P.; Jones, R.S.; Zhang, Y. Role of histone H3 lysine 27 methylation in Polycomb-group silencing. *Science* **2002**, *298*, 1039–1043. [CrossRef]

25.   Cook, N.; Chen, J.; Zhou, J.; Wu, D. Embryonic Ectoderm Development (EED) as a Novel Target for Cancer Treatment. *Curr. Top. Med. Chem.* **2021**. [CrossRef]

26.   Martin, M.C.; Zeng, G.; Yu, J.; Schiltz, G.E. Small Molecule Approaches for Targeting the Polycomb Repressive Complex 2 (PRC2) in Cancer. *J. Med. Chem.* **2020**, *63*, 15344–15370. [CrossRef]

27.   Pasini, D.; Bracken, A.P.; Jensen, M.R.; Lazzerini Denchi, E.; Helin, K. Suz12 is essential for mouse development and for EZH2 histone methyltransferase activity. *EMBO J.* **2004**, *23*, 4061–4071. [CrossRef]

28.   Kuzmichev, A.; Nishioka, K.; Erdjument-Bromage, H.; Tempst, P.; Reinberg, D. Histone methyltransferase activity associated with a human multiprotein complex containing the Enhancer of Zeste protein. *Genes Dev.* **2002**, *16*, 2893–2905. [CrossRef] [PubMed]

29.   Huang, J.; Zhang, J.; Guo, Z.; Li, C.; Tan, Z.; Wang, J.; Yang, J.; Xue, L. Easy or Not-The Advances of EZH2 in Regulating T Cell Development, Differentiation, and Activation in Antitumor Immunity. *Front. Immunol.* **2021**, *12*, 741302. [CrossRef] [PubMed]

30.   Stacchiotti, S.; Astolfi, A.; Gronchi, A.; Fontana, A.; Pantaleo, M.A.; Negri, T.; Brenca, M.; Tazzari, M.; Urbini, M.; Indio, V.; et al. Evolution of Dermatofibrosarcoma Protuberans to DFSP-Derived Fibrosarcoma: An Event Marked by Epithelial-Mesenchymal Transition-like Process and 22q Loss. *Mol. Cancer Res.* **2016**, *14*, 820–829. [CrossRef] [PubMed]

31.   Wagener, N.; Macher-Goeppinger, S.; Pritsch, M.; Hüsing, J.; Hoppe-Seyler, K.; Schirmacher, P.; Pfitzenmaier, J.; Haferkamp, A.; Hoppe-Seyler, F.; Hohenfellner, M. Enhancer of zeste homolog 2 (EZH2) expression is an independent prognostic factor in renal cell carcinoma. *BMC Cancer* **2010**, *10*, 524. [CrossRef]

32.   Gong, C.; Yao, S.; Gomes, A.R.; Man, E.P.; Lee, H.J.; Gong, G.; Chang, S.; Kim, S.B.; Fujino, K.; Kim, S.W.; et al. BRCA1 positively regulates FOXO3 expression by restricting FOXO3 gene methylation and epigenetic silencing through targeting EZH2 in breast cancer. *Oncogenesis* **2016**, *5*, e214. [CrossRef]

33. Varambally, S.; Dhanasekaran, S.M.; Zhou, M.; Barrette, T.R.; Kumar-Sinha, C.; Sanda, M.G.; Ghosh, D.; Pienta, K.J.; Sewalt, R.G.; Otte; et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature* **2002**, *419*, 624–629. [CrossRef]

34. van Kemenade, F.J.; Raaphorst, F.M.; Blokzijl, T.; Fieret, E.; Hamer, K.M.; Satijn, D.P.; Otte, A.P.; Meijer, C.J. Coexpression of BMI-1 and EZH2 polycomb-group proteins is associated with cycling cells and degree of malignancy in B-cell non-Hodgkin lymphoma. *Blood* **2001**, *97*, 3896–3901. [CrossRef]

35. Takahira, T.; Oda, Y.; Tamiya, S.; Yamamoto, H.; Kawaguchi, K.; Kobayashi, C.; Oda, S.; Iwamoto, Y.; Tsuneyoshi, M. Microsatellite instability and p53 mutation associated with tumor progression in dermatofibrosarcoma protuberans. *Hum. Pathol.* **2004**, *35*, 240–245. [CrossRef]

36. Khan, J.A.; Maki, R.G.; Ravi, V. Pathologic Angiogenesis of Malignant Vascular Sarcomas: Implications for Treatment. *J. Clin. Oncol.* **2018**, *36*, 194–201. [CrossRef] [PubMed]

37. Heinhuis, K.M.; NS, I.J.; van der Graaf, W.T.A.; Kerst, J.M.; Schrage, Y.; Beijnen, J.H.; Steeghs, N.; van Houdt, W.J. Neoadjuvant Systemic Treatment of Primary Angiosarcoma. *Cancers* **2020**, *12*, 8. [CrossRef] [PubMed]

38. Coindre, J.M.; Terrier, P.; Guillou, L.; Le Doussal, V.; Collin, F.; Ranchère, D.; Sastre, X.; Vilain, M.O.; Bonichon, F.; N'Guyen Bui, B. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: A study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer* **2001**, *91*, 1914–1926. [PubMed]

39. Zietz, C.; Rössle, M.; Haas, C.; Sendelhofert, A.; Hirschmann, A.; Stürzl, M.; Löhrs, U. MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. *Am. J. Pathol.* **1998**, *153*, 1425–1433. [CrossRef]

40. Hollstein, M.; Marion, M.J.; Lehman, T.; Welsh, J.; Harris, C.C.; Martel-Planche, G.; Kusters, I.; Montesano, R. p53 mutations at A:T base pairs in angiosarcomas of vinyl chloride-exposed factory workers. *Carcinogenesis* **1994**, *15*, 1–3. [CrossRef]

41. Li, Q.; Zhang, Y.; El-Naggar, A.K.; Xiong, S.; Yang, P.; Jackson, J.G.; Chau, G.; Lozano, G. Therapeutic efficacy of p53 restoration in Mdm2-overexpressing tumors. *Mol. Cancer Res.* **2014**, *12*, 901–911. [CrossRef]

42. Donehower, L.A.; Harvey, M.; Slagle, B.L.; McArthur, M.J.; Montgomery, C.A., Jr.; Butel, J.S.; Bradley, A. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature* **1992**, *356*, 215–221. [CrossRef] [PubMed]

43. Feller, J.K.; Mahalingam, M. c-myc and cutaneous vascular neoplasms. *Am. J. Dermatopathol.* **2013**, *35*, 364–369. [CrossRef]

44. Italiano, A.; Chen, C.L.; Thomas, R.; Breen, M.; Bonnet, F.; Sevenet, N.; Longy, M.; Maki, R.G.; Coindre, J.M.; Antonescu, C.R. Alterations of the p53 and PIK3CA/AKT/mTOR pathways in angiosarcomas: A pattern distinct from other sarcomas with complex genomics. *Cancer* **2012**, *118*, 5878–5887. [CrossRef] [PubMed]

45. Andersen, N.J.; Boguslawski, E.B.; Kuk, C.Y.; Chambers, C.M.; Duesbery, N.S. Combined inhibition of MEK and mTOR has a synergic effect on angiosarcoma tumorgrafts. *Int. J. Oncol.* **2015**, *47*, 71–80. [CrossRef]

46. Mentzel, T.; Kiss, K. Reduced H3K27me3 expression in radiation-associated angiosarcoma of the breast. *Virchows Arch.* **2018**, *472*, 361–368. [CrossRef]

47. Kumar, A.; Kumar, S.; Vikram, A.; Hoffman, T.A.; Naqvi, A.; Lewarchik, C.M.; Kim, Y.R.; Irani, K. Histone and DNA methylation-mediated epigenetic downregulation of endothelial Kruppel-like factor 2 by low-density lipoprotein cholesterol. *Arterioscler Thromb. Vasc. Biol.* **2013**, *33*, 1936–1942. [CrossRef] [PubMed]

48. Bastow, R.; Mylne, J.S.; Lister, C.; Lippman, Z.; Martienssen, R.A.; Dean, C. Vernalization requires epigenetic silencing of FLC by histone methylation. *Nature* **2004**, *427*, 164–167. [CrossRef] [PubMed]

49. He, J.; Kallin, E.M.; Tsukada, Y.; Zhang, Y. The H3K36 demethylase Jhdm1b/Kdm2b regulates cell proliferation and senescence through p15(Ink4b). *Nat. Struct. Mol. Biol.* **2008**, *15*, 1169–1175. [CrossRef]

50. Farcas, A.M.; Blackledge, N.P.; Sudbery, I.; Long, H.K.; McGouran, J.F.; Rose, N.R.; Lee, S.; Sims, D.; Cerase, A.; Sheahan, T.W.; et al. KDM2B links the Polycomb Repressive Complex 1 (PRC1) to recognition of CpG islands. *Elife* **2012**, *1*, e00205. [CrossRef]

51. Lehmann, L.; Ferrari, R.; Vashisht, A.A.; Wohlschlegel, J.A.; Kurdistani, S.K.; Carey, M. Polycomb repressive complex 1 (PRC1) disassembles RNA polymerase II preinitiation complexes. *J. Biol. Chem.* **2012**, *287*, 35784–35794. [CrossRef]

52. Tzatsos, A.; Paskaleva, P.; Lymperi, S.; Contino, G.; Stoykova, S.; Chen, Z.; Wong, K.K.; Bardeesy, N. Lysine-specific demethylase 2B (KDM2B)-let-7-enhancer of zester homolog 2 (EZH2) pathway regulates cell cycle progression and senescence in primary cells. *J. Biol. Chem.* **2011**, *286*, 33061–33069. [CrossRef]

53. Gulay, K.C.M.; Aoshima, K.; Shibata, Y.; Yasui, H.; Yan, Q.; Kobayashi, A.; Kimura, T. KDM2B promotes cell viability by enhancing DNA damage response in canine hemangiosarcoma. *J. Genet. Genomics* **2021**, *48*, 618–630. [CrossRef] [PubMed]

54. Yan, M.; Yang, X.; Wang, H.; Shao, Q. The critical role of histone lysine demethylase KDM2B in cancer. *Am. J. Transl. Res.* **2018**, *10*, 2222–2233.

55. Cesarman, E.; Chadburn, A.; Rubinstein, P.G. KSHV/HHV8-mediated hematologic diseases. *Blood* **2021**. [CrossRef] [PubMed]

56. Brenner, B.; Rakowsky, E.; Katz, A.; Gutman, H.; Sulkes, A.; Schacter, J.; Fenig, E. Tailoring treatment for classical Kaposi's sarcoma: Comprehensive clinical guidelines. *Int. J. Oncol.* **1999**, *14*, 1097–1102. [CrossRef]

57. Ducimetière, F.; Lurkin, A.; Ranchère-Vince, D.; Decouvelaere, A.V.; Péoc'h, M.; Istier, L.; Chalabreysse, P.; Muller, C.; Alberti, L.; Bringuier, P.P.; et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. *PLoS ONE* **2011**, *6*, e20294. [CrossRef]

58. Si, H.; Robertson, E.S. Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen induces chromosomal instability through inhibition of p53 function. *J. Virol.* **2006**, *80*, 697–709. [CrossRef] [PubMed]

59. An, F.Q.; Compitello, N.; Horwitz, E.; Sramkoski, M.; Knudsen, E.S.; Renne, R. The latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus modulates cellular gene expression and protects lymphoid cells from p16 INK4A-induced cell cycle arrest. *J. Biol. Chem.* **2005**, *280*, 3862–3874. [CrossRef] [PubMed]

60. Liu, J.; Martin, H.; Shamay, M.; Woodard, C.; Tang, Q.Q.; Hayward, S.D. Kaposi's sarcoma-associated herpesvirus LANA protein downregulates nuclear glycogen synthase kinase 3 activity and consequently blocks differentiation. *J. Virol.* **2007**, *81*, 4722–4731. [CrossRef]

61. Fujimuro, M.; Liu, J.; Zhu, J.; Yokosawa, H.; Hayward, S.D. Regulation of the interaction between glycogen synthase kinase 3 and the Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen. *J. Virol.* **2005**, *79*, 10429–10441. [CrossRef]

62. Fujimuro, M.; Hayward, S.D. Manipulation of glycogen-synthase kinase-3 activity in KSHV-associated cancers. *J. Mol. Med.* **2004**, *82*, 223–231. [CrossRef]

63. Fujimuro, M.; Wu, F.Y.; ApRhys, C.; Kajumbula, H.; Young, D.B.; Hayward, G.S.; Hayward, S.D. A novel viral mechanism for dysregulation of beta-catenin in Kaposi's sarcoma-associated herpesvirus latency. *Nat. Med.* **2003**, *9*, 300–306. [CrossRef] [PubMed]

64. Di Bartolo, D.L.; Cannon, M.; Liu, Y.F.; Renne, R.; Chadburn, A.; Boshoff, C.; Cesarman, E. KSHV LANA inhibits TGF-beta signaling through epigenetic silencing of the TGF-beta type II receptor. *Blood* **2008**, *111*, 4731–4740. [CrossRef] [PubMed]

65. Reik, W.; Dean, W.; Walter, J. Epigenetic reprogramming in mammalian development. *Science* **2001**, *293*, 1089–1093. [CrossRef]

66. Shamay, M.; Krithivas, A.; Zhang, J.; Hayward, S.D. Recruitment of the de novo DNA methyltransferase Dnmt3a by Kaposi's sarcoma-associated herpesvirus LANA. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 14554–14559. [CrossRef]

67. Suzuki, T.; Wada, S.; Eguchi, H.; Adachi, J.; Mishima, K.; Matsutani, M.; Nishikawa, R.; Nishiyama, M. Cadherin 13 overexpression as an important factor related to the absence of tumor fluorescence in 5-aminolevulinic acid-guided resection of glioma. *J. Neurosurg.* **2013**, *119*, 1331–1339. [CrossRef] [PubMed]

68. Andreeva, A.V.; Kutuzov, M.A. Cadherin 13 in cancer. *Genes Chromosomes Cancer* **2010**, *49*, 775–790. [CrossRef]

69. Li, W.; Wang, Q.; Qi, X.; Guo, Y.; Lu, H.; Chen, Y.; Lu, Z.; Yan, Q.; Zhu, X.; Jung, J.U.; et al. Viral interleukin-6 encoded by an oncogenic virus promotes angiogenesis and cellular transformation by enhancing STAT3-mediated epigenetic silencing of caveolin 1. *Oncogene* **2020**, *39*, 4603–4618. [CrossRef] [PubMed]

70. Racadot, E.; Audhuy, B.; Duvernoy, H.; Thyss, A.; Lang, J.M.; Wijdenes, J.; Hervé, P. Clinical and immunological follow-up of patients with AIDS-associated Kaposi's sarcoma treated with an anti-IL-6 monoclonal antibody. *Cytokines Mol. Ther.* **1995**, *1*, 133–138. [PubMed]

71. He, M.; Zhang, W.; Bakken, T.; Schutten, M.; Toth, Z.; Jung, J.U.; Gill, P.; Cannon, M.; Gao, S.J. Cancer angiogenesis induced by Kaposi sarcoma-associated herpesvirus is mediated by EZH2. *Cancer Res.* **2012**, *72*, 3582–3592. [CrossRef] [PubMed]

72. Bernstein, S.C.; Roenigk, R.K. Leiomyosarcoma of the skin. Treatment of 34 cases. *Dermatol. Surg.* **1996**, *22*, 631–635. [CrossRef] [PubMed]

73. Ciurea, M.E.; Georgescu, C.V.; Radu, C.C.; Georgescu, C.C.; Stoica, L.E. Cutaneous leiomyosarcoma—Case report. *J. Med. Life* **2014**, *7*, 270–273. [PubMed]

74. Vargas, A.C.; Gray, L.A.; White, C.L.; Maclean, F.M.; Grimison, P.; Ardakani, N.M.; Bonar, F.; Algar, E.M.; Cheah, A.L.; Russell, P.; et al. Genome wide methylation profiling of selected matched soft tissue sarcomas identifies methylation changes in metastatic and recurrent disease. *Sci. Rep.* **2021**, *11*, 667. [CrossRef] [PubMed]

75. Hasan, N.M.; Sharma, A.; Ruzgar, N.M.; Deshpande, H.; Olino, K.; Khan, S.; Ahuja, N. Epigenetic signatures differentiate uterine and soft tissue leiomyosarcoma. *Oncotarget* **2021**, *12*, 1566–1579. [CrossRef] [PubMed]

76. Shridhar, K.; Walia, G.K.; Aggarwal, A.; Gulati, S.; Geetha, A.V.; Prabhakaran, D.; Dhillon, P.K.; Rajaraman, P. DNA methylation markers for oral pre-cancer progression: A critical review. *Oral Oncol.* **2016**, *53*, 1–9. [CrossRef] [PubMed]

77. Zhai, X.; Brownell, J.E. Biochemical perspectives on targeting KMT2 methyltransferases in cancer. *Trends Pharmacol. Sci.* **2021**, *42*, 688–699. [CrossRef] [PubMed]

78. Poreba, E.; Lesniewicz, K.; Durzynska, J. Aberrant Activity of Histone-Lysine N-Methyltransferase 2 (KMT2) Complexes in Oncogenesis. *Int. J. Mol. Sci.* **2020**, *21*, 24. [CrossRef]

79. Donati, B.; Lorenzini, E.; Ciarrocchi, A. BRD4 and Cancer: Going beyond transcriptional regulation. *Mol. Cancer* **2018**, *17*, 164. [CrossRef]

80. De Carvalho Fischer, C.; Hu, Y.; Morreale, M.; Lin, W.Y.; Wali, A.; Thakar, M.; Karunasena, E.; Sen, R.; Cai, Y.; Murphy, L.; et al. Treatment with epigenetic agents profoundly inhibits tumor growth in leiomyosarcoma. *Oncotarget* **2018**, *9*, 19379–19395. [CrossRef]

81. Di Giorgio, E.; Dalla, E.; Franforte, E.; Paluvai, H.; Minisini, M.; Trevisanut, M.; Picco, R.; Brancolini, C. Different class IIa HDACs repressive complexes regulate specific epigenetic responses related to cell survival in leiomyosarcoma cells. *Nucleic Acids Res.* **2020**, *48*, 646–664. [CrossRef] [PubMed]

82. Monga, V.; Swami, U.; Tanas, M.; Bossler, A.; Mott, S.L.; Smith, B.J.; Milhem, M. A Phase I/II Study Targeting Angiogenesis Using Bevacizumab Combined with Chemotherapy and a Histone Deacetylase Inhibitor (Valproic Acid) in Advanced Sarcomas. *Cancers* **2018**, *10*, 2. [CrossRef] [PubMed]

83. Engström, K.; Bergh, P.; Gustafson, P.; Hultborn, R.; Johansson, H.; Löfvenberg, R.; Zaikova, O.; Trovik, C.; Wahlström, O.; Bauer, H.C. Liposarcoma: Outcome based on the Scandinavian Sarcoma Group register. *Cancer* **2008**, *113*, 1649–1656. [CrossRef] [PubMed]

84. Mashima, E.; Sawada, Y.; Nakamura, M. Recent Advancement in Atypical Lipomatous Tumor Research. *Int. J. Mol. Sci.* **2021**, *22*, 994. [CrossRef]
85. Mashima, E.; Sawada, Y.; Saito-Sasaki, N.; Yamamoto, K.; Ohmori, S.; Omoto, D.; Yoshioka, H.; Yoshioka, M.; Okada, E.; Aoki, T.; et al. A Retrospective Study of Superficial Type Atypical Lipomatous Tumor. *Front. Med.* **2020**, *7*, 609515. [CrossRef]
86. Kammerer-Jacquet, S.F.; Thierry, S.; Cabillic, F.; Lannes, M.; Burtin, F.; Henno, S.; Dugay, F.; Bouzillé, G.; Rioux-Leclercq, N.; Belaud-Rotureau, M.A.; et al. Differential diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma: Utility of p16 in combination with MDM2 and CDK4 immunohistochemistry. *Hum. Pathol.* **2017**, *59*, 34–40. [CrossRef]
87. Knösel, T.; Altendorf-Hofmann, A.; Lindner, L.; Issels, R.; Hermeking, H.; Schuebbe, G.; Gibis, S.; Siemens, H.; Kampmann, E.; Kirchner, T. Loss of p16(INK4a) is associated with reduced patient survival in soft tissue tumours, and indicates a senescence barrier. *J. Clin. Pathol.* **2014**, *67*, 592–598. [CrossRef]
88. Manji, G.A.; Schwartz, G.K. Managing Liposarcomas: Cutting Through the Fat. *J. Oncol. Pract.* **2016**, *12*, 221–227. [CrossRef]
89. Kanojia, D.; Nagata, Y.; Garg, M.; Lee, D.H.; Sato, A.; Yoshida, K.; Sato, Y.; Sanada, M.; Mayakonda, A.; Bartenhagen, C.; et al. Genomic landscape of liposarcoma. *Oncotarget* **2015**, *6*, 42429–42444. [CrossRef]
90. Iwasaki, H.; Ishiguro, M.; Nishio, J.; Aoki, M.; Yokoyama, R.; Yokoyama, K.; Taguchi, K.; Nabeshima, K. Extensive lipoma-like changes of myxoid liposarcoma: Morphologic, immunohistochemical, and molecular cytogenetic analyses. *Virchows Arch.* **2015**, *466*, 453–464. [CrossRef]
91. Yang, L.; Chen, S.; Luo, P.; Yan, W.; Wang, C. Liposarcoma: Advances in Cellular and Molecular Genetics Alterations and Corresponding Clinical Treatment. *J. Cancer* **2020**, *11*, 100–107. [CrossRef] [PubMed]
92. Sievers, S.; Fritzsch, C.; Lehnhardt, M.; Zahn, S.; Kutzner, N.; Kuhnen, C.; Müller, O. Hypermethylation of the APC promoter but lack of APC mutations in myxoid/round-cell liposarcoma. *Int. J. Cancer* **2006**, *119*, 2347–2352. [CrossRef]
93. Barretina, J.; Taylor, B.S.; Banerji, S.; Ramos, A.H.; Lagos-Quintana, M.; Decarolis, P.L.; Shah, K.; Socci, N.D.; Weir, B.A.; Ho, A.; et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. *Nat. Genet.* **2010**, *42*, 715–721. [CrossRef] [PubMed]
94. He, M.; Aisner, S.; Benevenia, J.; Patterson, F.; Harrison, L.E.; Hameed, M. Epigenetic alteration of p16INK4a gene in dedifferentiation of liposarcoma. *Pathol. Res. Pract.* **2009**, *205*, 386–394. [CrossRef] [PubMed]
95. Taylor, B.S.; DeCarolis, P.L.; Angeles, C.V.; Brenet, F.; Schultz, N.; Antonescu, C.R.; Scandura, J.M.; Sander, C.; Viale, A.J.; Socci, N.D.; et al. Frequent alterations and epigenetic silencing of differentiation pathway genes in structurally rearranged liposarcomas. *Cancer Discov.* **2011**, *1*, 587–597. [CrossRef]
96. Seligson, N.D.; Stets, C.W.; Demoret, B.W.; Awasthi, A.; Grosenbacher, N.; Shakya, R.; Hays, J.L.; Chen, J.L. Inhibition of histone deacetylase 2 reduces MDM2 expression and reduces tumor growth in dedifferentiated liposarcoma. *Oncotarget* **2019**, *10*, 5671–5679. [CrossRef]
97. Nakazawa, M.S.; Eisinger-Mathason, T.S.; Sadri, N.; Ochocki, J.D.; Gade, T.P.; Amin, R.K.; Simon, M.C. Epigenetic re-expression of HIF-2α suppresses soft tissue sarcoma growth. *Nat. Commun.* **2016**, *7*, 10539. [CrossRef]
98. Keung, E.Z.; Akdemir, K.C.; Al Sannaa, G.A.; Garnett, J.; Lev, D.; Torres, K.E.; Lazar, A.J.; Rai, K.; Chin, L. Increased H3K9me3 drives dedifferentiated phenotype via KLF6 repression in liposarcoma. *J. Clin. Investig.* **2015**, *125*, 2965–2978. [CrossRef]
99. Lazarides, A.L.; Eward, W.C.; Speicher, P.J.; Hou, C.H.; Nussbaum, D.P.; Green, C.; Blazer, D.G.; Kirsch, D.G.; Brigman, B.E. The Use of Radiation Therapy in Well-Differentiated Soft Tissue Sarcoma of the Extremities: An NCDB Review. *Sarcoma* **2015**, *2015*, 186581. [CrossRef]
100. Antwih, D.A.; Gabbara, K.M.; Lancaster, W.D.; Ruden, D.M.; Zielske, S.P. Radiation-induced epigenetic DNA methylation modification of radiation-response pathways. *Epigenetics* **2013**, *8*, 839–848. [CrossRef]
101. Herberg, M.; Siebert, S.; Quaas, M.; Thalheim, T.; Rother, K.; Hussong, M.; Altmüller, J.; Kerner, C.; Galle, J.; Schweiger, M.R.; et al. Loss of Msh2 and a single-radiation hit induce common, genome-wide, and persistent epigenetic changes in the intestine. *Clin. Epigenetics* **2019**, *11*, 65. [CrossRef] [PubMed]
102. Izutsu, K.; Ando, K.; Nishikori, M.; Shibayama, H.; Teshima, T.; Kuroda, J.; Kato, K.; Imaizumi, Y.; Nosaka, K.; Sakai, R.; et al. Phase II study of tazemetostat for relapsed or refractory B-cell non-Hodgkin lymphoma with EZH2 mutation in Japan. *Cancer Sci.* **2021**, *112*, 3627–3635. [CrossRef]
103. Munakata, W.; Shirasugi, Y.; Tobinai, K.; Onizuka, M.; Makita, S.; Suzuki, R.; Maruyama, D.; Kawai, H.; Izutsu, K.; Nakanishi, T.; et al. Phase 1 study of tazemetostat in Japanese patients with relapsed or refractory B-cell lymphoma. *Cancer Sci.* **2021**, *112*, 1123–1131. [CrossRef]
104. 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. [CrossRef]
105. Sarkozy, C.; Morschhauser, F.; Dubois, S.; Molina, T.; Michot, J.M.; Cullières-Dartigues, P.; Suttle, B.; Karlin, L.; Le Gouill, S.; Picquenot, J.M.; et al. A LYSA Phase Ib Study of Tazemetostat (EPZ-6438) plus R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma (DLBCL) with Poor Prognosis Features. *Clin. Cancer Res.* **2020**, *26*, 3145–3153. [CrossRef]
106. Morschhauser, F.; Tilly, H.; Chaidos, A.; McKay, P.; Phillips, T.; Assouline, S.; Batlevi, C.L.; Campbell, P.; Ribrag, V.; Damaj, G.L.; et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: An open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol.* **2020**, *21*, 1433–1442. [CrossRef]

107. Gounder, M.; Schöffski, P.; Jones, R.L.; Agulnik, M.; Cote, G.M.; Villalobos, V.M.; Attia, S.; Chugh, R.; Chen, T.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. [CrossRef]

108. Lyko, F. The DNA methyltransferase family: A versatile toolkit for epigenetic regulation. *Nat. Rev. Genet.* **2018**, *19*, 81–92. [CrossRef] [PubMed]

109. Amato, R.J.; Stephenson, J.; Hotte, S.; Nemunaitis, J.; Bélanger, K.; Reid, G.; Martell, R.E. MG98, a second-generation DNMT1 inhibitor, in the treatment of advanced renal cell carcinoma. *Cancer Investig.* **2012**, *30*, 415–421. [CrossRef] [PubMed]

110. Saunthararajah, Y.; Sekeres, M.; Advani, A.; Mahfouz, R.; Durkin, L.; Radivoyevitch, T.; Englehaupt, R.; Juersivich, J.; Cooper, K.; Husseinzadeh, H.; et al. Evaluation of noncytotoxic DNMT1-depleting therapy in patients with myelodysplastic syndromes. *J. Clin. Investig.* **2015**, *125*, 1043–1055. [CrossRef] [PubMed]

111. She, S.; Zhao, Y.; Kang, B.; Chen, C.; Chen, X.; Zhang, X.; Chen, W.; Dan, S.; Wang, H.; Wang, Y.J.; et al. Combined inhibition of JAK1/2 and DNMT1 by newly identified small-molecule compounds synergistically suppresses the survival and proliferation of cervical cancer cells. *Cell Death Dis.* **2020**, *11*, 724. [CrossRef]

112. Payet, M.; Dargai, F.; Gasque, P.; Guillot, X. Epigenetic Regulation (Including Micro-RNAs, DNA Methylation and Histone Modifications) of Rheumatoid Arthritis: A Systematic Review. *Int. J. Mol. Sci.* **2021**, *22*, 22. [CrossRef] [PubMed]

113. Zhao, S.; Zhang, X.; Li, H. Beyond histone acetylation-writing and erasing histone acylations. *Curr. Opin. Struct. Biol.* **2018**, *53*, 169–177. [CrossRef]

114. Jones, P.A.; Ohtani, H.; Chakravarthy, A.; De Carvalho, D.D. Epigenetic therapy in immune-oncology. *Nat. Rev. Cancer* **2019**, *19*, 151–161. [CrossRef] [PubMed]

115. Struhl, K. Histone acetylation and transcriptional regulatory mechanisms. *Genes Dev.* **1998**, *12*, 599–606. [CrossRef]

116. Jostes, S.; Nettersheim, D.; Schorle, H. Epigenetic drugs and their molecular targets in testicular germ cell tumours. *Nat. Rev. Urol.* **2019**, *16*, 245–259. [CrossRef]

117. Wu, L.; Zeng, S.; Cao, Y.; Huang, Z.; Liu, S.; Peng, H.; Zhi, C.; Ma, S.; Hu, K.; Yuan, Z. Inhibition of HDAC4 Attenuated JNK/c-Jun-Dependent Neuronal Apoptosis and Early Brain Injury Following Subarachnoid Hemorrhage by Transcriptionally Suppressing MKK7. *Front. Cell Neurosci.* **2019**, *13*, 468. [CrossRef] [PubMed]

118. Ravillah, D.; Mohammed, A.; Qian, L.; Brewer, M.; Zhang, Y.; Biddick, L.; Steele, V.E.; Rao, C.V. Chemopreventive effects of an HDAC2-selective inhibitor on rat colon carcinogenesis and APCmin/+ mouse intestinal tumorigenesis. *J. Pharmacol. Exp. Ther.* **2014**, *348*, 59–68. [CrossRef]

119. Jiao, F.Z.; Wang, Y.; Zhang, H.Y.; Zhang, W.B.; Wang, L.W.; Gong, Z.J. Histone Deacetylase 2 Inhibitor CAY10683 Alleviates Lipopolysaccharide Induced Neuroinflammation Through Attenuating TLR4/NF-κB Signaling Pathway. *Neurochem. Res.* **2018**, *43*, 1161–1170. [CrossRef]

120. Liu, Y.; Wang, Y.; Chen, Q.; Jiao, F.; Wang, L.; Gong, Z. HDAC2 inhibitor CAY10683 reduces intestinal epithelial cell apoptosis by inhibiting mitochondrial apoptosis pathway in acute liver failure. *Histol. Histopathol.* **2019**, *34*, 1173–1184.

121. Lubieniecka, J.M.; de Bruijn, D.R.; Su, L.; van Dijk, A.H.; Subramanian, S.; van de Rijn, M.; Poulin, N.; van Kessel, A.G.; Nielsen, T.O. Histone deacetylase inhibitors reverse SS18-SSX-mediated polycomb silencing of the tumor suppressor early growth response 1 in synovial sarcoma. *Cancer Res.* **2008**, *68*, 4303–4310. [CrossRef]

122. Laporte, A.N.; Barrott, J.J.; Yao, R.J.; Poulin, N.M.; Brodin, B.A.; Jones, K.B.; Underhill, T.M.; Nielsen, T.O. HDAC and Proteasome Inhibitors Synergize to Activate Pro-Apoptotic Factors in Synovial Sarcoma. *PLoS ONE* **2017**, *12*, e0169407. [CrossRef] [PubMed]

123. Schmitt, T.; Mayer-Steinacker, R.; Mayer, F.; Grünwald, V.; Schütte, J.; Hartmann, J.T.; Kasper, B.; Hüsing, J.; Hajda, J.; Ottawa, G.; et al. Vorinostat in refractory soft tissue sarcomas—Results of a multi-centre phase II trial of the German Soft Tissue Sarcoma and Bone Tumour Working Group (AIO). *Eur. J. Cancer* **2016**, *64*, 74–82. [CrossRef]

124. Kim, J.R.; Moon, Y.J.; Kwon, K.S.; Bae, J.S.; Wagle, S.; Kim, K.M.; Park, H.S.; Lee, H.; Moon, W.S.; Chung, M.J.; et al. Tumor infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. *PLoS ONE* **2013**, *8*, e82870. [CrossRef] [PubMed]

125. Que, Y.; Zhang, X.L.; Liu, Z.X.; Zhao, J.J.; Pan, Q.Z.; Wen, X.Z.; Xiao, W.; Xu, B.S.; Hong, D.C.; Guo, T.H.; et al. Frequent amplification of HDAC genes and efficacy of HDAC inhibitor chidamide and PD-1 blockade combination in soft tissue sarcoma. *J. Immunother. Cancer* **2021**, *9*, 2. [CrossRef] [PubMed]