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Epigenetic Regulators: New Therapeutic Targets for Soft Tissue Sarcoma

Pingyu Zhang[1] and **Raphael E Pollock**[2]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[2]Department of Surgical Oncology, Comprehensive Cancer Center, Ohio State University, Columbus, OH 43210, USA

Abstract

Soft tissue sarcoma is a malignancy that develops from human soft tissues such as muscle, nerve, fat, and blood vessels. The World Health Organization classification comprises about 50 different histologic types of soft tissue sarcoma. Soft tissue sarcoma is treated most often with surgery. Chemotherapy and radiotherapy have shown only minor effects on patient survival in this disease. The overall 5-year survival rate of soft tissue sarcoma is 50%; it has not changed for the past several decades. A new class of therapeutic targets for soft tissue sarcoma was identified recently. Epigenetic regulators, such as DNA methyltransferases, histone deacetylases, and histone-modifying enzyme enhancer of zeste homolog 2, have been found to be involved in pathogenesis of various soft tissue sarcomas. Small-molecule inhibitors of these epigenetic regulators may provide a new targeted therapy approach to soft tissue sarcomas in the future.

Keywords

Soft tissue sarcoma; DNA methyltransferase; histone deacetylases; enhancer of zeste homolog 2; epigenetics

Introduction

Soft tissue sarcoma by definition is a class of tumors that develop from nonepithelial, supporting, and connective tissues of the body, including muscle, fat, fibrous tissue, nerves, lymphatic tissue, and vascular tissue. Soft tissue sarcoma can be classified on the basis of its tissue of origin into any of about 50 different histologic subtypes defined by the World Health Organization[1]. These complex tumors are relatively rare, however. Approximately 10,000 new cases are diagnosed and 4000 deaths are attributed to soft tissue sarcoma in the USA every year[1]. Because of its heterogeneity and rarity, soft tissue sarcoma represents a therapeutic challenge.

Correspondence: Pingyu Zhang pinzhang@mdanderson.org.

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For primary soft tissue sarcoma, surgical resection remains the standard of care. Surgery combined with adjuvant radiotherapy and chemotherapy has been shown to decrease the local recurrence rate and improve the disease-free and overall survival rates of patients with this tumor[2]. For unresectable or metastastic soft tissue sarcoma, doxorubicin is the single most effective and widely used drug. A combination of doxorubicin and ifosfamide is currently the standard treatment for such cases[3]. Although systemic treatment increases the survival rate and quality of life among patients with metastatic disease, the overall 5-year survival rate for all soft tissue sarcoma cases is still approximately 50%. In order to further improve the survival rate and quality of life for soft tissue sarcoma patients, new therapeutic options are urgently needed. This paper reviews promising areas of research on molecular regulators of sarcoma oncogenesis and progression, especially epigenetic regulators as novel therapeutic targets for this disease.

Molecular Regulation of Sarcoma Tumorigenesis

To identify novel therapeutic targets and more effective drugs for soft tissue sarcoma, better understanding of the underlying molecular and genetic mechanisms is a necessity. Activating mutations in the c-*KIT* (or *PDGFRA*) gene have been identified as key molecular switches for tumorigenesis and development of gastrointestinal stromal tumors (GIST) [4]. Therefore, the use of imatinib, which targets active c-*KIT*, has dramatically improved clinical outcomes of adult GIST patients bearing mutations in this gene, with minimal side effects[5]. Although GIST tumor may develop resistance to imatinib after months or years of treatment, imatinib still results in a better survival rate than conventional chemotherapy[6].

In addition to imatinib, a number of novel targeted therapies are currently under evaluation in various stages of clinical trials for various soft tissue sarcomas. Tyrosine kinase inhibitors, such as sorafenib, sunitinib, and panzopanib, have potent inhibitory effects on angiogenic receptor VEGFR1-3 and c-KIT. Panzopanib achieved better progression-free survival rates for non-adipocytic soft tissue sarcoma than standard therapy in Phase III clinical trials, although this drug was noted to have substantial cardiotoxicity[7]. mTOR inhibitors have also been studied in preclinical and clinical settings. mTOR inhibitor ridaforolimus was confirmed to be have antitumor efficacy in sarcoma cell lines *in vitro* and in a xenograft animal model *in vivo*[8]. However, it showed only modest improvements in progression-free survival and overall survival rates in clinical trials in sarcoma patients[9]. Other new drugs, such as an MDM2 inhibitor and a CDK4 inhibitor for well-differentiated and dedifferentiated liposarcomas, are being tested in clinical trials now[10,11].

To identify more drug targets for sarcoma therapies, genomic, genetic and molecular approaches have been used. Recent reports have shown that mutations in retinoblastoma protein (Rb1) and isocitrate dehydrogenases 1 and 2 (IDH1/2) are involved in sarcoma initiation[12,13]. Mitotic spindle checkpoint kinase aurora A/B, cytoskeleton protein vimentin, growth factor midkine, hepatoma-derived growth factor, Wnt/β-catenin, and the AKT pathway have also been identified as potential drug targets for sarcoma[14-20]. Hypoxia-induced enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 has been shown to promote sarcoma metastasis but not primary tumor growth[21]. MicroRNAs such

as oncogenic miR-155 and tumor suppressive miR-143, miR-340, and miR-29 also were identified as potential therapeutic targets for sarcoma[22-25].

Epigenetic Regulators as Targets in Sarcoma

Among the novel and promising therapeutic targets for sarcoma are epigenetic regulators, which have been discovered recently as a new class of drug targets for human malignancies[26]. Epigenetic regulation of gene expression refers to the mechanisms that activate or suppress gene expression without changing underlying DNA sequences. In contrast to permanent and heritable genomic DNA changes, such as mutation, insertion or deletion; epigenetic changes of genomic DNA are temporal, spatial, reversible and not heritable. The molecular mechanisms of epigenetically gene regulation in cells include DNA methylation, histone modification, and RNA-associated silencing. Epigenetic regulation plays a vital role in stem cell maintenance, cell differentiation, and cell senescence[27].

DNA methylation of the CpG islands in the promoter region by DNA methyltransferases is an important regulator of gene transcription. Experimental evidence has revealed that aberrant DNA methylation of the promoter region of a gene is associated with abnormal gene expression, leading to various diseases and developmental defects[28]. Aberrant DNA methylation patterns on genomic DNA have been shown to cause a variety of human cancers and are shown in two distinct forms: hypermethylation and hypomethylation compared to non-tumor tissue[28]. Therfore, DNA-demethylating agents were developed and have been shown to be effective therapeutics for some types of hematological malignancies. For example, 5-azacytidine and 5-aza-2′-deoxycytidine, the most successful DNA-demethylating drugs, are currently used as the first-line treatment for high-risk myelodysplastic syndromes[29]. However, DNA methylation inhibitors have shown only minor effects on osteosarcoma cell proliferation and tumor growth[30]. Combinations of these agents with histone deacetylase (HDAC) inhibitors have exhibited synergistic effects in osteosarcoma cells in preclinical studies[30]. So far, no DNA methylation inhibitors have been tested in clinical trials for soft tissue sarcoma.

Histone modifications are also critically important for regulation of oncogenic and tumor suppressive genes. As the nucleosome core of the DNA assembly in chromatin, histones can be acetylated, methylated, ubiquitylated, phosphorylated, sumoylated, citrullinated, and ADP-ribosylated at multiple sites by different histone-modifying enzymes[27]. The histone acetylation balance, mediated by histone acetyltransferase and deacetylase, is crucial for maintenance of normal cell growth[31]. Deregulation induced by HDAC overexpression or malfunction occurs in many malignancies, resulting in abnormal modulation of target gene transcriptional activity. Therefore, HDAC inhibitors have been evaluated as anticancer therapeutics.

An HDAC inhibitor was recently studied for its effects on soft tissue sarcoma cell lines *in vitro* and animal xenograft models *in vivo*. Experimental data showed that HDAC inhibitor PCI-24781 inhibited cell proliferation of various soft tissue sarcoma cell lines *in vitro*[32]. The single-agent effects on tumor growth and metastasis *in vivo* were modest. However, combination of an HDAC inhibitor with chemotherapy produced substantial antitumor effects, and the HDAC inhibitor enhanced the effects of the chemotherapy agent on drug-

resistant sarcoma cells[32]. In malignant peripheral nerve sheath tumor (MPNST), neurofibromatosis 1–related (NF1-related) MPNST cell lines were sensitive to HDAC inhibitor treatment, which inhibited cell proliferation and induced cell apoptosis *in vitro* and blocked tumor growth in a xenograft mice model. However, sporadic (non-NF1-related) MPNST cell lines are resistant to HDAC inhibition *in vitro* and *in vivo* because HDAC inhibitor induced autophagy in these cells. When combined with an autophagy inhibitor, however, the HDAC inhibitor resumed strong inhibition of proliferation of sporadic MPNST cells *in vitro* and tumor growth *in vivo*[33]. HDAC inhibitors were also found to block growth of clear cell sarcoma, synovial sarcoma, and uterine sarcoma and to induce apoptosis and differentiation *in vitro* and *in vivo*[34-36]. These studies suggested that HDAC inhibition is a promising therapeutic strategy for sarcomas.

Another important histone modification enzyme is enhancer of zeste homolog 2 (EZH2), a histone methyltransferase that trimethylates histone H3 lysine 27[37]. EZH2 forms polycomb-repressor complex 2 (PRC2) with two other core proteins, SUZ12 and EED. PRC2 functions as a transcription repressor to critically coordinate gene expression and repression during many physiological and pathological processes[38]. Specifically in cancer, EZH2 has been identified as an oncogene in breast, lung, liver, prostate, blood and pancreatic cancers[38,39]. In mesenchyme-originating sarcomas, evidences show that EZH2 is involved in tumorigenesis and progression. High EZH2 expression is correlated with greater tumor size, distant metastasis, and poor prognosis in synovial sarcoma, and EZH2 mediates repression by SYT-SSX of the tumor suppressor ERG1[40]. In rhabdomyosarcoma, EZH2 is overexpressed and suppresses skeletal muscle differentiation through myofibrillary genes and miR-29 inhibition[41]. High EZH2 expression has also been found in Ewing sarcoma, in which EWS/FLI1 directly activates EZH2 expression and inhibits tumor cell differentiation[42]. Recently, the function of EZH2 and the molecular mechanisms that are regulated by EZH2 in MPNST pathogenesis have been investigated[43]. EZH2 expression is significantly higher in MPNST tumor samples than in neurofibromas and normal nerve tissues. In multiple MPNST cell lines, EZH2 protein expression is also higher than that in Schwann cells which are the potential origin of MPNST. Genetic knockdown of EZH2 in NF1-related and non-NF1-related MPNST cell lines induces cell death *in vitro* and inhibits tumor growth *in vivo*[43]. Evidences demonstrate that upregulated EZH2 in MPNST cells inhibits miR-30d expression via binding to miR-30d promoter. Decreased miR-30d expression leads to enhanced expression of *KPNB1*, because KPNB1 is inhibited by miR-30d targeting of the *KPNB1* 3′-untranslated region[43]. KPNB1 expression in MPNST cell lines and normal Schwann cells are positively correlated to EZH2 expression, and negative associated with mIR-30d expression[43]. These data suggest that EZH2 may play a critical role in the initiation and progression of MPNST. Compelling data from all these studies show the oncogenic function of EZH2 in different sarcomas and suggested that EZH2 inhibition may be a novel therapeutic approach for soft tissue sarcoma.

Conclusion

Taken together, epigenetic regulation mechanisms, specifically DNA methylation and histone modification, have been implicated as having important roles in sarcoma pathology. Preclinical studies have demonstrated that DNA methylation and histone modification

inhibitors have promise as new targeted therapies for sarcoma, either as single agents or combined with chemotherapy agents.

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