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Epigenetic modulation drives inflammatory responses in sarcoma

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Abstract

Compared with adult tumors, childhood malignancies are typically driven by a relatively small number of mutations, frequently in genes encoding epigenetic regulators. High-grade osteosarcoma (OS) is an aggressive bone malignancy characterized by massive genomic rearrangements and one of the most prevalent cancers in young adults. However, the role of epigenetic reprogramming in OS remains unclear. In this study, we sought to investigate the potential of histone modifications as prognostic and therapeutic biomarkers in OS. An *in silico* predictive algorithm of histone modification landscape from RNA sequencing data revealed that genome-wide levels of acetylation of the lysin 27 in histone 3 (H3K27ac) inversely correlated with survival. Notably, H3K27ac levels positively correlated with immune-related signatures indicating an inflamed tumor microenvironment. To investigate if H3K27ac expression influences inflammatory responses, the histone deacetylase 1-3 (HDAC) inhibitor Entinostat was used to induce H3K27ac expression in sarcoma tumors. Compared with untreated sarcoma tumors, Entinostat treatment resulted in higher infiltration of tissue resident T cells in *ex vivo* patient-derived sarcoma spheroids and in an *in vivo* model of OS. Mechanistically, our preliminary results highlight the involvement of the Hippo pathway mediators YAP1 and VGLL3 in Entinostat-mediated tumor infiltration of T cells. Together, these findings show that H3K27ac drives T cells infiltration into sarcoma. Furthermore, genome wide H3K27ac levels may be used to predict survival in OS. In addition, H3K27ac levels are associated with immune-related signatures and could be explored to promote inflammatory responses in sarcoma.