Inhibition of histone deacetylase 2 reduces MDM2 expression and reduces tumor growth in dedifferentiated liposarcoma

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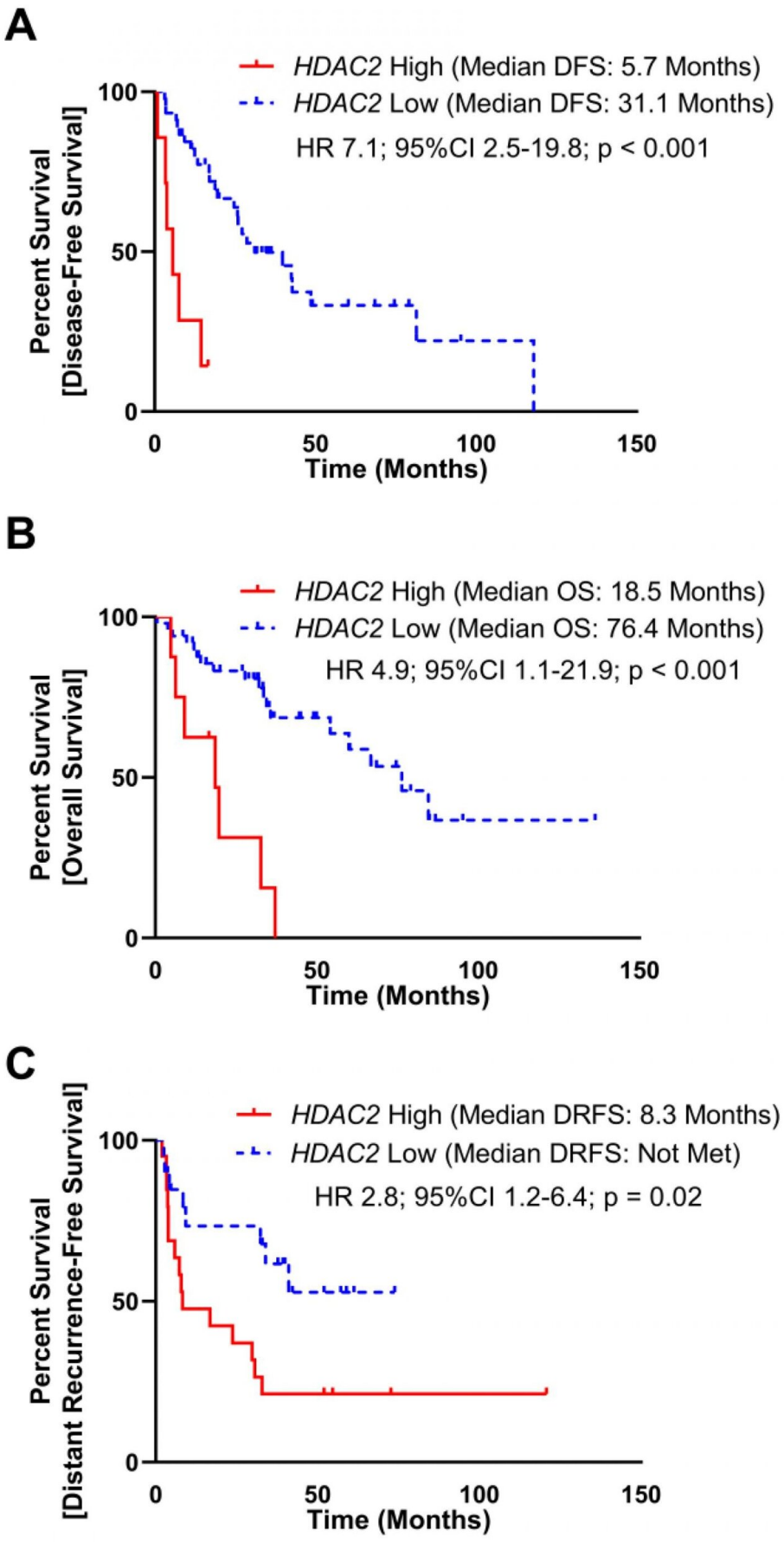
A
HDAC2 High (Median DFS: 5.7 Months)
HDAC2 Low (Median DFS: 31.1 Months)
HR 7.1; 95%CI 2.5-19.8; p < 0.001
Percent Survival [Disease-Free Survival]
100
50
0
0
50
100
150
Time (Months)
B
HDAC2 High (Median OS: 18.5 Months)
HDAC2 Low (Median OS: 76.4 Months)
HR 4.9; 95%CI 1.1-21.9; p < 0.001
Percent Survival [Overall Survival]
100
50
0
0
50
100
150
Time (Months)
C
HDAC2 High (Median DRFS: 8.3 Months)
HDAC2 Low (Median DRFS: Not Met)
HR 2.8; 95%CI 1.2-6.4; p = 0.02
Percent Survival [Distant Recurrence-Free Survival]
100
50
0
0
50
100
150
Time (Months)

Elevated HDAC2 mRNA expression is poorly prognostic in DDLPS. (A) mRNA expression of HDAC2 and disease-free survival (DFS) data from 52 subjects with DDLPS from The Cancer Genome Atlas (TCGA) were split into two groups utilizing maximally selected rank statistic (Supplementary Figure 1A). Subjects with elevated HDAC2 expression experienced reduced DFS (median DFS: HDAC2 High 5.7 months, HDAC2 Low 31.1 months; HR 7.1, 95%CI 2.5-19.8, p

The cover for issue 55 of *Oncotarget* features Figure 3, "Romidepsin exhibits anti-tumor effect in xenograft model of DDLPS," by Seligson, et al.

Here the researchers present in silico, in vitro, and mouse xenograft studies that suggest that specifically targeting HDAC2 reduces MDM2 expression and has anti-tumor affects in DDLPS. In a murine DDLPS xenograft model, romidepsin reduced tumor growth and lowered tumor MDM2 expression.

Taken together, their data supports the hypothesis that targeting HDAC2 may represent a potential strategy to modulate MDM2 expression in DDLPS.

Dr. James L. Chen from the Department of Pharmacy, The Ohio State University Wexner Medical Center and Comprehensive Cancer Center, Columbus, Ohio, USA and the Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, Ohio, USA said, "Dedifferentiated liposarcoma is a highly morbid mesenchymal tumor accounting for approximately 20% of all soft-tissue sarcomas"

MDM2 degrades p53, thus, an amplification in MDM2 results in reduced p53 activity and a shift towards pro-survival pathways.

The author's previous work has demonstrated that the amplification of MDM2 is directly tied to biological activity and clinical response to chemotherapy in this disease; furthermore, eliminating or reducing MDM2 activity may reduce of the oncogenicity of DDLPS tumors.

A primary strategy to target MDM2 in DDLPS has been to sterically inhibit the ability of MDM2 to bind p53.

Results presented here suggest that inhibition of HDAC2, specifically utilizing the HDAC1/2 inhibitor romidepsin, reduces MDM2 expression and promotes apoptosis in DDLPS.

The Chen Research team concluded, "The data presented here suggests a potential role for HDAC2 inhibition in DDLPS as a modulator of the MDM2:p53 pathway."

More information: Inhibition of histone deacetylase 2 reduces MDM2 expression and reduces tumor growth in dedifferentiated liposarcoma, *Oncotarget* (2019). DOI: 10.18632/oncotarget.27144

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