Title: Chemical targeting of epigenetic vulnerabilities in Atypical Teratoid/Rhabdoid tumors

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Keywords:

AT/RT, epigenetics, BAF

Abstract

Atypical teratoid/ rhabdoid tumors (AT/RTs) are highly aggressive childhood brain tumors, defined by the inactivation of SMARCB1, a core subunit of the BAF chromatin remodelling complex. Loss of BAF activity during a critical developmental window disrupts chromatin state and alters key differentiation programs, ultimately driving tumorigenesis. Recent studies have shown increased activity of non-canonical BAF (ncBAF) complex playing central roles with common SMARCA4 and unique BRD9 subunits in absence of functional BAF complex.

To investigate these vulnerabilities, we chemically targeted AT/RT cell lines cultured in either progenitor state or differentiation-promoting conditions. Spheroid growth was continuously monitored using live-cell imaging. The HDAC inhibitor induced a strong suppression of spheroid growth while DNMT inhibitor and BRD9 inhibition both effectively blocked proliferation. The differentiating conditions by itself affected growth, and across all treatments, differentiation-promoting conditions consistently enhanced drug sensitivity compared to stem-like conditions, suggesting differentiation-promoting conditions modulate drug response and cell growth.

These findings provide functional evidence for epigenetic dependencies of AT/RTs and validate BRD9 as a vulnerability across cellular states. Together, our findings establish a foundation for mechanistic studies into how ncBAF and related epigenetic modulators sustain AT/RT growth and provide a promising targeting strategy in AT/RTs.