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Histone deacetylase inhibitors interact with MDA-7/IL-24 to kill primary human glioblastoma cells and prolong animal survival

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Abstract

We presently demonstrate that histone deacetylase inhibitors (HDACIs) enhance toxicity of melanoma differentiation associated gene-7/interleukin 24 (*mda*-7/IL-24) in invasive primary human GBM cells. Additionally, a method is described to augment efficacy of adenoviral delivery of *mda*-7/IL-24 in these cells. HDACIs synergized with MDA-7/IL-24 killing GBM cells. Enhanced lethality correlated with increased autophagy that was dependent on expression of ceramide synthase 6. HDACIs interacted with MDA-7/IL-24 prolonging generation of ROS and Ca^{2+}. Quenching of ROS and Ca^{2+} blocked HDACI and MDA-7/IL-24 killing. *In vivo* MDA-7/IL-24 prolonged survival of animals carrying orthotopic tumors and HDACIs enhanced survival further. A serotype 5/3 adenovirus more effectively delivers *mda*-7/IL-24 to GBM tumors than a serotype 5 virus. Hence, we constructed a serotype 5/3 adenovirus that conditionally replicates in tumor cells expressing MDA-7/IL-24, in which the adenoviral E1A gene was driven by the cancer-specific promoter progression elevated gene-3 (Ad.5/3-PEG-E1A-*mda*-7; Ad.5/3-*CTV-M7*). Ad.5/3-*CTV-M7* increased survival of mice carrying GBM tumors to a significantly greater extent than did a non-replicative virus Ad.5/3-*mda*-7. Ad.5/3-*CTV-M7* exhibited no toxicity in the brains of Syrian hamsters. Our data demonstrates that HDACIs enhance MDA-7/IL-24 lethality and adenoviral delivery of *mda*-7/IL-24 combined with tumor specific viral replication is an effective pre-clinical GBM therapeutic. Our studies are progressing to a Phase I trial in recurrent GBM.

Biography

Paul Dent completed his Ph.D. at The University of Dundee and postdoctoral studies at The University of Virginia. He has been a faculty member at Virginia Commonwealth University since 1996 and is presently the vice chair for research in Neurosurgery. He has published over 350 papers and is an Associate Editor of multiple Journals. He has served on NIH and DoD review panels, as well as formerly being a chartered member on two NIH study sections. His major interest area is developmental cancer therapeutics with a focus on the rational combination of signaling modulatory agents to kill tumor cells.