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Targeting Hippo/YAP-TEAD increases the antitumor activity of darovasertib in uveal melanoma

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Abstract:
Activating mutations in *GNAQ* and *GNA11* (*GNAQ* oncogenes) are found in ~93% of uveal melanoma (UVM) and 4% of skin cutaneous melanoma (SKCM), where they act as driver oncogenes. UVM is the most common primary cancer of the eye in adults, affecting more than 2,500 patients each year in the US alone, nearly 50% of whom will die from liver metastasis. To date, there are limited effective therapeutic options to prevent or treat UVM metastatic disease (mUVM), which typically also fails to respond to immunotherapies. By combining synthetic biology approaches, CRISPR/Cas9 genome-wide screens, and high-throughput chemogenetic drug screening, our team has revealed that classical and novel non-canonical GNAQ signaling circuits converge to promote UVM growth, survival, metastasis, and treatment resistance. Ultimately, elucidating GNAQ oncogenic signaling networks may reveal system vulnerabilities that can be exploited to develop new precision therapies for mUVM. In this regard, we have recently shown that darovasertib acts as a dual PKC-PKN inhibitor and exhibits the highest activity among thousands of drugs tested. Darovasertib has demonstrated encouraging activity in UVM patients, and clinical trials using darovasertib as a single agent in primary UVM lesions and in combination with crizotinib in mUVM are currently ongoing. However, few patients achieve complete responses, and tumors often progress due to the acquisition of resistance mechanisms. We aim to identify new targets that can overcome resistance to darovasertib. RNA-seq analysis revealed that long-term treatment with darovasertib increased the expression of YAP-target genes, and we hypothesized that YAP/TEAD activation may contribute to darovasertib resistance. Indeed, expression of an active YAP mutant (YAP2-5SA) or LATS1/2 inhibition was sufficient to induce darovasertib resistance in UVM cells. In turn, knockdown of YAP or TEAD, or the expression of a doxycycline-induced TEAD inhibitor (TEADi) peptide, increases darovasertib-induced apoptosis. Remarkably, co-targeting with small molecule TEADi decreases the expression of darovasertib-induced YAP targets and acts synergistically to reduce cell viability and increase UVM cell death. Ongoing studies are now exploring the preclinical benefit of combining darovasertib with small-molecule TEADi for the treatment of human UVM tumor xenografts in mice. Emerging evidence will be presented supporting that the Hippo YAP/TEAD pathway represents an adaptive mechanism of resistance to darovasertib treatment, and that the combination of TEADi with darovasertib may prevent the development of treatment resistance, thereby increasing the depth and duration of the anti-tumor response in UVM.

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