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HSP90 Supports Tumor Growth and Angiogenesis through PRKD2 Protein Stabilization

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Abstract

The kinase PRKD2 (protein kinase D) is a crucial regulator of tumor cell-endothelial cell communication in gastrointestinal tumors and glioblastomas, but its mechanistic contributions to malignant development are not understood. Here, we report that the oncogenic chaperone HSP90 binds to and stabilizes PRKD2 in human cancer cells. Pharmacologic inhibition of HSP90 with

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Disclosure of Potential Conflicts of Interest
G. Chiosis is director of Samus Therapeutics. No potential conflicts of interest were disclosed by the other authors.

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structurally divergent small molecules currently in clinical development triggered proteasome-dependent degradation of PRKD2, augmenting apoptosis in human cancer cells of various tissue origins. Conversely, ectopic expression of PRKD2 protected cancer cells from the apoptotic effects of HSP90 abrogation, restoring blood vessel formation in two preclinical models of solid tumors. Mechanistic studies revealed that PRKD2 is essential for hypoxia-induced accumulation of hypoxia-inducible factor-1α (HIF1α) and activation of NF-κB in tumor cells. Notably, ectopic expression of PRKD2 was able to partially restore HIF1α and secreted VEGF-A levels in hypoxic cancer cells treated with HSP90 inhibitors. Taken together, our findings indicate that signals from hypoxia and HSP90 pathways are interconnected and funneled by PRKD2 into the NF-κB/VEGF-A signaling axis to promote tumor angiogenesis and tumor growth.