A Surprising Role for PTP1B in Breast Cancer

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Abstract

Deletion of *Ptpn1*, which encodes Protein-Tyrosine Phosphatase-1B (PTP1B), delays the onset of *Her2/Neu*-driven breast cancers in mice, but the underlying mechanism(s) has been controversial. The role of PTP1B in *HER2*+ human breast cancer also is unresolved. We found that, unexpectedly, PTP1B protects *HER2*+ breast cancer (BC) cell lines and tumors from hypoxia-induced death. Although there was no consistent effect of *PTPN1* depletion or PTP1B inhibition on growth factor signaling or proliferation of *HER2*+ BC cells *in vitro*, PTP1B-deficient *HER2*+ xenografts showed increased hypoxia, necrosis and impaired growth. *PTPN1*-knockdown (1B-KD) also sensitized *HER2*+ BC lines to hypoxia-induced death *in vitro*. Remarkably, all known hypoxia response pathways appear normal or increased in PTP1B-deficient cells. Instead, biochemical and genetic analysis reveal a novel pathway for regulating tumor cell response to hypoxia, and a new function for PTP1B, acting via the Moyamoya disease gene *RNF213*, in the control of α-KG-dependent dioxygenases in *HER2*+ BC cells. Control of α-KG-dependent dioxygenase activity by this novel PTP1B/RNF213 hypoxia-regulatory pathway appears to be critical for the survival of breast cancer and possibly other malignant cells in the tumor microenvironment.