

## **The roles of PTPROt in chronic lymphocytic leukemia**

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Abstract

The hematopoietic tyrosine phosphatase PTPROt is a putative tumor suppressor in B cell chronic lymphocytic leukemia (CLL), where its expression is reduced. In order to examine the role of PTPROt in CLL we abrogated expression of PTPROt in mice and followed progression of CLL in them. Unexpectedly, complete loss of PTPROt delayed disease detection and progression and lengthened survival, indicating that PTPROt fulfills a novel tumor-promoting role in CLL. PTPROt-deficient tumor cells exhibited reduced B-cell receptor (BCR) signaling and increased apoptosis and autophagy. Inhibition of BCR/Src family kinases (SFK) in CLL cells induced apoptosis in a dose-dependent manner, indicating these events are linked causally. Complete loss of PTPROt thus reduces SFK activity, leading to reduced BCR signaling and reduced tumor cell survival, in agreement with the weakened CLL phenotype of PTPROt-deficient mice. These findings uncover non-redundant, cell-autonomous roles for PTPROt in support of BCR signaling and survival of CLL cells. In contrast, loss of only one Ptpro allele induced the opposite phenotype - earlier detection and progression of CLL and reduced mouse survival, consistent with the putative tumor suppressing role of PTPROt. Tumor cells from mice lacking one Ptprot allele exhibited normal BCR signaling and cell death, suggesting that their more aggressive disease is associated with its earlier initiation or dissemination. PTPROt thus functions in CLL as an obligate haploinsufficient tumor suppressor, a class of gene products whose expression levels determine their functions as tumor promoters or tumor suppressors. Partial loss of PTPROt generates the strongest disease phenotype, suggesting that its intermediate expression levels in CLL in humans are selected for.