

Chronic myelogenous leukemia stem cells require cell-autonomous pleiotrophin signaling.

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Public Summary:

Scientific Abstract:

Tyrosine kinase inhibitors (TKIs) induce molecular remission in the majority of patients with chronic myelogenous leukemia (CML), but persistence of CML stem cells hinders cure and necessitates indefinite TKI therapy. We report that CML stem cells upregulate expression of pleiotrophin (PTN) and require cell-autonomous PTN signaling for CML pathogenesis in BCR/ABL+ mice. Constitutive PTN deletion substantially reduced the numbers of CML stem cells capable of initiating CML in vivo. Hematopoietic cell-specific deletion of PTN suppressed CML development in BCR/ABL+ mice, suggesting that cell-autonomous PTN signaling was necessary for CML disease evolution. Mechanistically, PTN promoted CML stem cell survival and TKI resistance via induction of Jun and the unfolded protein response. Human CML cells were also dependent on cell-autonomous PTN signaling and anti-PTN antibody suppressed human CML colony formation and CML repopulation in vivo. Our results suggest that targeted inhibition of PTN has therapeutic potential to eradicate CML stem cells.

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