Targeting PIM kinases impairs survival of hematopoietic cells transformed by kinase inhibitor-sensitive and kinase inhibitor-resistant forms of Fms-like tyrosine kinase 3 and BCR/ABL.

Previously, it has been shown that activation of the signal transducer and activator of transcription 5 (STAT5) plays an essential role in leukemogenesis mediated through constitutively activated protein tyrosine kinases (PTK). Because PIM-1 is a STAT5 target gene, we analyzed the role of the family of PIM serine/threonine kinases (PIM-1 to PIM-3) in PTK-mediated transformation of hematopoietic cells. Ba/F3 cells transformed to growth factor independence by various oncogenic PTKs (TEL/JAK2, TEL/TRKC, TEL/ABL, BCR/ABL, FLT3-ITD, and H4/PDGFBetaR) show abundant expression of PIM-1 and PIM-2. Suppression of PIM-1 activity had a negligible effect on transformation. In contrast, expression of kinase-dead PIM-2 mutant (PIM-2KD) led to a rapid decline of survival in Ba/F3 cells transformed by FLT3-ITD but not by other oncogenic PTKs tested. Coexpression of PIM-1KD and PIM-2KD abrogated growth factor-independent growth of Ba/F3 transformed by several PTKs, including BCR/ABL. Targeted down-regulation of PIM-2 by RNA interference (RNAi) selectively abrogated survival of Ba/F3 cells transformed by various Fms-like tyrosine kinase 3 (FLT3)-activating mutants [internal tandem duplication (ITD) and kinase domain] and
attenuated growth of human cell lines containing FLT3 mutations. Interestingly, cells transformed by FLT3 and BCR/ABL mutations that confer resistance to small-molecule tyrosine kinase inhibitors were still sensitive to knockdown of PIM-2, or PIM-1 and PIM-2 by RNAi. Our observations indicate that combined inactivation of PIM-1 and PIM-2 interferes with oncogenic PTKs and suggest that PIMs are alternative therapeutic targets in PTK-mediated leukemia. Targeting the PIM kinase family could provide a new avenue to overcome resistance against small-molecule tyrosine kinase inhibitors.