Possible use of the PP2A activating drug FTY720 in the therapy of oncogenic kinase-driven hematological malignancies.

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A tight control of kinase and phosphatase activity is fundamental for normal cell growth, survival and differentiation, as deregulated function of critical signal transducers is often associated with tumor development and progression. Indeed, different hematological malignancies are characterized by the aberrant activation of kinases and the genetic or functional inactivation of the phosphatases that regulate their activity. We recently reported that the activity of the tumor suppressor protein phosphatase PP2A is gradually inactivated during progression of chronic myelogenous leukemia (CML) from the indolent chronic phase (CML-CP) to the fatal blast crisis (*Neviani P. et al., Cancer Cell 2005*). Likewise, PP2A activity was found markedly impaired in other types of leukemia including Ph1(+) ALL (*Neviani P. et al. J. Clin. Invest 2007*), CLL (*Liu Q. et al., Blood 2008*), and in myeloid precursors transformed by the Jak2 V617F (*Oaks J. et al. Blood ASH* 2007) or by the imatinib-resistant D816V Kit kinase (*Roberts K. et al., 2008; MS in preparation 2008*). In blast crisis CML (CML-BC) and Ph1 ALL, PP2A inactivation results from increased expression of SET, a physiological inhibitor of PP2A, which is induced by the aberrant tyrosine kinase activity of BCR/ABL in a dose- and kinase-dependent manner and, like BCR/ABL, progressively increases during transition to blast crisis. Remarkably, several targets are shared by BCR/ABL and PP2A. Among these, expression and/or activity of certain PP2A substrates are either essential for BCR/ABL leukemogenesis or have been found altered in Ph1(+) leukemias. In BCR/ABL-, Jak2 V617F- or D816V Kit-expressing myeloid progenitors and in $CD34^+$ bone marrow cells from CML-CP and -BC (wild type and T315I BCR/ABL), Ph1 ALL, and CLL patient samples. Restoration of PP2A activity via SET downregulation or PP2Ac overexpression and/or treatment with potent PP2A activators [e.g. FTY720 (Fingolimod); Novartis] induced marked apoptosis, reduced proliferation, impaired colony formation and/or inhibited in vivo leukemogenesis without exerting any toxicity. Furthermore, FTY720 antagonized blastic transformation in a mouse model of CML disease progression and induced apoptosis of the quiescent imatinib/dasatinib-resistant BCR/ABL^+ stem/leukemia-initiating cells isolated from marrow of SCL-tTA-BCR/ABL animals or CML patients (*Neviani et al., 2008; MS in preparation*), suggesting that restoring PP2A activity may eradicate CML at stem cell level and, perhaps, prevent blastic transformation. As the *in vitro* and *in vivo* anti proliferative and pro-apoptotic effects of FTY720 can be suppressed by sub-nanomolar concentrations of okadaic acid or by forced SV40 small t-Ag expression, our data not only highlight the importance of PP2A inactivation in the development/progression of hematological malignancies characterized by the aberrant activity of wild type or mutated oncogenic tyrosine kinases (e.g. BCR/ABL, Kit D816V and Jak2 V617F), but they also strongly support the use of PP2A activators like FTY720 in the treatment of patients resistant or refractory to tyrosine kinase inhibitor monotherapy.