Titolo breve
Repurposing pexmetinib as an inhibitor of TKI-resistant BCR::ABL1

Parole chiave (4)
Pexmetinib, BCR::ABL1, tyrosine kinase inhibitors, resistance

Sessione
Ricerca di base

Abstract (max 1500 battute)
Chronic myeloid leukemia is a clonal disorder caused by the Philadelphia (Ph) chromosome encoding for the BCR::ABL1 fusion gene. The development of imatinib and other tyrosine kinase inhibitors (TKIs) targeting the ABL1 tyrosine kinase allowed a dramatic change in CML prognosis. However, a significant number of patients fails to achieve a complete remission or develops resistance to TKIs due to the acquisition of point mutations. The T315I substitution at the gatekeeper site is the most intractable BCR::ABL1 mutant. We screened a kinase-focused compound library for selective inhibition of $ABL1^{T315I}$ in cells, using an isogenic Ba/F3 cellular model, and we identified pexmetinib as an inhibitor of drug-resistant BCR::ABL1, including G250E, Y253F, E255K/V and T315I mutants. When tested on human Ph+ CML cell lines carrying the T315I substitution, pexmetinib showed cell growth inhibition both in vitro and in an in vivo xenograft model. Moreover, pexmetinib showed dose-dependent inhibition of colony formation both in WT and T315I mutated Ph+ CML patients without affecting Ph− cells. Docking studies of pexmetinib on $ABL1^{T315I}$ binding showed the binding of the compound to $ABL1^{T315I}$ in the active conformation. In conclusion, we report here preclinical proof of concept for pexmetinib repurposing as a novel inhibitor of the highly resistant BCR::$ABL1^{T315I}$ mutant, as well as of other imatinib-resistant mutations.