A cell-based screening strategy that predicts mutations in oncogenic tyrosine kinases: implications for clinical resistance in targeted cancer treatment.

Abstract:
The discovery of tyrosine kinases that, once deregulated, can cause malignancy, allowed the development of specifically acting anti-cancer compounds. In chronic myeloid leukaemia (CML), the Bcr-Abl kinase inhibitor imatinib (STI571, Gleevec) induces impressive response rates. However, resistance occurs especially in advanced phase CML and Ph+ ALL, primarily as a consequence of point mutations within the Bcr-Abl kinase domain that prevent imatinib from binding. To overcome imatinib resistance, alternative Abl kinase inhibitors are finding their way into clinical trials. However, it is likely that resistance to second-generation compounds will occur as well. Therefore, it will be critical to determine specific resistance profiles for each particular compound. We recently developed a cell-based screening strategy that allows one to predict the pattern and relative abundance of Bcr-Abl resistance mutations emerging in the presence of imatinib or an alternative Abl-kinase inhibitor. Using this strategy, the findings in inhibitor resistant sublines reflect observations made in CML patients with imatinib resistance, including Bcr-Abl mutations, amplification of the Bcr-Abl gene, and overexpression of the Bcr-Abl protein. We here provide a detailed methodological description, and discuss the implications of this strategy for different clinically relevant...
oncogenic tyrosine kinases.