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Abstract: The kinase inhibitor imatinib mesylate targeting the oncoprotein Bcr-Abl has revolutionized the treatment of chronic myeloid leukemia (CML). However, even though imatinib successfully controls the leukemia in chronic phase, it seems not to be able to cure the disease, potentially necessitating lifelong treatment with the inhibitor under constant risk of relapse. On a molecular level, the cause of disease persistence is not well understood. Initial studies implied that innate features of primitive progenitor cancer stem cells may be responsible for the phenomenon. Here, we describe an assay using retroviral insertional mutagenesis (RIM) to identify genes contributing to disease persistence in vivo. We transplanted mice with bone marrow cells retrovirally infected with the Bcr-Abl oncogene and subsequently treated the animals with imatinib to select for leukemic cells in which the proviral integration had affected genes modulating the imatinib response. Southern blot analysis demonstrated clonal outgrowth of cells carrying similar integration sites. Candidate genes located near the proviral insertion sites were identified, among them the transcription factor RUNX3. Proviral integration near the RUNX3 promoter induced RUNX3 expression, and Bcr-Abl-positive cell lines with stable or inducible expression of RUNX1 or RUNX3 were protected from imatinib-induced...
apoptosis. Furthermore, imatinib treatment selected for RUNX1-expressing cells in vitro and in vivo after infection of primary bone marrow cells with Bcr-Abl and RUNX1. Our results demonstrate the utility of RIM for probing molecular modulators of targeted therapies and suggest a role for members of the RUNX transcription factor family in disease persistence in CML patients.

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