SPECIAL REPORT

New Abelson interactor-1 (Abi-1)-driven mechanism of acquired drug resistance

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The majority of chronic myeloid leukemia (CML) (actually all, according to WHO) and ~30% of acute lymphoblastic leukemia (ALL) cases in adults originate from transformation of a hematopoietic stem cell by the oncogenic kinase Bcr-Abl1.¹ Despite the indisputable success of small-molecule inhibitors of Bcr-Abl1 in prolonging the survival of patients with Bcr-Abl1-positive leukemia, leukemic stem cells (LSCs) remain detectable in the bone marrow.^{2–4} There are two well-documented mechanisms of Bcr-Abl1-dependent resistance to tyrosine kinase inhibitor (TKI) treatment, both leading to cell autonomous activation of Bcr-Abl1 kinase: mutations in the catalytic domain and amplification of the oncogene.^{5–7} In addition, detailed mechanistic studies of imatinib mesylate (IM) resistance and persistence of Bcr-Abl1-containing hematopoietic stem cells (HSCs) have shown that primitive CML cells are capable of survival in the absence of Bcr-Abl1 kinase activity.^{2,4,8} These studies suggested the existence of a kinase activity-independent mechanism of acquired drug resistance. It is thought that primitive LSCs that are insensitive to the presence of TKI are responsible for relapse after TKI discontinuation. In this scenario, non-catalytic, adapter functions of Bcr-Abl1 are believed to contribute to the oncogenic characteristics of CML stem cells, indicating the necessity of identifying Bcr-Abl1 kinase-independent mechanisms of survival of LSCs in the presence of TKI.

Interactions of HSCs with the bone marrow microenvironment (BMME) are critical for sustaining stem cell pools.⁹ The stem cell niche regulates stem cell-specific properties, including self-renewal, multi-potentiality and relative quiescence.¹⁰ Evidence points to the involvement of the BMME in survival and systemic retention of LSCs.^{11,12} Integrins, particularly $\alpha 4 \beta 1$ and $\alpha v \beta 3$, which control trafficking to and lodging of HSCs in the BMME, are also crucial for the persistence of minimal residual disease.^{13–15} The Berlin–Frankfurt–Münster ALL trial (ALL-REZ BFM 2002) revealed that high expression of $\alpha 4 \beta 1$ at first relapse was associated with a poor molecular response to therapy and significantly worse event-free and overall survival.¹⁶ Based on these and other reports,¹⁷ a concept emerged suggesting that a subpopulation of LSCs are quiescent and exhibit relative drug resistance as a result of enhanced adhesive properties toward bone marrow stroma.^{18,19} Abelson interactor 1 (Abi-1) was originally identified as Abl kinase associating protein²⁰ and was later confirmed to be one of the Bcr-Abl interactors.²¹ Recent reports indicate that the N-terminus of Abi-1 interacts with the cytoplasmic tail of $\alpha 4$ integrin, and may mediate specific functions associated with $\alpha 4$ -dependent processes in normal and pathological conditions.²² Abi-1-deficient mice exhibit defects in placental and cardiovascular development

leading to midgestational embryonic lethality;^{22,23} these phenotypes mirror those found in mice deficient for $\alpha 4$ integrin or its ligand vascular cell adhesion molecule-1.^{24,25} We have recently obtained evidence that Abi-1 plays a role in signaling cross talk between Bcr-Abl1 and $\alpha 4$ integrin. We have found that loss of Abi-1 leads to increased adhesion and quiescence, resulting in increased chemoresistance of leukemic CD34+ progenitor cells. An inverse correlation between Abi-1 and $\alpha 4$ integrin expression, as well as linkage of Abi-1 to elevated phospho-Akt and phospho-Erk signaling, was confirmed in IM-resistant leukemic cells. These results indicated that the $\alpha 4$ -Abi-1 signaling pathway may mediate acquisition of the drug-resistant phenotype of leukemic cells.¹⁵ These results suggest that the $\alpha 4$ integrin–Abi-1–Bcr-Abl1 signaling module may play a significant role in interactions between LSCs and the BMME, and that alterations in this cross talk may be causative in the acquired drug-resistant phenotype of LSCs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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