Abstract

Adhesion of hematopoietic cells to the bone marrow microenvironment is important for their proper development. It is proven that Src-family kinases (SFK) regulate cell adhesion, although their exact role in the regulation of adhesion signaling remains unclear. Since adhesion processes are investigated mainly in adherent cell types, far less is known about hematopoietic cells. However, defects in the cell adhesion accompany a number of hematological diseases, like chronic myeloid leukaemia (CML). SFK overexpression is one of the proposed mechanisms of resistance to the first-line CML treatment, imatinib mesylate. Second generation drugs (e. g. dasatinib) inhibit SFK together with Bcr-Abl. Additionally, SFK-specific inhibitors (PP2, Src inhibitor-1) are also available, but there are no studies about effects of these drugs on cellular adhesivity of hematopoietic precursors. To explore the dynamics of hematopoietic cell adhesion to the extracellular matrix, we introduced a new approach using the RTCA xCELLigence DP system along with the well-established method of fluorimetric detection of adherent cell fraction. Our general observation is that various drugs (dasatinib, imatinib, PP2, Src inhibitor-1) induce pro-adhesive effects in several leukemic cell lines. Direct comparison of the kinetics of dasatinib and imatinib-mediated changes in cell interaction with fibronectin showed a delay in the response to imatinib. Among others, during further exploration of this observation we questioned the reliability of the clinically-used test for Bcr-Abl kinase activity from the phosphorylation status of CrkL protein. On the other hand, our results indicate that SFK inhibition does not have any significant effect on proliferation and viability of leukemic cell lines. Taken together, the results of this work indicate that the active Src family kinases weaken the interaction of hematopoietic precursors with the extracellular matrix, which can contribute to leukaemia progression in patients with elevated SFK levels.

Key words:

cell adhesion, extracellular matrix, Src kinase, dasatinib, chronic myeloid leukaemia, xCELLigence