Constitutive activation of the MAP kinase p38 is critical for MMP-9 production and survival of B-CLL cells on bone marrow stromal cells.

Abstract:
In the present work we investigated the role and biological significance of mitogen activated protein kinases (MAPK) in B-cell chronic lymphocytic leukaemia (B-CLL). The MAPK p38 was constitutively activated in B-CLL, but not in normal peripheral B cells. In addition, we demonstrated that the upstream kinases of p38, MKK3/6 were also constitutively activated in B-CLL cells. Furthermore, we determined by EMSA that the p38 MAP kinase pathway was not linked to the constitutive high expression of NF-kappaB, a critical survival factor of B-CLL cells. Recently, it has been shown that serum levels of angiogenic factors like VEGF, bFGF and MMP-9 are elevated in the serum of CLL patients and correlate with an unfavorable prognosis. We showed that the constitutive expression of MMP-9 was dependent on p38-activity and inhibition of p38 strongly downregulated MMP-9 expression. Coculture of B-CLL cells and stromal cells can protect spontaneous apoptosis of leukemic B cells. To determine the role of permanently activated p38 and MMP-9 expression, we cocultured B-CLL cells with bone marrow stromal cells. Survival of B-CLL cells on stroma was severely impaired when p38 was inhibited. Furthermore, blockade of MMP-9 activity also antagonized the antiapoptotic effect of stromal cells.