Overexpression of SH2-containing inositol phosphatase contributes to chronic lymphocytic leukemia survival.


Key points:

B cell specific deletion of Ship2 phosphatase reduces CLL formation in a mouse model

Ship2 inhibition reduces Akt/mTORC1/S6 signaling in murine and human CLL cells

Ship2 supports survival of CLL cells via the key anti-apoptotic protein Mcl-1

Abstract:

Balanced activity of kinases and phosphatases downstream of the B cell receptor (BCR) is essential for B cell differentiation and function and is disturbed in chronic lymphocytic leukemia (CLL). Here, we employed IgH.TEμ mice, which spontaneously develop CLL, and stable EMC CLL cell lines derived from these mice to explore the role of phosphatases in CLL. Genome-wide expression profiling comparing IgH.TEμ CLL cells with wild-type splenic B cells identified 96 differentially expressed phosphatase genes, including SH2-containing inositol phosphatase (Ship2). We found that B cell-specific deletion of Ship2, but not of its close homologue Ship1, significantly reduced CLL formation in IgH.TEμ mice. Treatment of EMC cell lines with Ship1/2 small molecule inhibitors resulted in the induction of caspase-dependent apoptosis. Using flow cytometry and western blot analysis we observed that blocking Ship1/2 abrogated EMC cell survival by exerting dual effects on the BCR signaling cascade. On one hand, specific Ship1 inhibition enhanced calcium signaling and thereby abrogated an anergic response to BCR stimulation in CLL cells. On the other hand, concomitant Ship1/Ship2 inhibition or specific Ship2 inhibition reduced constitutive activation of the mTORC1/ribosomal protein S6 pathway and downregulated constitutive expression of the anti-apoptotic protein Mcl-1, in both EMC cell lines and primary IgH.TEμ CLL cells. Importantly, also in human CLL we found overexpression of many phosphatases including SHIP2. Inhibition of SHIP1/SHIP2 reduced cellular survival and S6 phosphorylation and enhanced basal calcium levels in human CLL cells. Taken together, we provide evidence that SHIP2 contributes to CLL pathogenesis in mouse and human CLL.