Abstract:
The crucial dependence of chronic lymphocytic leukemia (CLL) cells on signals derived from the B cell receptor (BCR) has encouraged the development of new inhibitors, which interfere with BCR signaling and demonstrate clinical benefits in nearly all patients. In addition, signaling through Toll-like receptor (TLR) 9 of the innate immune system has been shown to further contribute to the activation of CLL cells. However, responses to TLR9 engagement are not uniform, but diametrically opposed with cell death in some patients and cell proliferation in others. We now provide evidence that heterogeneous responses to TLR agonists are related to differences in the ability of CLL cells to activate the BCR-associated kinase Syk. Notably, expression of ZAP-70 appears to be of crucial importance for TLR9-mediated activation of Syk. We show that the activation of Syk provides an antiapoptotic signal, which is independent of Mcl-1, Bcl-2, and Bcl-XL, but related to the degradation of the proapoptotic Bim. Mechanistically, TLR9-mediated antiapoptotic signals in ZAP-70-positive CLL trigger secretion of immunoglobulin M, which then serves as (auto-) antigen for a prosurvival BCR signal. Thus, our data show that single activation of the innate immune receptor TLR9 is
sufficient to fully engage BCR signaling in ZAP-70-positive CLL, protecting malignant cells from apoptosis. We conclude that the integration of TLR signaling into an adaptive immune response can further promote survival of CLL cells and may contribute to the unfavorable prognosis of ZAP-70-positive CLL.

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