ABSTRACT (EN)

Chronic lymphocytic leukemia (B-CLL) represents a disease of mature-like B-cells. Due to failed apoptosis but also due to enhanced proliferative signals, the leukemic B-cells accumulate in the peripheral blood, bone marrow, lymph nodes and spleen. The clinical course of B-CLL is very heterogeneous; in some patients B-CLL progresses very rapidly into an aggressive form. Such patients need therapy sooner while in other patients with indolent B-CLL the onset of therapy takes years. Several standard prognostic and disease progression markers are used for disease staging and monitoring, however a reliable marker that will suggest when to start therapy is unknown. Expression of small, non-coding microRNAs is often deregulated and represent important prognostic markers in variety of cancers including leukemia. Hence in our study we concentrated to miR-155, an important molecule regulating differentiation of hematopoietic cells, inflammation process and antibody production. Its aberrant expression was described in Hodgkin’s as well as in non-Hodgkin’s lymphoma, including indolent lymphoproliferations like B-CLL. Our results confirmed elevated levels of both, primary miR-155 transcript and mature form of miR-155 in our B-CLL patient samples (N=239). The aberrant expression of miR-155 in B-CLL samples associated with unfavorable prognosis. Moreover, we also observed elevated miR-155-mediated decrease of its direct target – PU.1 in B-CLL cells that is important regulator of B-cell maturation. Next, we demonstrated that proto-oncogen MYB directly binds at the promoter region of the miR-155 gene - MIR155HG and stimulates its transcription. This coincided with enrichment of activated epigenetic marks: hypermethylated histone H3K4 residue and spreaded hyperacetylation of H3K9 at the MIR155HG promoter. Our in vitro functional assays on the primary B-CLL cells and Raji cell line confirmed the negative relationship between miR-155 and PU.1 and positive relationship between MYB and miR-155. We also have shown that unfavorable prognosis of B-CLL associates with low expression of miR-150 (inhibitor of Myb) and high expression of MYB mRNA. Based on above-mentioned results, we created working model of relationship between miR-155, MYB and PU.1 that can be applied to around 20% of more aggressive B-CLL patients. The success of therapy of B-CLL patients depends on the accurate start of the therapy. Our data also indicate that the levels of miR-155 in B-CLL patients associate with the disease progression and can be used to predict therapy onset. We conclude that measurement of miR-155, MYB and PU.1 expression associates with B-CLL progression and could help in making valuable clinical decisions.