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MicroRNA miR-150 contributes to the proficiency of B-cell receptor signaling (BCR) in malignant B cells

Marek Mraz
Masaryk University, Czech Republic

Abstract

We have shown that expression of miRNAs associates with disease aggressiveness in chronic lymphocytic leukemia (CLL) (Mraz et al. 2009, 2012, 2013), which is a disease where (dys)regulation of BCR signaling plays a prominent pathogenic role. Here we screened for abundantly expressed miRNAs in CLL hypothesizing that miRNAs with strong expression are likely involved in the regulation of key cell functions. This identified miR-150 as the most abundant miRNA and we observed that its lower levels associated with unfavorable clinic-biological markers (like ZAP-70, unmutated IgHV). To describe the genes regulated by miR-150 we performed microarray-based transcriptome analyses of 100 CLL samples. This identified two novel targets of miR-150 (GAB1 and FOXP1). GAB1 is an adaptor molecule that allows for amplification of PI3K signaling after BCR activation (Ingham et al. 2001). FOXP1 is a transcription factor crucial for B cell development and implicated in progression of B-cell lymphomas (Hu et al. 2006). Silencing of GAB1 or FOXP1 decreased the responsiveness of B cells to BCR stimulation. CLL cells with higher expression of *GAB1* or *FOXP1* were more responsive to BCR stimulation *in vitro*. Patients with high-level expression of *GAB1/FOXP1* had shorter overall survival (OS) (13.9 vs. 22.7 years, 13.9 vs. 21.1 years; N=168; $P<0.05$). A reverse trend was observed for miR-150, where higher levels associated with lower BCR responsiveness and longer OS in a multivariate analysis (not-reached vs. 13.9 years, $P=0.006$). We conclude that miR-150 is a novel regulator of genes that control BCR-signaling, which is a factor that prominently affects the biology of malignant B cells.

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Biography

Marek Mraz has obtained his M.D. in 2009 from Masaryk University (Czech Rep.) and performed postdoctoral studies at Mayo Clinic (laboratory of Dr. G. S. Nowakowski) and University of California-San Diego (laboratory of Dr. T.J. Kipps). He is currently a junior group leader at the Center of Molecular Medicine and Gene Therapy at the University Hospital Brno (Czech Rep.) and actively collaborates with many researchers in the field of B cell malignancies. He has published more than 25 scientific papers or book chapters (total impact factor 85) that have been cited over 170 times. Dr. Mraz serves as a reviewer for a dozen of scientific journals.