Systematic analysis of BCR-ABL interactome in chronic myeloid leukemia

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T. Gregor1, J. Rynes1, S. Foldynova-Trantirkova1, J. Mayer1, P. Krejci1, L. Trantirek1

1Central European Institute of Technology, Masaryk University, Brno, Czech Republic, Brno, Czech Republic, 2Department of Internal Medicine, Hematology and Oncology, Masaryk University Hospital, Brno, Czech Republic, Brno, Czech Republic, 3Department of Biology, Faculty of Medicine, Masaryk University & International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic, Brno, Czech Republic

Chronic myeloid leukemia (CML) is a myeloproliferative cancer that is caused by “Philadelphia chromosome” translocation that results in a formation of fusion protein BCR-ABL. This constitutively active tyrosine kinase is necessary and sufficient to cause CML. Several small molecule tyrosine kinase inhibitors (TKI) targeting BCR-ABL kinase activity had been developed and greatly improved CML prognosis. However, significant number of patients develops resistance to TKIs and relapse. Growing evidence shows the importance of other BCR-ABL interaction partners in CML pathogenesis. Precise elucidation of the interactome can lead to design of conceptually new drug targeting different pathways and overcoming TKI resistance. One of our goals is to elucidate precise binding interface among BCR-ABL and it’s “core complex” interaction partners. Our approach involves use of peptide microarrays, which allow us to map the binding interface with single amino acid resolution. Binding motifs discovered in unstructured parts of BCR-ABL can be used to generate synthetic peptide abolishing particular protein interaction. Furthermore, we created large pallet of BCR-ABL deletion/substitution mutants in order to verify interaction boundaries and co-immunoprecipitation experiments have yielded potential new binding sites for some of the core complex interactors. The realization of this project was allowed due to financial support from Ministry of Health of the Czech Republic (15-33232A, 15-34405A); National Program of Sustainability II (MEYS CR: LQ1605 and LQ1601) and European Union ICRC-ERA-HumanBridge (No. 316345).