Ústav hematologie a krevní transfuze

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Resistance to therapy in chronic myeloid leukemia - novel markers and possible treatment targets

Chronic myeloid leukemia (CML) is characterized by the presence of the bcr-abl fusion gene formed by translocation of the chromosomes 9 and 22. The first-line therapy targeting the constitutively active BCR-ABL kinase, the product of this gene, has been shown to be very effective, however, about a third of patients have either resistance or intolerance to the treatment. BCR-ABL kinase activates countless pathways which afterwards affect disease progression and resistance to the treatment. Despite the key role of BCR-ABL, CML is becoming a heterogeneous disease after time, and therefore it is essential to look for another indicators that could help to detect resistance in advance and for possible therapeutic targets.

In our laboratory, under the terms of the study of resistance to therapy, we focused on 1) a search of parameters detecting resistance to therapy in time, and 2) identification of possible treatment targets.

For instance, the level of the WT1 transcript (Wilms' tumor gene) and some of its splicing variants [1] or the protein level of the HSP90 protein [2] were proved to be possible early markers of resistance. Another possible helpful indicator of resistance is *ex vivo* monitoring of primary leukemia cell sensitivity to tyrosine kinase inhibitors. In our study of 51 patients, the *ex vivo* sensitivity to TKI correlated in 90% of cases with *in vivo* response during the next 12 months. We also found out that this test could be used at any stage of the disease [3].

Searching for a possible therapeutic target, based on a protein chip analysis in patients who did not respond to imatinib and dasatinib, we selected the casein kinase 2 (CK2) as a potential target of therapy. Our data are in accord with the published fact that CK2 is involved in imatinib resistance. Studies on imatinib and dasatinib-resistant cell models have confirmed the involvement of CK2 kinase in resistance not only to imatinib but also to dasatinib. The CK2 kinase inhibitor CX-4945 (Silmitasertib) reduced the proliferation of leukemic cells and increased the proportion of dead cell fraction (Fig. 1A). This was also confirmed by preliminary *ex vivo* tests of primary cells of patients who did not respond to TKI treatment (Fig. 1B) [4].

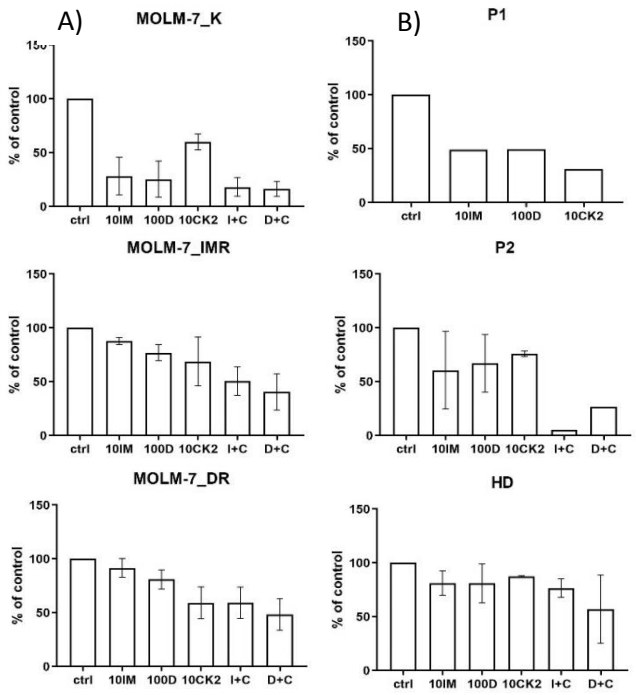

Fig. 1 Effect of inhibitors on cell proliferation

Graphs show the rate of proliferation / cell activity after treatment with various inhibitors. (IM - imatinib, D - dasatinib, CK2 - silmitasertib) and their combinations.

A) MOLM-7 - CML derived cell line

(K-control, IMR / DR - resistant to imatinib / dasatinib)

B) P1 / P2 - primary cells of patients resistant to TKI treatment, HD -healthy donors

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Publications:

[1] Lopotová T, Polák J, Schwarz J, Klamová H, Moravcová J. Expression of four major WT1 splicing variants in acute and chronic myeloid leukemia patients analyzed by newly developed four real-time RT PCRs. Blood Cells Mol Dis. 2012 Jun 15;49(1):41-7.

[2] Žáčková M, Moučková D, Lopotová T, Ondráčková Z, Klamová H, Moravcová J. Hsp90 – a potential prognostic marker in CML. Blood Cells Mol Dis. 2013 Mar;50(3):184-9.

[3] Žáčková M, Macháčková-Lopotová T, Ondráčková Z, Kuželová K, Klamová H, Moravcová J. Simplifying procedure for prediction of resistance risk in CML patients – Test of sensitivity to TKI ex vivo. Blood Cells Mol Dis. 2016 May;58:67-75.

[4] Mitrovský, O.; Myslivcová, D.; Lopotová-Macháčková, T.; Klamová, H.; Žáčková, M. Protein casein kinase 2 is involved in chronic myeloid leukemia resistance to imatinib and also to dasatinib. HemaSphere. 2019, vol. 3, no. S1, s. 533-534. ISSN 2572-9241.