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Differentially expressed genes responsible for insensitivity of CD34+ cells to kinase inhibitors in patients with chronic myeloid leukemia

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Background

Chronic Myeloid Leukemia (CML) is a clonal myeloproliferative disorder characterized by formation of *BCR-ABL* fusion that encodes the p210 oncoprotein, which has a tyrosine kinase activity that confers an adaptive advantage to leukemic cells. Imatinib mesylate (IM) acts specifically on p210. Imatinib is able to reduce the differentiated cells (CD66b+) efficiently, but it has not the same effect on the stem cells (CD34+), which can be kept alive during treatment. Our aim was to identify expressed genes in CD34+ and CD66b+ cells as candidates for kinase inhibitors transport.

Materials and methods

CD34+ and CD66b+ cells were isolated from bone marrow (BM) and peripheral blood (PB) of five patients with CML, in optimal response, and 1 control. The samples were sequenced on SOLiD^{TM} platform for whole transcriptome analysis. We analyzed the Gene Ontology annotation, and the software Cufflinks were used to identify the differential expression of genes in patients (BM x PB) and controls (BM x PB).

Results

In pooled patient samples, we identified the expression of *SLC22A1* influx gene in both, BM and PB samples, without any significant change ($p \leq 0,05$), and expression of *SLCO1A2* influx gene only in PB sample. Thus its presence could not be identified in any of the control samples. The overexpression of ABC efflux gene family (*ABCB1; ABCG2; ABCC1*), were found only in BM cells of patients. The presence of other two genes responsible for the drug efflux was also found exclusively in BM pool sample of patients, *SLC47A1* and *SLC47A2*.

Conclusions

Over-representation of drug influx and absence of drug efflux channels in mature cells, and the reverse in stem cells of patients with CML may explain the insensitivity of CD34+ cells to IM treatment and consequent failure to eliminate minimal residual disease.

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