PROTEOMICS-DRIVEN CANCER BIOMARKER DISCOVERY IN LEUKEMIAS

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Chronic myeloid leukemia (CML) is a malignant clonal disorder characterized by the Philadelphia (Ph) chromosome translocation, which generates the BCR-ABL fusion gene. It expresses an oncoprotein, known as $p210^{BCR-ABL}$, with constitutive tyrosine kinase activity. Blast crisis is the terminal phase of CML, that typically presents three distinct clinical stages: chronic, accelerated phase and blast crisis. The chronic phase lasts several years and is characterized by accumulation of myeloid precursors and mature cells in bone marrow. The blast crisis lasts only a few months and is characterized by rapid expansion of a population of myeloid or lymphoid differentiation-arrested blast cells. Improvement of treatment was accomplished by the use of selective tyrosine inhibitor, Imatinib mesylate (IM). However, due to Imatinib Mesylate resistance mechanisms, new generation of tyrosine kinase inhibitors have been developed. The mechanisms responsible for transition of CML chronic phase into blast crisis, as well as its biomarkers, remain poorly understood and although the extensive utilization of this drug in the clinical therapy of CML, the proteins and signaling pathways altered in CML biology and during remission of the disease are completely unknown. Furthermore the identification and analysis of the proteomic targets that are related with CML diagnose, evolution and treatment response to imatinib mesylate are extremely necessary to patients follow-up. To address this problem our lab have been analyzing through a comparative proteomics approach, the modifications in the protein profile of mononuclear bone marrow cells from patients in chronic phase, blastic phase and in imatinib mesylate treatment. Using 2DE gel and mass spectrometry analysis we could identify several putative biomarkers of disease diagnose, evolution and treatment response. All these identification shed new light on the CML biology and also instigates new approaches. On the other hand, acute myeloid leukemia (AML) is characterized by specific cytogenetic aberrations that are strong determinants of prognostic outcome and therapeutic response. Because the pathological outcome of AML patients with cytogentic abnormalities differs considerably we hypothesized that their proteome may also differ specifically in their expression pattern, protein interaction pathways and posttranslational modifications. To begin to solve this issue comparative proteomics are also applied in AML biomarkers identification in our lab using patients' bone marrow samples achieving promising results.