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Protein microarray analysis of aberrant signaling pathways in Acute Myeloid Leukemia to predict the patients responsiveness to PI3K/Akt/mTOR inhibitors

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Mapping of deregulated kinases and protein signalling networks within tumors can provide a means to stratify patients with shared biological characteristics to the most optimal treatment, and identify drug targets. In particular, the PI3K/AKT/mTOR signaling pathways are frequently activated in blast cells from patients with acute myelogenous leukemia (AML), a neoplastic disorder characterized by the accumulation of genetically altered myelogenous cells displaying deregulated intracellular signalling pathways and aggressive clinical behavior with poor prognosis. Using Reverse Phase Protein Microarrays (RPMA), we have analyzed the phosphorylated epitopes of signal pathway proteins of 81 peripheral blood and bone marrow specimens with newly diagnosed AML. Patients are diagnosed according to blast content, FAB classification and cytogenetic analysis. Samples are enriched for leukemic cells by performing Ficoll separation to yield a mononuclear fraction with >60% blast cells. The objective of the study was to predict the sensitivity of each patient to PI3K/Akt/mTor inhibitors, to avoid unnecessary and toxic ineffective treatment of non-responsive patients. To this goal, fresh blast cells were grown for 16 h untreated or treated with phase I or phase II mTor or Akt inhibitors either alone or in combination. Remarkably, by unsupervised hierarchical clustering a strong phosphorylation/activity of most of the sampled members of the PI3K/Akt/mTOR pathway was observed in 70% of samples from AML patients. This confirms that this pathway might indeed represent a pharmacological target in many patients. Moreover, treatment with the above inhibitors had no effect on the phosphorylation of other selected targets, demonstrating the specificity of the above results (more than one different inhibitor was used to avoid off-target effects). More importantly, by the use of the above drugs, we have been able to discriminate within the "high pAkt" population a PI3K/Akt/mTOR inhibitor-responsive group of patients and a PI3K/Akt/mTOR inhibitor non-responsive group. In addition, our data indicate that the Akt pathway is hyper-activated in M4, M5 patients, compared to M0, M2 patients, and that a strong activation of most upstream and downstream Akt effectors correlates with an over-expression of the c-kit receptor (CD117). We believe these data are important because they, have the potential to define a profile for the personalized administration of targeted drugs.

Keywords: phospho-proteomics, acute leukemia, protein kinase inhibitors, drug-resistance, xenografts, multichannel-cytometry

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