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International
Translational and Regenerative Medicine Conference
April 25-27, 2018 Rome, Italy

Can Phosphoproteomic Analysis Combined to Metabolic and Mutational Phenotyping Help define Individual Profiles of T-ALL Cells?

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Prognosis of chemo resistant or relapsed T-ALL patients is still very poor. Several key signaling pathways are deregulated in T-ALL, such as the PI3K/mTOR cascade, downstream of Notch1 mutations (found in >60% patients) or PTEN gene deletion/inactivation. These alterations frequently lead to reprogramming of metabolism, whereby cancer cells display glycolytic features even in normoxic conditions to boost rapid growth and energy demand. In spite of the heterogeneity of this malignancy, however, hitherto most patients are still treated with conventional chemotherapy regimens.

A panel of highly characterized T-ALL cell lines, recapitulating the heterogeneity of T-ALL phenotypes, and primary cells from patients were analyzed by NGS for Notch mutation, by GEP for expression of genes involved in regulation of cell metabolism downstream of the PI3K pathway, and by RPPA for the phospho profile of the PI3K/Akt/mTOR cascade. Analysis of the energy metabolism phenotypes was carried out by the Seahorse XFe96Analyzer. Next, we examined the responses of all cell lines to treatments with drugs blocking PI3K signaling (PF-4691502) and/or glycolysis (2DG).

Overall, our results indicate that cells carrying both Notch1 and PTEN mutations display higher signaling and a more glycolytic phenotype, compared to those with wild type and/or a single mutation. Besides, in these cells 2-DG and PF-4691502 show strong synergistic cytotoxicity and abrogate cell proliferation even at very low concentration, evaluated by CFU assay. Moreover, cells carrying mutant/cleaved Notch1 alone are more sensitive to 2-DG as monotherapy, indicating that Notch1 may be more effective in driving metabolic rewiring. On the other side, cells carrying mutant PTEN alone are highly sensitive to PF-4691502, indicating a prevailing role of the signaling over activation in these cells.

These results, though preliminary, suggest that mutational and phosphorylome analysis of T-ALL correlated to metabolic phenotypes can allow to define individual profiles and to predict specific treatments effectiveness.

Biography:

Dr. Sandra Marmiroli has done her PhD in Cellular and Molecular Biology and is an Associate Professor of Histology. She is the author or co-author of 71 full-length peer-reviewed papers (Scopus), 1570 citations (Scopus), H-index 27 (Scopus + WOS). Her main research topics include "Identification of glycolytic vs. oxidative cellular phenotypes and their modulation by the PI3K pathway in primary blast cells from leukemia patients". "Definition of the phosphorylome of primary blast cells from leukemia patients, and its modulation by the PI3K pathway:" "Targeted therapy in hematological malignancies" (Bertacchini et al., Leukemia 2014; Serafin et al., Leukemia 2017)