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622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

The Characterization of Metabolic Profile and Substrates Dependencies of Richter's Syndrome Cells Open for Translational Opportunities

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Richter's syndrome (RS) is a high-grade aggressive lymphoma transformed from chronic lymphocytic leukemia (CLL), with a generally poor clinical outcome. The presence of sites of abnormally increased fluorodeoxyglucose F18 (18F-FDG) uptake on PET/CT of patients with CLL is predictive of Richter's transformation. The higher uptake of glucose in RS infiltrated lymph nodes compared to non-infiltrated ones together with evidence of metabolic reprogramming as a hallmark of cancer, prompt us to investigate the metabolic profile of RS cells and characterize their substrates dependencies.
Exploiting 4 RS-patient-derived xenograft (PDX) models and the RS cell line U-RT1, we aimed to i) provide a complete picture of the metabolic landscape of RS cells, ii) identify the undeniable metabolites for these neoplastic cells, and iii) provide a proof-of-principle that metabolism can be a target for RS cells.
Taking advantage of primary RS and CLL publicly available transcriptomic data, a clear shift in RNA expression was highlighted between the two disease phases, with an enrichment in metabolic processes-related terms within the upregulated genes. These results were validated in an internal cohort of primary RS samples and in the 4 RS-PDXs, with a complete overlap of the enriched "metabolic terms", making these models representative tools to study the metabolic profile of RS cells. Specifically, gene sets enrichment analyses revealed oxidative phosphorylation, reactive oxygen species pathway, glycolysis, and fatty acid metabolism among the most significantly enriched gene sets in RS. This expression profile was supported by the measurement of the enzymatic activity of key enzymes belonging to glucose, glutamine, and fatty acid metabolic pathways. Three out of 4 PDXs and the U-RT1 cell line were characterized by an elevated metabolic rate compared to CLL, in terms of Krebs cycle, oxidative phosphorylation and glutamine metabolism, while the remaining RS-PDX model showed a more pronounced Warburg profile, with a stronger lactate dehydrogenase activity. These pathways are sustained by an increased glucose and glutamine uptake in RS cells leading to an elevated ATP content. Simultaneously, RS cells showed activation of anabolic processes that result in the synthesis of nucleotides and fatty acids. In line with these data, an unbiased approach based on metabolomic analyses identified a limited number of products of reaction, mainly attributable to pathways necessary both to produce energy and to provide building blocks (nucleotides, proteins and lipids) for cell proliferation.
The metabolic dependencies of RS cells from glucose and glutamine were formally demonstrated by ex-vivo treatment with highly selective metabolic inhibitors. BPTES, a glutaminase inhibitor, and UK5099, a mitochondrial pyruvate carrier blocker, led to a significant decrease in the oxygen consumption rate and ATP production, while limited effects were observed when treating RS cells with Etomoxir, a fatty acid oxidation inhibitor. These reductions ultimately led to a significant induction of apoptosis in RS-PDXs derived cells.

Finally, we showed that selective inhibitors of PI3K (duvelisib) and NF-kB (p65 inhibitor), two major regulators of energy metabolism and biosynthetic pathways, by interfering with the activity of these molecules, impacted on RS cells metabolism with a marked reduction of the oxidative phosphorylation and glycolytic cascade.
Overall, these data depict the metabolic features of RS cells and their dependency from glucose and glutamine, at variance with CLL cells that mostly depend on fatty acid oxidation, thus suggesting a metabolic rewiring because of disease evolution. Moreover, they provide a proof-of-principle that metabolism can be envisaged as a candidate target for RS using either direct metabolic inhibitors or drugs that inhibit key metabolic regulators.

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