

## Relevance of fatty acid metabolism in proliferating CLL cells

Elena Gugiatti - Claudya Tenca - Fabio Ghiotto - Silvia Bruno - [Franco Fais](#)

MiAO Lab, Dipartimento di Medicina Sperimentale, Università di Genova, Genova, Italia

Chronic lymphocytic leukemia (CLL) cells undergo, during their life, iterative cycles of re-activation and subsequent clonal expansion. We previously demonstrated that the antidiabetic drug metformin, known to also inhibit oxidative phosphorylation (OXPHOS), inhibits cell cycle entry of leukemic cells derived ex-vivo from the peripheral blood of CLL patients and stimulated in vitro by cell culture systems that recreate a microenvironment to drive their proliferation (Bruno et al, *Oncotarget*, 2015). However, overtly proliferating CLL cells were resistant to the cytostatic effects of metformin. Since metformin switched the energetic metabolism of activated, not yet proliferating, CLL cells from OXPHOS to accelerated glycolysis, in the present study we asked whether combining metformin with glycolysis impairment could inhibit also proliferating CLL cells. Still, CLL cells recovered from a transitory block and rescued in vitro proliferation. What kind of energetic reprogramming was involved in the resistance of proliferating CLL cells to glucose utilization? Recent studies highlight on the role of fatty acid utilization of CLL cells. We asked 1) whether inhibitors of lipid metabolism could impair proliferation of in vitro stimulated CLL cells; 2) whether impairing glucose energetic pathways could act synergistically with beta oxidation inhibitors. We found that inhibitors of critical steps of fatty acid metabolisms, such as carnitine-palmitoyl transferase 1A (CPT1A) -rate-limiting enzyme for fatty acid import into mitochondria- or Peroxisome Proliferator-Activated Receptor (PPAR)-alpha -regulator of beta-oxidation- administered at clinically achievable doses, were ineffective on quiescent CLL cells and on CLL cells stimulated by the microenvironment during the first stages of activation. Conversely, remarkable susceptibility to undergo apoptosis was observed at later stages of cell activation and during overt proliferation. Synergism with impairment of other energetic pathways occurred depending on the stage of activation of the in vitro stimulated CLL cells. The results suggest that energetic metabolic pathways could be relevant targets for CLL treatment, provided that the complex metabolic reprogramming network during the transition of leukemic cells from quiescence to proliferation, and back, are clearly elucidated.

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### Keywords

Energetic metabolism; cell proliferation; chronic lymphocytic leukemia.