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Abstract

Immunometabolism adaptation in CLL and new therapeutic opportunities

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Chronic lymphocytic leukemia (CLL) is an incurable B-cell lymphoproliferative disorder that relies on a highly immunosuppressive microenvironment. Despite initial promise, immune checkpoint inhibitors have yielded disappointing results in clinical trials, highlighting the need for alternative immune-based approaches to target this disease. Firstly, CD4+ cytotoxic T cells (CD4+ CTLs) have emerged as a promising therapeutic avenue due to their ability to exert direct cytolytic activity on tumor cells. However, the role of CD4+ CTLs in antitumor immunity remains poorly understood. In this project, we demonstrate a strong antitumor function of human CD4+ T cells in a CLL mouse model. We show that donor-derived CD4+ T cells activated in vitro control the development of an aggressive CLL cell line in an immunodeficient mouse model. We also establish a correlation between the acquisition of the CD4+ CTL phenotype and metabolic changes associated with ex vivo cold storage of donor peripheral blood. The second part of our project aims to identify metabolic vulnerabilities of leukemic and pro-tumoral immune cells that could be therapeutically targeted and combined with immunotherapies to reactivate antitumor immunity. We will study the metabolic adaptation of leukemic B cells during leukemogenesis in vivo and immune cells in the tumor microenvironment using mouse models and metabolic tracing. In vitro studies on cell lines and patient samples, as well as conditional knockout mice, will elucidate the mechanisms involved. Preliminary data indicate the sensitivity of leukemic cells and regulatory T cells to specific one-carbon metabolism inhibitors, suggesting a major role for metabolism in leukemia