Targetting glutaminase to starve lymphoma cells

by Charles Dumontet

Received: November 16, 2022.
Accepted: November 23, 2022.

Citation: Charles Dumontet. Targetting glutaminase to starve lymphoma cells. Haematologica. 2022 Dec 1. doi: 10.3324/haematol.2022.282348 [Epub ahead of print]

Publisher’s Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors’ final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Title
Targetting glutaminase to starve lymphoma cells

Charles Dumontet
INSERM UMR1052/CNRS5286; Hospices Civils de Lyon; University of Lyon
Lyon, France
Mail: charles.dumontet@chu-lyon.fr
Phone +33 6 82 13 66 14

The discovery of Bruton Tyrosine Kinase inhibitors (BTKi) such as ibrutinib have had a significant impact on the outcome of patients with mantle cell lymphoma (MCL). However a majority of these patients will relapse under BTKi therapy, with a poor prognosis since overall survival after BTKi failure is less than 12 months (1). In their article, Li et al. provide promising preclinical evidence suggesting that tumor cell glutaminase could constitute a potential therapeutic target in this difficult-to-treat patient population (2).

Glutamine addiction has been reported in various subtypes of hematological malignancies, including acute lymphoblastic leukemia and NK-cell lymphoma, allowing neoplastic cells to thrive in glucose low or hypoxic environments. Le et al. showed that Myc induction enhanced glucose consumption and lactate production in a model NHL line and that glutamine contributed significantly to citrate carbons under hypoxia (3). This work demonstrated the existence of an alternative energy-generating glutaminolysis pathway involving a glucose-independent tricarboxylic acid cycle (TCA). Glutamine metabolism thus appears to be essential for cell survival and proliferation under conditions of hypoxia and glucose deprivation. Gao et al. reported that c-Myc induces increased expression of mitochondrial glutaminase (GLS), up-regulating glutamine conversion to glutamate which is further catabolized in the TCA cycle to generate ATP (4). Using cell lines containing GLS variants as well as in vivo modulation of murine and human GLS, Xiang et al. showed that targeted inhibition of tumor-specific glutaminase reduced tumorigenesis in a human NHL xenograft model (5). There thus seems to be a well established correlation between Myc, tumor cell glutaminase and the use of glutamine as a key ATP-generating energetic substrate in lymphomas.

Targeting glutamine addiction in cancer has been explored in various preclinical settings and more recently in early phase clinical trials using teglenastat. Targeting mitochondrial glutaminase has been shown to inhibit oncogenic transformation in preclinical models of fibroblasts and breast cancer (6). Matre et al. have reported that glutaminase inhibition by various GLS inhibitors inhibited the growth of AML cell lines as well as a subset of primary AML samples (7). Interestingly the antitumor of recombinant L-asparaginase, which is widely used to treat various lymphoid malignancies, is believed to rely at least in part on its glutaminase activity which results in extracellular glutamine depletion (8).
Telaglenastat (CB-839) has been evaluated in early phase clinical trials, mainly in combination regimens in patients with solid tumors. In a combination study with cabozantinib or everolimus, telaglenastat displayed promising activity in patients with advanced or metastatic renal cell carcinoma, with mostly grade 1 to 2 treatment-related adverse events (9). A single agent phase 1 has been conducted in patients with hematological malignancies (NCT02071888) but results have not yet been reported.

Targeting glutaminase appears to be particularly relevant in the context of ibrutinib resistance. Lee et al. analyzed the impact of ibrutinib in various MCL lines and found that inhibition of BTK had a profound effect on several metabolic pathways, including glutaminolysis (10). Importantly glutaminolysis was found to contribute to over 50% of mitochondrial ATP production. By showing that GLS expression and glutamine addiction are enhanced in ibrutinib-resistant MCL models, Li et al. provide compelling evidence suggesting that targeted inhibition of glutaminase could benefit MCL patients who have progressed under BTKi therapy.

More generally these results support the tantalizing possibility that tumor-associated metabolic specificities may represent an Achilles heel allowing the selective destruction of neoplastic cells. Exploiting these characteristics, either using single agent therapies or in the context of synthetic lethality approaches, has proven to be challenging. To date attempts to target the Warburg effect, i.e. preferential cytosolic fermentation of glucose to lactic acid rather than mitochondrial oxidative fermentation even in the presence of abundant oxygen, has not lead to major breakthroughs in cancer therapy. These attempts underline the difficulty to induce systemic alterations in key metabolic processes to specifically target tumors while preserving healthy tissues. For this reason it is possible that use of metabolic inhibitors such as telaglenastat in combination with BTKi, rather than after failure of such therapies, will reduce or differ the emergence of resistant phenotypes.
References