Targeting glutaminase to starve lymphoma cells

Charles Dumontet

INSERM UMR1052/CNRS5286, Hospices Civils de Lyon and University of Lyon, Lyon, France

Correspondence: C. Dumontet
charles.dumontet@chu-lyon.fr

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The discovery of Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib has had a significant impact on the outcome of patients with mantle cell lymphoma. However, most of these patients will relapse under BTK inhibitor therapy, with a poor prognosis since overall survival after failure of BTK inhibitor therapy is less than 12 months.[1] In their article, published in this issue of *Haematologica*, Li *et al.* provide promising preclinical evidence suggesting that tumor cell glutaminase (GLS) could constitute a potential therapeutic target in this difficult-to-treat population of patients.[2]

Glutamine addiction has been reported in various subtypes of hematologic 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 non-Hodgkin lymphoma line and that glutamine contributed significantly to citrate carbons under hypoxic conditions.[3] This work demonstrated the existence of an alternative energy-generating glutaminolysis pathway involving a glucose-independent tricarboxylic acid cycle. 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 GLS, upregulating glutamine conversion to glutamate, which is further catabolized in the tricarboxylic acid 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 GLS reduced tumorigenesis in a human non-Hodgkin lymphoma xenograft model.[5] There does, therefore, seem to be a well-established correlation between Myc, tumor cell GLS and the use of glutamine as a key ATP-generating energy 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 GLS has been shown to inhibit oncogenic transformation in preclinical models of fibroblasts and breast cancer.[6] Matre *et al.* reported that inhibition of GLS by various inhibitors blocked the growth of acute myeloid leukemia cell lines as well as a subset of primary acute myeloid leukemia samples.[7] Interestingly, the antitumor effect of recombinant L-asparaginase, which is widely used to treat various lymphoid malignancies, is believed to rely at least in part on its GLS 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 I study has been conducted in patients with hematologic malignancies (NCT02071888) but the results have not yet been reported.

Targeting GLS appears to be particularly relevant in the context of ibrutinib resistance. Lee *et al.* analyzed the impact of ibrutinib in various mantle cell lymphoma 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 mantle cell lymphoma models, Li *et al.* provide compelling evidence suggesting that targeted inhibition of GLS could benefit patients with mantle cell lymphoma whose disease has progressed under BTK inhibitor 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 led to major breakthroughs in cancer therapy. These

attempts highlight the difficulty of inducing systemic alterations in key metabolic processes to specifically target tumors while preserving healthy tissues. For this reason it is possible that the use of metabolic inhibitors, such as telaglenastat, in combination with BTK inhibitors, rather than after failure of such therapies, will reduce or defer the emergence of resistant phenotypes.

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