



## Commentary

## Targetable Metabolic Vulnerability in Diffuse Large B-Cell Lymphoma

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Targeting metabolic alterations has become a promising therapeutic strategy in treating hematological malignancies nowadays. Recurrent mutations of metabolic enzyme isocitrate dehydrogenase (IDH) are identified in acute myeloid leukemia and proven critically involved in leukemogenesis. AG-211, a small-molecular inhibitor of mutant IDH2, is successful in a phase I clinical trial of relapsed or refractory acute myeloid leukemia, downregulating oncogenic metabolite 2-hydroxyglutarate and leading to differentiation of malignant myeloblasts into mature neutrophils (Stein, 2016). Besides, in natural killer/T-cell lymphoma, asparaginase-based regimens significantly improve the prognosis of the patients through targeting aspartate-related metabolites (Jaccard et al., 2011). However, metabolomic profiling and targetable metabolic vulnerability remain largely undefined in diffuse large B-cell lymphoma (DLBCL).

Through unveiling metabolic signatures, molecular subsets of malignancies characterized with distinct biomarkers could be identified, which opens new therapeutic opportunities, especially in the clinically and biologically heterogeneous DLBCL. According to the different fingerprints of energy metabolism, DLBCL is categorized into OxPhos- and non-OxPhos-subtypes. Increased mitochondrial oxidative phosphorylation is observed in OxPhos-DLBCL, while non-OxPhos-DLBCL presents with remarkable reliance on activation of B-cell receptor signaling (Caro et al., 2012). From the view of lipid metabolism, in the journal *EBioMedicine*, Pera et al. (2018) report the metabolic effects of lysine deacetylase inhibitors (KDACI) panobinostat in DLBCL and uncover KDACI-induced lymphoma cell dependency on choline metabolism. This was first identified through comparison of pre- and post-treatment serum metabolomics patterns in patients and then confirmed by both in vitro and in vivo study that DLBCL showed an increased sensitivity to the choline pathway inhibitor after treatment with panobinostat. Their findings not only prove the power of metabolomics in identifying mechanism of action of epigenetic agents, but also reveal the potential targets for combination therapies with KDACI in DLBCL. Metabolic reprogramming is an adaptation for survival during oncogenesis, disease progression, and also upon treatment, which confer for drug sensitivity.

Of note, altering lipid metabolism, KDACI subsequently modulates downstream survival signaling in DLBCL. Choline kinase alpha, as one of the key enzymes in choline metabolism, was upregulated upon panobinostat treatment, resulting in activation of PI3K pathway relevant for lymphoma cell growth. This provides a clinical rationale for the synergistic anti-tumor activity of KDACI combined with PI3K inhibitors. Moreover, high throughput compounds library is employed to screen panobinostat-induced dependency on metabolic and signaling pathways. With clinically achievable concentrations, the potential of combined treatment using KDACI and signaling pathway inhibitors for bench-to-bedside translation is clearly evident.

On the other hand, dysregulated metabolites can result directly from genetic/epigenetic mutations and cancer-associated modifications in protein expression (Sullivan et al., 2016). In DLBCL, MYC overexpression and TP53 mutation are associated with aggressive disease behavior and poor disease outcome. Aberrant choline metabolism is significantly associated with MYC overexpression, indicating a potential lipid-modifying strategy in treating MYC-driven DLBCL (Xiong et al., 2017). Functional mutation of TP53 induces metabolic shift to aerobic glycolysis and free radicals generation through activating glucose transporter, glutaminase, and fructose 2,6-biphosphatase during lymphomagenesis (Li et al., 2012). Therefore, with better understanding of metabolomic alterations, it would be possible to translate these undruggable targets to druggable onco-metabolites and develop potential anti-metabolic treatment for high-risk DLBCL.

Finally, further studies are needed to investigate the clinical efficacy of co-targeting epigenetic and metabolic alterations. Well-designed clinical trials should be established to confirm durable treatment response and safety, as well as optimization and standardization of regimens. As for basic research, multi-omics landscape should be delineated, integrating genetic, epigenetic, proteomic and metabolomic signatures, to pave the way for precision medicine in DLBCL.

**Disclosure**

The authors declared no conflicts of interest.

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