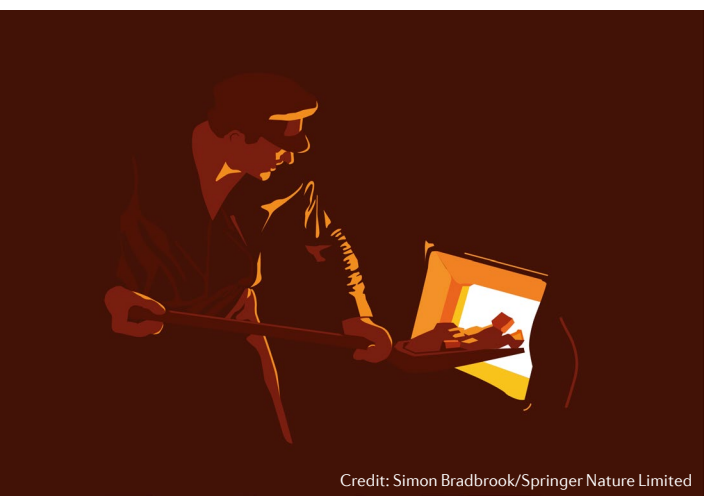
TUMOUR METABOLISM

Glutamine-fuelled OXPHOS — a new target in MCL

> resistance in MCL cells is mediated by OXPHOS pathway upregulation

Despite promising initial responses to ibrutinib, long-term survival outcomes are poor in patients with relapsed–refractory mantle cell lymphoma (MCL) owing to progression, warranting investigation of resistance mechanisms. A new study now reports a therapeutically targetable ibrutinib resistance mechanism in preclinical MCL models, involving metabolic reprogramming towards reliance on glutamine-fuelled oxidative phosphorylation (OXPHOS).

To identify dysregulated pathways underpinning resistance, Zhang et al. used integrative genomics approaches to profile tumour specimens from ibrutinib-sensitive and ibrutinib-resistant patients with MCL. Unsupervised hierarchical clustering of RNA sequencing data uncovered a response-specific gene expression signature, and inspection of the differentially expressed genes (DEGs) between ibrutinib-resistant ($n = 6$) and ibrutinib-sensitive ($n = 15$) tumours revealed that many were related to glycolytic metabolism, the TCA cycle and glutamine transport. These findings were validated using a nanoString assay (based on 63 DEGs) in an independent cohort.



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Subsequent gene set enrichment analysis uncovered marked enrichment for metabolic pathways, such as OXPHOS, and oncogenic pathways linked to oxidative metabolism and glutaminolysis (which can fuel OXPHOS), such as MYC and mTORC1 signalling, in ibrutinib-resistant tumours, implicating metabolic reprogramming towards glutamine-fuelled OXPHOS as a resistance hallmark.

"Once we identified OXPHOS among the most significantly upregulated pathways in the ibrutinib-resistant clinical specimens, we wished to further confirm and validate this finding with functional metabolic studies," explains investigator Michael Wang. Notably, compared with ibrutinib-sensitive cell lines, ibrutinib-resistant lines exhibited increased OXPHOS activity, evidenced by higher basal, ATP-coupled and reserve oxygen consumption rates (OCRs). In addition, targeted metabolomics analyses revealed increased glutaminase and α-ketoglutarate levels in ibrutinib-resistant cells, suggesting enhanced glutamine metabolism.

"Our finding that ibrutinib resistance in MCL cells is mediated by OXPHOS pathway upregulation coincided with the timing of the MD Anderson Therapeutics Discovery team formulating a potent OXPHOS inhibitor, IACS-010759, which we tested for anti-MCL activity," adds author Linghua Wang. IACS-010759 dose-dependently inhibited proliferation in ibrutinib-resistant cell lines, with IC_{50} values ~10-fold lower than those in ibrutinib-sensitive lines, and reduced OCRs in both ibrutinib-resistant cell lines and primary cells. Mechanistically, IACS-010759 was found to decrease mitochondrial potential and ATP production. Moreover, concomitant treatment with IACS-010759 and glutamine metabolism inhibitor BPTES further reduced mitochondrial potential, implicating glutamine as the major metabolite powering OXPHOS. Single-agent IACS-010759 or BPTES treatment induced a greater degree of apoptosis in ibrutinib-resistant lines than in ibrutinib-sensitive lines, providing a mechanistic basis for their inhibitory effects on proliferation.

The anti-MCL effects of OXPHOS inhibition were also evaluated in two ibrutinib-resistant patient-derived xenograft (PDX) MCL mouse models, in which IACS-010759 markedly inhibited tumour growth relative to vehicle, with no apparent toxicities, and extended survival compared with vehicle and ibrutinib treatment. Similar findings were reported in an ibrutinib-resistant B cell lymphoma PDX model, demonstrating the broad anti-lymphoma effects of IACS-010759.

The authors plan to expand these promising findings into the clinical setting, and will include a cohort of patients with ibrutinib-resistant MCL in an ongoing phase I trial of IACS-010759 in patients with lymphoma (NCT03291938). "If IACS-010759 proves efficacious for these patients, we will pursue larger trials and further development of the drug for lymphoma," concludes L. Wang.

Conor A. Bradley

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