PARSACLISIB HAS ACTIVITY IN PATIENTS WITH B-CELL MALIGNANCIES

Constitutive signaling of B-cell receptors (BCR) plays a critical role in the pathogenesis of many B-cell malignancies and leads to downstream activation of phosphatidylinositol 3 kinases (PI3K). The PI3Kδ isoform functions as a critical node in signaling networks that regulate B-cell growth and survival, and its aberrant activation is a key event in the malignant transformation of B cells. Many patients with relapsed non-Hodgkin lymphoma (NHL) suffer from poor prognosis, and although PI3K inhibitors have shown promise in treating patients with relapsed or refractory NHL, high hepatotoxicity has limited their use in the clinic. To evaluate the safety and efficacy of parsaclisib, a structurally distinct and highly potent next-generation PI3Kδ inhibitor achieved objective responses and long-term tolerability in patients with refractory NHL.

Major finding: A next-generation PI3Kδ inhibitor achieved objective responses and long-term tolerability in NHL.
Concept: Parsaclisib potently and selectively inhibits PI3Kδ without inducing severe hepatotoxicity.
Impact: Parsaclisib alone or with itacitinib or chemotherapy is safe in patients with refractory NHL.

PYRUVATE MEDIATES ECM REMODELING IN THE LUNG METASTATIC NICHE

Cancer cells promote metastatic outgrowth in part by inducing collagen hydroxylation to remodel the extracellular matrix (ECM) within the metastatic niche. Elia and colleagues investigated whether specific nutrients are required for cancer cell–mediated ECM remodeling, and found that depletion of pyruvate impaired the three-dimensional growth of breast cancer cells without affecting monolayer growth. Consistent with a role for this nutrient in collagen modification, pyruvate enhanced collagen hydroxylation and stability in breast cancer cells but not nontumorigenic cells, and this effect was abrogated by inhibition of the pyruvate transporter monocarboxylate transporter 2 (MCT2, also known as SLC16A7). Mechanistically, pyruvate uptake induced production of the metabolite α-ketoglutarate, which stimulated collagen hydroxylation by metabolically activating the enzyme collagen prolyl 4-hydroxylase (P4HA) in transformed cells; conversely, the addition of succinate, a coproduct of the P4HA enzymatic reaction, decreased the abundance of hydroxylated collagen. Of note, the metabolic regulation of P4HA by pyruvate was independent of the transcriptional regulation of P4HA by HIF1α. Furthermore, pyruvate-driven production of α-ketoglutarate was required for remodeling of the ECM in the lung metastatic niche in vivo; pharmacologic or genetic inhibition of MCT2 in two mouse models of breast cancer reduced collagen hydroxylation levels and suppressed lung metastasis, both of which were restored by concomitant treatment with α-ketoglutarate. These findings identify a critical role for pyruvate in the lung metastatic niche in mediating ECM modification by cancer cells to support metastatic outgrowth and suggest that targeted inhibition of pyruvate metabolism may impair lung metastasis by preventing aberrant collagen remodeling.

Parsaclisib Has Activity in Patients with B-cell Malignancies

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