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**PHARMACOLOGIC LDH INHIBITION REDIRECTS  
INTRATUMORAL GLUCOSE CONSUMPTION AND  
IMPROVES RESPONSE TO CTLA-4 BLOCKADE**

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**Background** Tumor reliance on glycolytic metabolism represents a hallmark of cancer and a mechanism of resistance to immune based therapies.<sup>1-2</sup> Competition for glucose between T cells and tumor cells as well as lactate-mediated immune suppression contribute to this resistance. Thus, immune checkpoint blockade (ICB) more effectively controls glycolysis-low tumors lacking lactate dehydrogenase (LDH), primarily due to enhanced glucose availability within the tumor microenvironment.<sup>3</sup> The development of LDH inhibitors (LDHi) have been reported to reduce glucose uptake and growth of preclinical models of cancer,<sup>4</sup> but their impact on infiltrating T cells within the tumor microenvironment remains unexplored.

**Methods** B16F10 and MC38 tumor-bearing C57BL/6 mice were treated with LDHi GNE-140 and/or anti-CTLA-4 and tumor volume was measured twice per week. Tumors were also processed for flow cytometric analysis of tumor-infiltrating lymphocytes to assess infiltration, activation, and function. Glucose uptake, LDH, and Glut1 expression was assessed in tumor and T cells by flow cytometry. Seahorse analysis was performed on mouse and human tumor and T cells.

**Results** Tumor cells exhibit higher basal levels of LDH and glucose consumption compared to tumor-infiltrating T cells, exposing a therapeutic window for tumor-specific targeting of glycolysis. We show that effective LDH inhibition relies on tumoral overexpression of LDH and the adaptive immune system to impede murine tumor progression. Mechanistically, we demonstrate that LDHi treatment 1) decreases tumor cell glucose uptake and expression of the glucose transporter GLUT1 while 2) increasing glucose uptake and GLUT1 expression in tumor-infiltrating CD8<sup>+</sup> T cells. Compared to activated T cells, tumor cells display significantly higher metabolic sensitivity to LDH inhibition via reduction of glucose uptake and extracellular acidification rates while also downregulating LDH and GLUT1 expression. Strikingly, LDH inhibition combined with anti-CTLA-4 effectively controls murine melanoma and colon cancer progression. This dual therapy also promotes effector T cell infiltration and activation while functionally destabilizing regulatory T cells (Tregs). Accordingly, increasing glucose availability leads to improved T cell killing of tumor cells, and impaired Treg-mediated suppression of T cells.

**Conclusions** Increasing intratumoral glucose levels contributes to anti-tumor efficacy of CTLA-4 blockade by supporting effector T cell function while impairing Tregs. Our results establish LDH inhibition as an effective tumor-specific strategy to reduce tumor glucose uptake and increase glucose availability within the tumor microenvironment, thereby boosting T cell glucose uptake. This study provides a comprehensive rationale for combining immune checkpoint blockade with inhibitors of glycolysis for patients with highly glycolytic cancers.

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