Glutaminase Inhibition With CB-839 Enhances Anti-Tumor Activity of PD-1 and PD-L1 Antibodies by Overcoming a Metabolic Checkpoint Blocking T Cell Activation

Abstract
Recent studies have highlighted the importance of the tumor metabolic environment for controlling immune activity. Tumor fragile metabolic processes such as glutaminolysis, which allows tumor cells to produce ATP and glutamate for de novo protein synthesis, and glutamine consumption and fermentation, drive tumor growth and proliferation. However, immune checkpoint therapies, PD-1 and PD-L1, require T cells to have high glutamine consumption and glutaminolysis rates. This study explores the effects of CB-839, a glutaminase inhibitor, on tumor cells and T cells in a PD-1/PD-L1 checkpoint blockade setting. First, we measured the metabolic activities of T cell lines (SUM159P, HCC1395, H2347, and KMS27) in the presence and absence of CB-839. Our findings indicate that CB-839 can enhance T cell proliferation and survival in a PD-1/PD-L1 checkpoint blockade setting. These results suggest that CB-839 could be a potential therapeutic target for enhancing the efficacy of immune checkpoint blockades.

References