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Title: Design and Development of Novel Malic Enzyme 1 Inhibitors for the Treatment of Pancreatic Ductal Adenocarcinoma

Abstract:

In the United States, pancreatic cancer is the third leading cause of cancer-related deaths, with pancreatic ductal adenocarcinoma (PDAC) constituting over 85% of these cases and having a 5-year overall survival rate of only 12%. Treatment options for PDAC mainly depend on the disease stage; however, most patients are diagnosed at an advanced stage where chemotherapy is the only viable option, often accompanied by significant side effects. Currently, there are no targeted or immune-based therapies available for PDAC, highlighting the urgent need for novel treatment strategies. Malic enzyme 1 (ME1) plays a critical role in the metabolic pathways that support PDAC growth. Belonging to the malic enzyme family, ME1 is localized in the cytosol, while the other isoforms, ME2 and ME3, are found in the mitochondria. There is functional redundancy between ME1 and ME2, evidenced by an inverse correlation between ME2 expression and sensitivity to ME1 knockdown. Notably, ME1 inhibition significantly reduces tumor growth in various ME2-deficient models and is well-tolerated in several ME2-intact models. Approximately 20% of PDACs exhibit ME2 loss, suggesting a biomarker-driven approach for deploying ME1 inhibitors in ME2-null cancers. We propose that targeting ME1 in patients with diminished or absent ME2 expression could provide a precision approach, selectively curtailing or eradicating tumor growth. Therefore, our long-term goal is to investigate selective and orally administered ME1 inhibitors with high efficacy and minimal adverse effects to expand treatment options for PDAC, particularly in patients with ME2 loss. Previously, the Lyssiotis lab, collaborating with the pharmaceutical company Astellas, has identified multiple small molecule inhibitors of ME1 by high throughput screening that provide a starting point for further medicinal chemistry. Our project objective is to identify and characterize selective, orally administered ME1 inhibitors capable of inhibiting PDAC cell growth with absorption, distribution, metabolism, and excretion (ADME) profiles compatible with oral administration, in collaboration with the Lyssiotis lab. The first aim focuses on developing analogs of the lead compound AS3244702 from Astellas with high ME1 selectivity and a favorable ADME profile. The second aim involves discovering new scaffolds through virtual screening followed by experimental validation and optimization. Successful achievement of these aims will yield potent ME1 inhibitors, and provide crucial preliminary data for subsequent animal studies. Ultimately, our work aims to advance PDAC targeted therapy, offering new hope and improved outcomes for patients, families, and caregivers.