Targeting a Novel Metabolic Network for Pancreatic Ductal Adenocarcinoma (PDAC) Treatment

New and innovative therapeutic approaches for efficient PDAC treatment

Technology

The Kimmelman Lab at NYU Langone Health has identified a novel metabolic network in PDAC between cancer cells and the surrounding pancreatic stellate cells (PSCs). As described in prior work (*Sousa et al. Nature 2016*), they discovered a new alanine cross-talk network between PSCs and pancreatic cancer cells that drives tumor progression. More recently, the Kimmelman group identified SLC38A2 (also called SNAT2) as the neutral amino acid transporter mediating alanine uptake into pancreatic cancer cells. In proof-of-concept (PoC) studies (*Parker et al. Cancer Discovery 2020*), pancreatic cancer cells lacking SLC38A2 failed to concentrate intracellular alanine, resulting in profound metabolic changes, including a dramatic reduction in tumor growth. Together, these results suggest that the metabolic demands of pancreatic cancer cells – namely, intracellular alanine levels regulated by SLC38A2 – present a new and innovative therapeutic strategy for selectively targeting PDAC cells.

Background

Pancreatic ductal adenocarcinoma (PDAC) has one of the lowest survival rates among cancer types, as evidenced by a dismal 5-year survival rate of ~9% and few therapeutic options for prolonged survival. Therapeutic shortcomings are attributed, in part, to the dense stromal environment and characteristic desmoplastic reaction present in PDAC tumors. As a result, new and innovative therapeutic approaches are desperately needed for efficient PDAC treatment. Metabolic networks, for example, which play important physiological roles in normal and diseased tissue function, offer new and under-appreciated avenues for therapeutic intervention.

Development Stage

NYU has identified 70+ primary screen hits from high-throughput screening of a 40,000 compound library in partnership with Evotec. Testing of these hits in secondary functional screens is underway and several lead series are expected to emerge from such efforts .
NYU is seeking strategic partners interested in helping support this drug discovery program.

Application

The treatment of Pancreatic Ductal Adenocarcinoma (PDAC).

Advantages

Category

Life Sciences/Biochemicals & Small Molecules
Life Sciences/Therapeutics/Oncology
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- Target location: SLC38A2 is a membrane-embedded transporter with an extracellular exposed surface (substrate binding pocket and interhelical loops) accessible to drug targeting
- Target physiology: Disruption of SLC38A2's catalytic transport cycle provides a clear mechanism for lowering intracellular alanine levels
- Validated target function in PDAC: SLC38A2 is a well-characterized alanine transporter that when upregulated fuels the metabolic demands of PDAC cells
- Downstream intracellular metabolic effect: Lower intracellular alanine levels from SLC38A2 knockout negatively modulate downstream metabolic pathways

Intellectual Property

A U.S. non-provisional patent application has been filed pertaining to the method of targeting SLC38A2 for the treatment of PDAC.

References

1. Sousa CM, Biancur DE, Wang X, et al. , Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion
2. Parker SJ, Amendola CR, Hollinshead KER, et al. , Selective Alanine Transporter Utilization Creates a Targetable Metabolic Niche in Pancreatic Cancer