Methylated Glutamic-Oxaloacetic Transaminase-2: A Therapeutic Target for Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most malignant cancers worldwide. However, the current treatments fail to control its progression. PDAC cells utilize glutamine as the major source of building blocks and energy production for cell proliferation and progression. Glutamic-Oxaloacetic Transaminase 2 (GOT2), regulates glutamine metabolism to produce ATP in the malate(Mal)-aspartate(Asp) shuttle. Enhancer of Zeste Homolog 2 (EZH2), the histone methyltransferase of polycomb repressor complex 2 (PRC2), is highly expressed in PDAC cells. EZH2 promotes tumor progression via epigenetically suppressing the expressions of tumor suppressor genes This study investigated whether the dysregulated GOT2 is a potential metabolic therapeutic target for PDAC and the underlying mechanisms. First of all, we found that EZH2 expression is important for cell proliferation when GOT2 was inhibited. In addition, EZH2 signaling could methylate GOT2 to regulate glutamine metabolism. In this study, we further found that EZH2, GOT2 expression have clinical significance, and cell viability was influenced by knockdown and inhibition of GOT2. Nonetheless, EZH2 inhibitor could reduce GOT2 activity in cells, instead of protein expression at all. Besides, EZH2 could interact with GOT2 and methylate GOT2, implying that EZH2 activity may play an important role in the glutamine-deprivation status. Our findings indicated that EZH2/GOTs axis might be a potential therapeutic target for pancreatic cancer. Further detail investigations would be helpful to development a novel therapeutic strategy targeting on GOT2 for this disease.

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