

The function and regulation of MiT/TFE activation in autophagy and pancreatic ductal adenocarcinoma

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is a lethal type of cancer that lacks effective therapies. Growth of PDAC cells depends on high levels of autophagy, which promotes cell survival under stressful conditions. High levels of autophagy in PDAC require the microphthalmia (MiT) family of transcription factors, including MiTF, TFEB, and TFE3. MiT/TFE proteins can be phosphorylated by nutrient-sensing kinase mTORC1, leading to their cytoplasmic retention and suppression of their transcriptional activity. Strikingly, despite the presence of active mTORC1 in PDAC, MiT/TFE proteins are located in the nucleus, suggesting the existence of mTORC1-independent pathway(s) that activates MiT/TFE for a potent autophagy program to sustain the growth and viability of PDAC.

The objective of this proposal is to identify genes and small molecules that modulate transcriptional activities of MiT/TFE independent on mTORC1 signaling in PDAC cells, to determine the molecular basis underlying autophagy and MiT/TFE activation in the presence of mTORC1 activity in PDAC cells, and to investigate whether and how MiT/TFE can be targeted therapeutically for PDAC. In Aim 1, we will perform high content genomic and chemical screening to identify novel genes that regulate MiT/TFE function and to develop therapeutic agents that block MiT/TFE activation. In Aim 2, we will investigate the molecular mechanisms underlying mTORC1-independent MiT/TFE modulation in PDAC, and determine the role of MiT/TFE activation in the treatment of PDAC by using organoid and mouse models. Success of the proposed research will unveil novel insights into PDAC biology and shed light to the development of novel therapies.