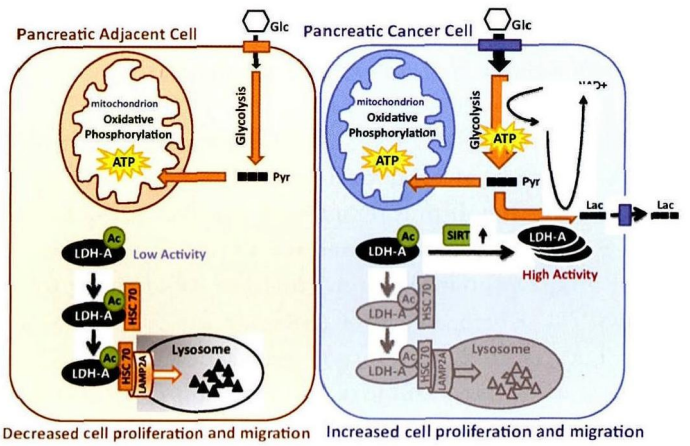
LDH-A acetylation: Implication in pancreatic cancer



Pancreatic cancer, the eighth most common cause of cancer-related death worldwide, has an extremely poor prognosis, while the median survival for metastatic disease is about 6 months. For most pancreatic cancer patients, they are usually diagnosed at late stages with metastasis and have limited options for treatment. The effect of chemotherapy/radiotherapy on pancreatic cancer is rather poor. Thus, early diagnose is critical for pancreatic cancer patients to have a time window for treatment. The current diagnosis depends on the descriptions of symptoms, computed tomography (CT scan), magnetic resonance imaging (MRI), ultrasound, and positron emission tomography (PET scan). A definite diagnosis is by biopsy, such as percutaneous needle biopsy. Therefore, more convenient and credible early diagnosis is urgently needed for pancreatic cancer. Supported by National Science Fund for Distinguished Young Scholars from NSFC, MOST, Prof. Lei Qunying from Fudan University with her collaborators have demonstrated not only a novel mechanism of LDH-A regulation, but also a potential early diagnosis marker? and therapeutic target for pancreatic cancer. This work has recently been published in *Cancer Cell* (**2013**, 23(4):464—476).

It has long been known that high levels of LDH-A are expressed in many tumor cells and tissues, which have been correlated with poor prognosis and resistance to chemotherapy and radiotherapy. Inhibition of LDH-A by either RNA interference or pharmacological agents blocks tumor progression *in vivo*, supporting an important role of elevated LDH-A in tumorigenesis and LDH-A as a potential therapeutic target. Elevated activities of c-Myc or HIF1a transcription factor contribute to the increased LDH-A expression in some cancer types. Recently, Prof. Lei's group has demonstrated that LDH-A is acetylated at lysine 5 (K5) which reduces LDH-A catalytic activity. Furthermore, acetylation decreases LDH-A protein level via chaperon mediated autophagy. Replacement of endogenous LDH-A with an acetylation mimetic mutant decreases cancer cell proliferation and migration, indicating a critical role of LDH-A acetylation in cell growth control. Importantly, K5 acetylation of LDH-A is reduced and accompanied by increased LDH-A protein levels in both early and late stages of pancreatic cancers. Their data suggest a possible role of K5 acetylation contributing to pancreatic cancer initiation, but not progression.

LDH-A has been considered as a potential therapeutic target as LDH-A inhibitors and siRNA inhibited tumor growth in mouse models. Considering the inhibitory effect of K5 acetylation LDH-A, drugs that stimulate LDH-A acetylation by targeting the LDH-A acetyl transferase or deacetylase should inhibit LDH-A, therefore may have therapeutic value for cancers with high LDH-A activity. Because elevated LDH-A is detected in almost every type of cancer, LDH-A has been used to monitor treatment of some cancers because of its correlation with poor prognosis and chemotherapy/radiotherapy resistance. Given the fact that LDH-A K5 acetylation can be readily detected by specific antibody, it may serve as a valuable marker for diagnosis of some cancers. They further speculate that LDH-A K5 acetylation labeling coupled with PET/CT would be a potential early diagnose marker for pancreatic cancer.