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## FOXO3a-driven epigenetic alternation of metabolism dictates the gemcitabine sensitivity of pancreatic cancer

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Gemcitabine has been a first-line therapeutic agent for pancreatic ductal adenocarcinoma (PDAC); however, the acquisition of resistance to gemcitabine remains a major challenge. Here, we investigated the metabolite profiles by liquid chromatography-mass spectrometry between gemcitabine-resistant PDAC and parental PDAC cells, and found that lactic acid amount and lactate dehydrogenase activity were increased in gemcitabine-resistant PDAC cells. We observed the elevated lactate dehydrogenase A (LDHA) expression significantly correlated with recurrent pancreatic cancer patients following gemcitabine treatment and with cancer stem cell (CSC) properties. By approaching the comparative array-based microRNA (miRNA) expression and miRNA transcription analysis, we further identified that FOXO3a-induced miR-4259 directly targeted the 3' untranslated region of *LDHA* and reduced LDHA expression, leading to decreased gemcitabine resistance and a reduction in the CSC phenotypes of pancreatic cancer *in vitro* and *in vivo*. Our findings suggest that LDHA might serve as a potential prognostic marker and therapeutic target for pancreatic cancer, particularly gemcitabine-resistant pancreatic cancer, and may provide evidence of an underlying epigenetic regulation of LDHA by FOXO3a/miR-4259, which appears to be involved in cancer stemness and the chemoresistance of pancreatic cancer.

### Biography:

Ching-Feng Chiu has completed his Ph.D from National Cheng Kung University of Taiwan and postdoctoral studies from Taipei Medical University and National Health Research Institutes. Now he serves as an Independent-Postdoctoral Fellowship of National Institute of Cancer Research in National Health Research Institutes, and his studies focus on the roles of microRNAs and metabolism in tumor metastasis and drug resistance from basic research to clinical application. Over the past 5 years, he has published more than 12 original research papers, and he was awarded the 9<sup>th</sup> National Innovation Award in 2012 and obtained the three-year research grant of Ministry of Science & Technology of Taiwan in 2015.