P127

Metformin inhibited pancreatic cancer growth by upregulating miR-143/145 cluster and suppressing MAPK signaling pathway

Yaolin XU[1], Zizhen WU[1], Peng YUAN[2], Mofang LIU[2], Wenhui LOU[1]

[1]*General Surgery Department, Zhongshan Hospital Fudan University, China*
[2]*Shanghai Key Laboratory of Molecular Andrology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, China*

Introduction : Accumulating evidence suggests that metformin treatment is associated with decreased risk and better survival outcome of pancreatic cancer (PC) in patients with diabetes. Besides, our previous study revealed that miR-143 was as essential regulator of cancer glycolysis and miR-143/145 cluster was reported as a tumor suppressor in a range of cancer. The aim of present study was to investigate whether miR-143/145 cluster was associated with antitumor effect of metformin in PC and its potential mechanism.

Methods : We analyzed miRNA sequencing dataset of PC from NCBI (GSE37406) to identify miRNA that were differently expressed between metformin treatment and control group. MiR-143/145 expression level were determined by qRT-PCR, and expression level of target protein were detected by western blot. Potential target genes of miR-143/145 were identified by bioinformatic analyses and confirmed by luciferase reporter assays. Furthermore, biological consequences of miR-143/145 alternation and metformin treatment were examined by cell proliferation, invasion, and apoptosis assays in vitro and by patient derived xenograft models in vivo.

Results : MiR-143/145 was upregulated in metformin-treated PC. Overexpression of miR-143/145 inhibited proliferation and induce apoptosis of PC in vitro. Metformin inhibited tumor growth while downregulation of mir-143/145 cluster downstream of metformin treatment abrogated its antitumor effect both in vitro and vivo. Furthermore, miR-143/145 cluster directly targeted 3′-UTR of MAPK and AKT and repressed their expression. Low MAPK and AKT expression level correlated with better prognosis in PC.

Conclusions : Our data demonstrated the pivotal role of metformin/miR-143/145 cluster/MAPK axis and suggested miR-143/145 cluster as a candidate therapeutic target in PC.

Corresponding Author. : **Yaolin XU** (xuyaolin920816@gmail.com)