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Desmoplasia suppression by metformin-mediated AMPK activation inhibits pancreatic cancer progression

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The desmoplastic reaction is one of the most prominent histological features of pancreatic ductal adenocarcinoma (PDAC), and it contributes to the aggressive nature of PDAC cells. Persistent activation of pancreatic stellate cells (PSCs) induced by cancer cells is responsible for the desmoplastic reaction in PDAC. AMP-activated protein kinase (AMPK) is a highly conserved serine/threonine protein kinase that is involved in regulating pathological fibrosis processes. Recently, emerging evidence has suggested that metformin may be useful in preventing and treating cancer; however, the underlying mechanism remains relatively unknown. In this study, using histological analysis, we found that low P-AMPK staining correlated with a dense stroma reaction and a poorer prognosis in PDAC. Furthermore, metformin-induced AMPK activation in cancer cells inhibited the desmoplastic reaction and prevented tumor growth in mice with subcutaneous pancreatic cancer. *In vitro* experiments demonstrated that metformin inhibited pancreatic cancer cell migration and invasion; more interestingly, metformin suppressed PSC activation during direct and indirect PC-PSC co-culture conditions by inducing AMPK phosphorylation only in PCs and down-regulating fibrogenic-related cytokine production in PCs. More importantly, the combination of metformin with gemcitabine enhanced the antitumor effect of gemcitabine without affecting the blood glucose levels of mice. In conclusion, our findings uncover the mechanism underlying the antitumor effect of metformin. Additionally, inducing AMPK activation in PCs can reduce the desmoplastic reaction by targeting the interaction between PSCs and PDAC cells and may represent a novel therapeutic approach for treating advanced PDAC.

Biography

Qingyong Ma has completed his PhD from Queen's University of Belfast during 1992 to 1996. He is the Professor and Head of Department of Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. He has published more than 100 papers in reputed journals and has been serving as an Editorial Board Member of reputed.

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