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Targeting RET signaling pathway: A novel molecular mechanism of action of metformin in pancreatic cancer prevention and treatment

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Pancreatic cancer (PaCA) is one of the most lethal human cancers and is the fourth leading cause of cancer-related deaths in the United States. However, there are currently no established recommendations for prevention of PaCA using pharmacological agents. Metformin has recently gained attention as an anti-cancer drug and/or a chemoprevention agent because of its effects on inhibiting mTOR, lowering hyperinsulinemia, modulating inflammatory responses, and selectively killing cancer stem cells. However, the key underlying molecular mechanisms for the inhibitory effects of metformin on PaCA progression remain largely unknown. Using RNA sequencing followed by the confirmation of RT-PCR and Western blotting, we found that metformin significantly decreased the mRNA and protein levels of RET (REarranged during Transfection), a single-pass transmembrane receptor tyrosine kinase (RTK). RET and its ligand, glial cell-derived neurotrophic factor (GDNF), are strongly expressed in PaCA and correlated to invasion and reduced survival after surgical resection. GDNF, as a chemoattractant for PaCA cells, can activate RET to induce tumor progression, migration and invasion *in vitro* and *in vivo*. We further demonstrated that metformin significantly inhibited GDNF-induced migration and invasion of PANC-1 cells. These data indicate that targeting RET with metformin or the combination of metformin and RET inhibitors may be an attractive and novel strategy for the prevention and treatment of PaCA progression and metastasis. To further examine the inhibitory effects of metformin on the growth and spread of PaCA tumors in humans, further *in vitro* and *in vivo* studies are warranted to investigate how metformin modulates RET signaling to inhibit the progression and metastasis of PaCA. Such studies have potential clinical significance using metformin as adjuvant preventive and therapeutic options for PaCA prevention and treatment.

Biography:

Dr. Xiang-Lin Tan received a M.D. degree from Tongji Medical College, and a Ph.D in Epidemiology from German Cancer Research Center at Heidelberg University. He was a Postdoctoral fellow at Wadsworth Center and Albert-Einstein College of Medicine, and a Senior Research Fellow at Mayo Clinic. He is currently an Assistant Professor of Medicine and Epidemiology at Rutgers Cancer Institute of New Jersey. Dr. Tan's current research is focusing on repurposing exiting drugs for prostate and pancreatic cancer prevention and treatment. He is an Editorial Reviewer Board member of several international journals, and reviewed articles for more than 10 peer-reviewed journals.