TGIF1 loss contributes to progression of Kras\textsuperscript{G12D}-induced pancreatic ductal adenocarcinoma involving HAS2-CD44 activation and PD-L1 upregulation

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The identification of the TGIF1 (TG-interacting factor 1) was found to be a nuclear transcriptional corepressor of TGF\textbeta1/Smad signaling pathway. TGIF1 has been implicated in the pathogenesis of various types of human cancer, however, the prognostic role of TGIF1 is still controversial, and no role for TGIF1 has yet been indicated in pancreatic ductal adenocarcinoma (PDAC). In this study, we demonstrated that conditional deletion of TGIF1 in the mouse pancreas had no discernible effect on pancreatic development or physiology. Notably, TGIF1 loss cooperated with Kras\textsuperscript{G12D} in the rapid development of PDAC in mice, with a penetrance of 100%. Moreover, we demonstrated that Kras\textsuperscript{G12D} in the context of TGIF1 plus p53 loss induced PDAC with shorter latency and greater propensity for distant metastases, compared with the Pdx-1CreKrasP53L/L model. Deciphering the molecular mechanism highlighted the activation of the hyaluronan synthase 2 (HAS2)-CD44 cancer stemness pathway and upregulation of the immune checkpoint regulator PD-L1 upon TGIF1 loss in PDAC facilitate the epithelial-mesenchymal transition (EMT) and tumor immune suppression, thereby accelerating the development of PDAC metastasis. Notably, TGIF1 silencing also contributed to the alteration of the protein levels of DNMT1, HAT1 and HDAC1 in PDAC, suggesting that TGIF1 might function as an epigenetic regulator and response for aberrant EMT gene expression during PDAC progression. Ultimately, we demonstrate that targeting the HAS2 pathway in TGIF1 loss of PDAC could be a promising therapeutic strategy for improving the clinical efficacy against PDAC metastasis.

Biography
Kuang-hung Cheng has received his PhD in Pathology and Laboratory Medicine, Boston University School of Medicine, USA in 2004. His PhD thesis studies focus on TGF\textbeta1/Smad signaling in gastrointestinal diseases. He spent 5 years for Post-doctoral training in the Massachusetts General Hospital Cancer Center and the Department of Pathology, Brigham’s and Women’s Hospital, Harvard Medical School, USA during 2004-2008. He has joined National Sun Yat-sen University (NSYSU), Taiwan as a Faculty Member in 2008. He is presently an Associate Professor of Biomedical Science Institute in NSYSU. He has received the Program of Excellence Award, the Ovarian Cancer Research Fund, Inc., USA in 2007.

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