Kuang-hung Cheng, J Cell Sci Ther 2018, Volume 9
DOI: 10.4172/2157-7013-C2-044

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

Kuang-hung Cheng
National Sun Yat-sen University, Taiwan

The identification of the *TGIF1* (TG-interacting factor 1) was found to be a nuclear transcriptional corepressor of TGFβ1/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 $Kras^{G12D}$ in the rapid development of PDAC in mice, with a penetrance of 100%. Moreover, we demonstrated that $Kras^{G12D}$ 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 TGFβ1/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.

kuanghung.cheng@gmail.com

Notes: