Original research

Inflammatory cell-derived CXCL3 promotes pancreatic cancer metastasis through a novel myofibroblast-hijacked cancer escape mechanism

Xiaoting Sun,[1,2,3] Xingkang He,[2] Yin Zhang,[2] Kayoko Hosaka,[2] Patrik Andersson,[2] Jing Wu,[2] Jieyu Wu,[2] Xu Jing,[2] Qiqiao Du,[2] Xiaoli Hui,[4] Bo Ding,[5] Ziheng Guo,[6] An Hong,[7] Xuan Liu,[8] Yan Wang,[1,3] Qing Ji,[1,3] Rudi Beyaert,[9] Yunlong Yang,[10] Qi Li,[1,3] Yihai Cao [2]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-322744).

For numbered affiliations see end of article.

Correspondence to
Dr. Yunlong Yang, Department of Cellular and Genetic Medicine, School of Basic Medical Sciences, Fudan University, Shanghai, China; yunlongyang@fudan.edu.cn, Dr. Qi Li, Department of Medical Oncology, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China; qili@shutcm.edu.cn and Dr. Yihai Cao, Department of Microbiology, Tumor and Cell Biology, Biomedicum, Karolinska Institutet, Stockholm, Sweden; yihai.cao@ki.se

Received 5 August 2020
Revised 12 January 2021
Accepted 20 January 2021

To cite: Sun X, He X, Zhang Y, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2020-322744

ABSTRACT

Objective Pancreatic ductal adenocarcinoma (PDAC) is the most lethal malignancy and lacks effective treatment. We aimed to understand molecular mechanisms of the intertwined interactions between tumour stromal components in metastasis and to provide a new paradigm for PDAC therapy.

Design Two unselected cohorts of 154 and 20 patients with PDAC were subjected to correlation between interleukin (IL)-33 and CXCL3 levels and survivals. Unbiased expression profiling, and genetic and pharmacological gain-of-function and loss-of-function approaches were employed to identify molecular signalling in tumour-associated macrophages (TAMs) and myofibroblastic cancer-associated fibroblasts (myoCAFs). The role of the IL-33–ST2–CXCL3–CXCR2 axis in PDAC metastasis was evaluated in three clinically relevant mouse PDAC models.

Results IL-33 was specifically elevated in human PDACs and positively correlated with tumour inflammation in human patients with PDAC. CXCL3 was highly upregulated in IL-33-stimulated macrophages that were the primary source of CXCL3. CXCL3 was correlated with poor survival in human patients with PDAC. Mechanistically, activation of the IL-33–ST2–MYC pathway attributed to high CXCL3 production. The highest level of CXCL3 was found in PDAC relative to other cancer types and its receptor CXCR2 was almost exclusively expressed in CAFs. Activation of CXCR2 by CXCL3 induced a CAF-to-myoCAF transition and α-smooth muscle actin (α-SMA) was uniquely upregulated by the CXCL3–CXCR2 signalling. Type III collagen was identified as the CXCL3–CXCR2-targeted adhesive molecule responsible for myoCAF-driven PDAC metastasis.

Conclusions Our work provides novel mechanistic insights into understanding PDAC metastasis by the TAM-CAF interaction and targeting each of these signalling components would provide an attractive and new paradigm for treating pancreatic cancer.

Significance of this study

What is already known on this subject?
- Pancreatic ductal adenocarcinoma (PDAC) is a highly metastatic cancer.
- PDAC possesses high contents of inflammatory and fibrotic components, which contribute to tumour growth and invasion.
- Lack of effective therapy for treating PDAC.

What are the new findings?
- The CXCL3–CXCR2 signalling specifically targeted cancer-associated fibroblasts (CAFs) and converted CAFs into myoCAFs, which hijacked low metastatic cancer cells for metastasis.
- The interleukin (IL)-33–ST2–TAMs axis was the primary driver for upregulating CXCL3 that mediated the tumour-associated macrophage (TAM) and CAF communication.
- Adhesive molecule type III collagen was the target of the CXCL3–CXCR2 signalling and responsible for hijacking PDAC metastasis by myoCAFs.
- IL-33 and CXCL3 levels reversely correlated with survivals in patients with PDAC.

How might it impact on clinical practice in the foreseeable future?
- The IL-33–ST2–CXCL3–CXCR2 signalling axis serves as an independent predictive marker for prognosis in patients with PDAC.
- Blocking the IL-33–ST2–CXCL3–CXCR2–collagen III signalling axis for effective treatment of PDAC.

INTRODUCTION

According to statistics, there were 448 000 pancreatic ductal adenocarcinoma (PDAC) cases globally in 2017 and new incident cases continue to increase each year.[1] Pancreatic cancer has the poorest prognosis, with an overall 5-year survival rate of about 5%, and no much difference between countries.[2] At the time of diagnosis, PDAC often develops at the late stage with distal metastasis.[3 4] Surgery is the only curative treatment option although the prognosis is still very limited.[5] In the last 20 years, a paradigm-shift of cancer therapy from conventional therapeutics to targeted therapies has generated new hopes and excitements for treating PDAC.[6]