Cancer Research

Tumor Biology

Abstract 2029: Identification of cancer-associated fibroblasts that suppress pancreatic cancer progression

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DOI: 10.1158/1538-7445.AM2019-2029 Published July 2019

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Proceedings: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA

Abstract

Cancer-associated fibroblasts (CAFs) constitute a major component of the cancer stroma. They can promote cancer progression t variety of mechanisms including the production of growth factors, chemo/cytokines, and extracellular matrix (ECM). Recent observ genetically engineered mouse models and clinical studies have suggested that there may exist at least two subpopulations of CAF cancer-promoting CAFs (pCAFs) and cancer-restraining CAFs (rCAFs). Although various pCAF markers have been identified, the rCAFs is unknown due to a lack of specific rCAF marker(s). Here, we show that Meflin, a glycosylphosphatidylinositol (GPI)-ancho that maintains the undifferentiated state of mesenchymal stromal/stem cells (MSCs) (Maeda et al., Sci Rep, 6:22288, 2016), is a marker pancreatic stellate cells (PSCs). We find that Meflin-positive CAFs represent rCAFs in pancreatic ductal adenocarcinoma (PDAC). Infiltration of Meflin-positive CAFs correlated with favourable prognosis in patients with PDAC, consistent with our observation that Meflin deficiency led to tumour progression with poorly differentiated histology in a PDAC mouse model. Notably, Meflin-positive cells gave rise to α-smooth muscle actin (SMA)-positive CAFs during cancer progression. Both genetic ablation of Meflin-positive CAFs and delivery of a Meflin-expressing lentivirus into the stroma suppressed xenografted tumour differentiation and growth, respectively. Mechanistically, Meflin interacts with lysyl oxidase (Lox) to inhibit collagen crosslinking activity, and Meflin deficiency led to straightened and wide stromal collagen fibers as demonstrated by a second harmonic generation microscopy. These data demonstrate the presence of rCAFs in the cancer stroma and the significance of their differentiation to pCAFs in cancer progression, which may be exploited for the development of therapeutic strategies to specifically target pCAFs or reprogram them into rCAFs.

Citation Format: Atsushi Enomoto, Yasuyuki Mizutani, Hiroki Kobayashi, Tadashi Iida, Susan L. Woods, Daniel L. Worthley, Masahide Takahashi. Identification of cancer-associated fibroblasts that suppress pancreatic cancer progression [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; Cancer Res 2019;79(13 Suppl):Abstract nr 2029.

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July 2019
Volume 79, Issue 13 Supplement
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