News Release

**Identification of cancer-associated fibroblasts that suppress pancreatic cancer progression**

**Key points:**
1. Scientists have uncovered a novel type of fibroblasts that suppresses the progression of pancreatic cancer (rCAF: cancer-retarding cancer-associated fibroblasts).
2. The study showed that changes in the amount and gene expression of rCAF are crucial for the determination of malignant features and differentiation of pancreatic cancer.
3. The study also showed that an increase in the number of rCAF suppressed tumor progression in mouse models.
4. The results of this study indicated the possibility that modulation of the function of CAFs could be a strategy for the development of new anti-cancer therapies.

**Summary:**
The group led by Prof. Masahide Takahashi and Assoc. Prof. Atsushi Enomoto (Department of Pathology, Nagoya University Graduate School of Medicine, Japan) and their colleagues identified Meflin as a specific marker of cancer-associated fibroblasts that suppress the progression of pancreatic cancer and showed the possibility that the modulation of fibroblasts that proliferate in the stroma of pancreatic cancer could be a potential strategy to develop new therapies against the disease. The study has been published online in Cancer Research on Aug 22, 2019.

**Background:**
Previous studies have shown that cancer-associated fibroblasts (CAFs) constitute a major component of the cancer stroma. They can promote cancer progression through a variety of mechanisms including the production of growth factors, chemo/cytokines, and extracellular matrix (ECM). Recent observations from genetically engineered mouse models and clinical studies have suggested that there may exist at least two subpopulations of CAFs, i.e., cancer-promoting CAFs (pCAFs) and cancer-restraining CAFs (rCAFs) (Kobayashi H, et al., Nat Rev Gastroenterol Hepatol. 16:282-295, 2019). Although various pCAF markers have been identified, the identity of rCAFs is unknown due to a lack of specific rCAF marker(s).

**Results:**
The study has showed that Meflin, a glycosylphosphatidylinositol (GPI)-anchored
protein that maintains the undifferentiated state of mesenchymal stromal/stem cells (MSCs) (Maeda et al., Sci Rep, 6:22288, 2016), is a marker of pancreatic stellate cells (PSCs) that have been known to be one of the origin of CAFs in pancreatic cancer. The authors found that Mefflin-positive CAFs represent rCAFs in both human and mouse pancreatic cancer. Infiltration of Mefflin-positive CAFs correlated with favourable prognosis in patients with pancreatic cancer, consistent with their observation that Mefflin deficiency led to tumour progression with poorly differentiated histology in a pancreatic cancer mouse model. A lineage trace experiment showed that Mefflin-positive cells gave rise to α-smooth muscle actin (SMA)-positive CAFs during cancer progression, showing a mechanism of CAF heterogeneity in pancreatic cancer. Both genetic ablation of Mefflin-positive CAFs and delivery of a Mefflin-expressing lentivirus into the stroma suppressed xenografted tumour differentiation and growth, respectively. Finally, the study showed that Mefflin deficiency led to straightened and wide stromal collagen fibers as demonstrated by a second harmonic generation microscopy.

Figure Perspective:
These data demonstrate the presence of rCAFs in the cancer stroma and the significance of their differentiation to another type of CAFs in cancer progression, which may be exploited for the development of therapeutic strategies to specifically target pCAFs or reprogram them into rCAFs.

Publication:
1Department of Pathology, 2Gastroenterology and Hepatology, 4Division of Molecular Pathology, Center for Neurological Disease and Cancer, 9Anatomy and Cell Biology, 12Department of Gastroenterological Surgery (Surgery II), 13Division of Surgical Oncology, Department of Surgery, and 14Division of Systems Biology, Nagoya University Graduate School of Medicine, Nagoya, 466-8550, Japan
3School of Medicine, University of Adelaide and South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia
5Division of Gastroenterology, Tohoku University Graduate School of Medicine,
Meflin-positive cancer-associated fibroblasts inhibit pancreatic carcinogenesis.
DOI: 10.1158/0008-5472.CAN-19-0454

Japanese ver.