News Release

Title

Discovery of a novel pancreatic stellate cell marker — a key to understanding pancreatic fibrosis

Key Points

1. The research group identified Meflin, a membrane protein as a novel pancreatic stellate cell (PSC) marker. The identification of this new marker will provide a deeper insight into the morphology and function of PSCs in health and disease.
2. PSCs are considered to be a key player in the two major pancreatic diseases, chronic pancreatitis and pancreatic cancer. A comprehensive understanding of PSCs will contribute to elucidating the pathogenesis of the pancreatic diseases and providing future therapeutic strategies.
3. Using the new marker Meflin, the present study showed *in vivo* that PSCs were a source of fibroblasts that are responsible for fibrosis in chronic pancreatitis and pancreatic cancer. Furthermore, the results suggested a potential role of PSCs in the repair of damaged tissues in chronic pancreatitis.

Summary

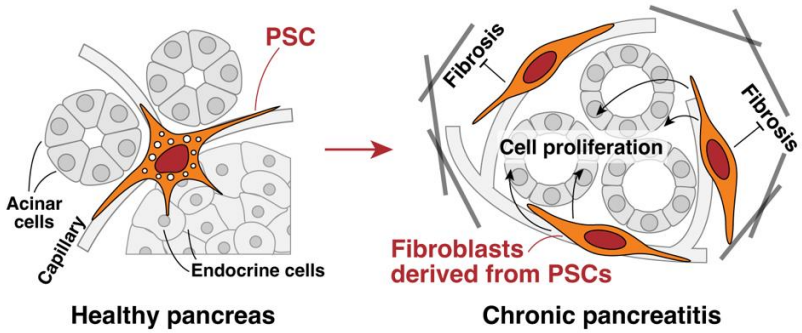
A research group from Nagoya University has identified a membrane protein called Meflin (gene name: *Islr*) as a novel marker for pancreatic stellate cells (PSCs). Until now, PSCs lacked their specific marker(s) for *in vivo* studies, which was a major bottleneck in the field of pancreatic disease research.

This advance now enables more detailed investigations into the *in vivo* PSCs' behavior in the context of pancreatic diseases. Notably, this research highlights the role of PSCs as a source of fibroblasts, which are directly involved in fibrosis seen in chronic pancreatitis and pancreatic cancer. Additionally, the study suggests a potential reparative role for PSCs in chronic pancreatitis, and that they may suppress fibrosis and support epithelial regeneration in context-dependent manners. These findings underscore PSCs' complex and ambivalent functions in fibrosis, a hallmark of pancreatic diseases.

PSCs have attracted much attention in recent years, given their association with fibrosis, a central process in the pathogenesis and resistance to treatment of pancreatic diseases. However, the morphology and functions of these cells *in vivo* have remained partially uncovered due to the lack of a

reliable marker. Therefore, researchers have been trying to identify PSC-specific markers to elucidate the pathogenesis and provide future therapeutic strategies in chronic pancreatitis and pancreatic cancer.

The study, “Meflin is a marker of pancreatic stellate cells involved in fibrosis and epithelial regeneration in the pancreas” was published online in *The Journal of Pathology* on October 5, 2023.



Research Background

The two major pancreatic diseases, chronic pancreatitis and pancreatic cancer, are characterized by prominent stromal fibrosis. Fibrosis is the accumulation of extracellular matrix such as collagen in the stroma surrounding epithelial cells, including glandular cells producing digestive enzymes and endocrine cells integral to insulin secretion. Unfortunately, this process has been associated with the progression of the diseases and their resistance to treatments.

At the core of fibrosis are fibroblasts, which are rarely found in healthy pancreas but are prominent in chronic pancreatitis and pancreatic cancer. These cells cause fibrosis by overproducing collagen and other extracellular matrices. However, the origin and detailed function of fibroblasts remain largely unknown.

Over the past two decades, a growing number of research has suggested the involvement of pancreatic stellate cells (PSCs) in pancreatic fibrosis. Substantial progress has been made through *in vitro* experiments with PSCs isolated from pancreatic tissue and cultured in the laboratory. However, *in situ* observations and analyses are imperative to foster a precise understanding of PSCs. To this end, a reliable PSC marker is needed to distinguish them from other types of cells in pancreatic tissue. The current study focused on a membrane protein called Meflin existing on the surface of PSCs, utilizing it as a PSC marker to explore *in situ* morphology and functions of PSCs.

Research Results

The research team has confirmed the expression of Meflin in PSCs, while confirming its absence in other types of cells in the pancreas, such as epithelial cells and vascular endothelial cells. In cultured cells dissociated from the pancreas, Meflin expression was found in cells with lipid droplets, a well-known hallmark of PSCs. This means that Meflin can serve as a marker for identifying PSCs. Using this newly identified PSC marker, they performed the following experiments.

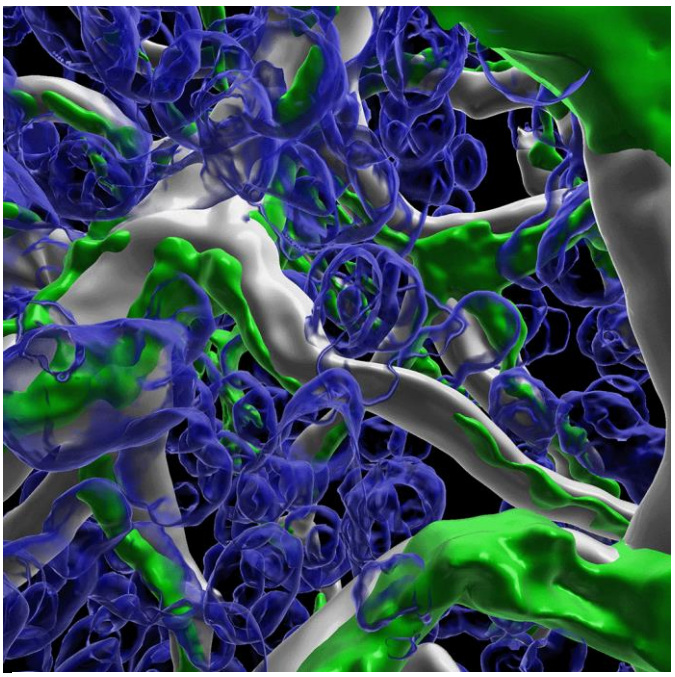


Figure 1. PSCs in 3D view. PSCs and capillaries are shown in green and white, respectively. Blue denotes the nuclei of the other cells (e.g., epithelial cells).

First, they investigated the distribution and morphology of PSCs. They used genetically engineered mouse models (Meflin reporter mice), in which Meflin-positive cells express a fluorescent protein, to perform observation of PSCs. By applying tissue-clearing methods on the pancreas of these mice, they successfully observed PSCs in three dimensions within the pancreas. PSCs were primarily distributed along the capillaries in the pancreas, exhibiting long cellular projections adhering closely to the capillaries (Figure 1).

Next, the researcher conducted lineage tracing experiments of Meflin-positive cells to track down the offspring of the PSCs in mice with chronic pancreatitis and pancreatic cancer. The results revealed that a portion of fibroblasts, which induce fibrosis in the pancreas, originate from Meflin-positive PSCs (Figure 2). While previous studies using cultured PSCs have suggested that they produce fibroblasts, this research was the first one that has successfully demonstrated this within living animals.

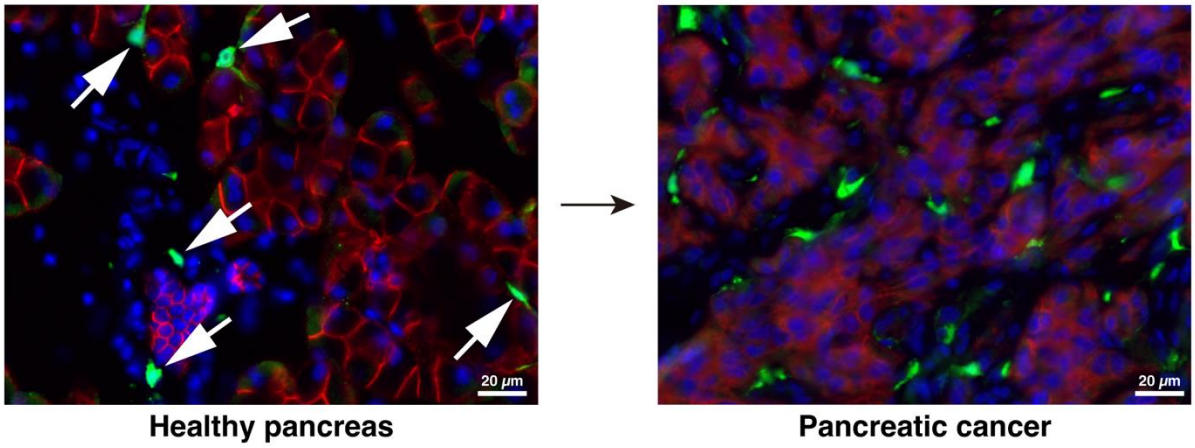


Figure 2. Meflin-positive PSCs were labeled with a fluorescent protein (green) in the healthy pancreas (arrows, left panel) of a Meflin reporter mouse. When cancer cells were orthotopically transplanted into the pancreas of the mouse to develop pancreatic cancer, the offspring of the PSCs (green) became cancer-associated fibroblasts (right panel). Epithelial and cancer cells are in red; cell nuclei are in blue.

Furthermore, this research revealed two critical insights suggesting the potential role of PSCs by an experiment in which Meflin-positive cells were artificially depleted in mice with chronic pancreatitis. Firstly, the fibrosis was enhanced upon PSC depletion. Although this outcome seems to contradict the role of PSCs in generating fibroblasts responsible for fibrosis, it raised the possibility that some PSCs and fibroblasts might have a role in inhibiting fibrosis in some contexts. Secondly, the researchers identified that PSCs produce R-spondin 3, a secreted protein that enhances Wnt signaling to promote cell proliferation. When PSCs are artificially depleted, the proliferation of regenerative epithelial cells was hampered along with attenuated Wnt signaling. This suggests that PSCs may support epithelial regeneration by producing R-spondin 3.

Research Summary and Future Perspective

This study provides important clues for understanding the roles of PSCs, which are deeply involved in the pathogenesis of pancreatic diseases. The researchers will further aim to shed light on the mechanisms of fibrosis in pancreatic diseases, with the goal of developing innovative therapeutic strategies in the future.

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Publication

Journal: The Journal of Pathology
Title: Meflin is a marker of pancreatic stellate cells involved in fibrosis and epithelial regeneration in the pancreas
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DOI: 10.1002/path.6211

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