News Release

Title

The origin and contribution of cancer-associated fibroblasts in colorectal carcinogenesis

Key Points

- It is known that fibroblasts, spindle-shaped non-malignant cells, regulate cancer progression. However, the origin of fibroblasts in cancer remains to be fully elucidated.
- The research group identified the origin of fibroblasts in colorectal cancer (CRC).
- Fibroblasts in cancer emerge through proliferation from colonic stromal cells that express Leptin receptor.
- These fibroblasts, in turn, express melanoma cell adhesion molecule (MCAM) to promote colorectal carcinogenesis.
- Targeting this fibroblast population could be a novel potential therapeutic approach to treat CRC.

Summary

Prof. Atsushi Enomoto (Department of Pathology, Nagoya University Graduate School of Medicine), Prof. Masahide Takahashi, Dr. Hiroki Kobayashi (International Collaborative Program in Comprehensive Medical Science between Nagoya University and the University of Adelaide/Joint Degree Program), and Prof. Naoya Asai (Fujita Health University), in collaboration with Dr. Susan Woods (the University of Adelaide, Australia) and Dr. Daniel Worthley (South Australian Health and Medical Research Institute, Australia) identified the cellular origin of colorectal cancer-associated fibroblasts (CAFs), a critical regulator of tumor progression. They showed that Leptin receptor (*Lepr*)-lineage stromal cells in the colon are a major contributor to melanoma cell adhesion molecule $(MCAM)^{+}$ CAFs that promote colorectal cancer progression. This study was published online in *Gastroenterology* on Dec 6, 2021.

Research Background

Cancer is composed of not only cancer cells but also non-malignant stromal cells. One vital component of the non-malignant cells is spindle-shaped cells named fibroblasts. Fibroblasts within cancer tissues are called cancer-associated fibroblasts (CAFs). Previous studies have revealed that CAFs are heterogeneous cell populations that regulate cancer progression. However, the cellular origins of CAFs and how specific CAF lineages promote tumorigenesis remain unknown. Our poor understanding of stromal evolution has made it challenging to target CAFs therapeutically.

Research Results

The research team revealed that, in colorectal cancer (CRC), most CAFs are derived from proliferation of colonic leptin receptor (*Lepr*)$^+$ stromal cells (**Figure 1**). These CAFs express melanoma cell adhesion molecule (MCAM) to recruit macrophages, thereby promoting colorectal carcinogenesis.

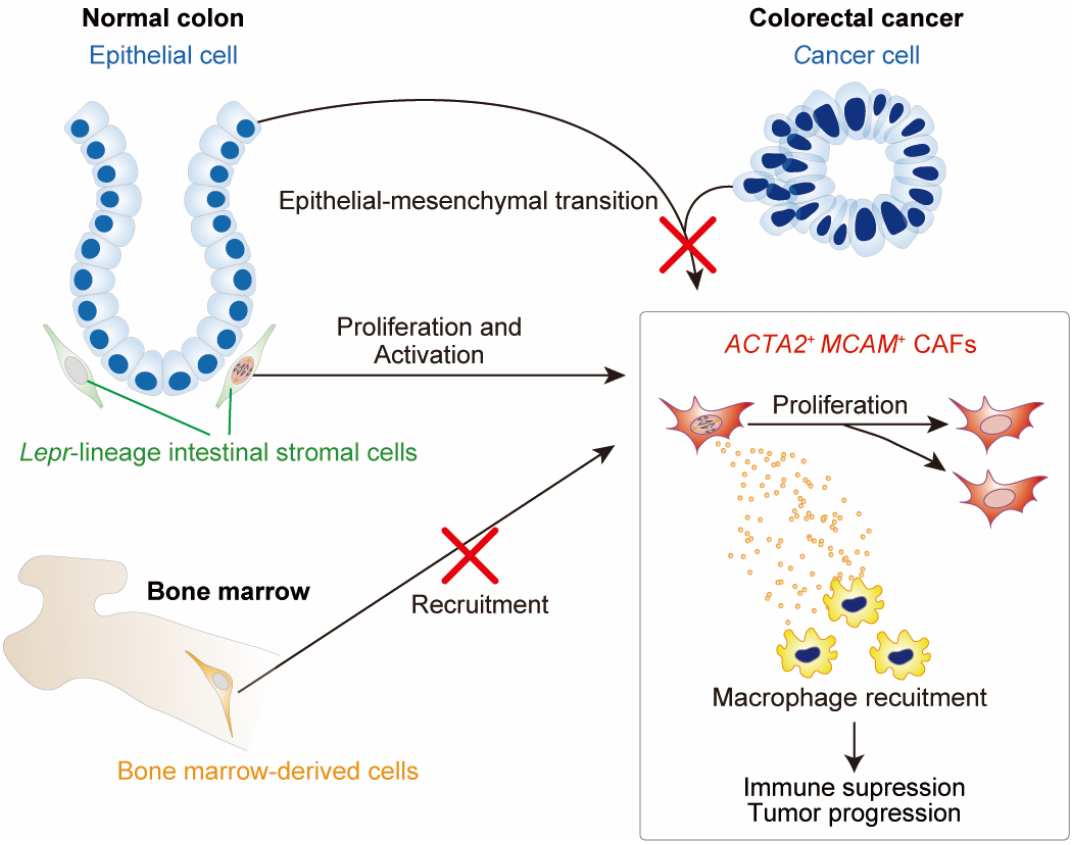

Figure 1: The origin of cancer-associated fibroblasts in colorectal cancer.
In colorectal cancer, cancer-associated fibroblasts (CAFs) originate from proliferation and activation of colonic stromal cells that express Leptin receptor (*Lepr*). In this study, no CAFs arose from bone marrow-derived or epithelial cells in a mouse model of colorectal cancer. *Lepr*-lineage CAFs express melanoma cell adhesion molecule (MCAM) to increase macrophage recruitment. This alters the immune microenvironment and accelerates colorectal cancer progression.

To explore whether fibroblast number increases during colorectal cancer progression, the

research team analyzed the expression of *Acta2*, a marker gene for CAFs that encodes α-smooth muscle actin, using human and mouse colon samples. They found that the number of *Acta2*$^+$ fibroblasts was increased throughout colorectal tumorigenesis. Next, the researchers examined whether these CAFs are generated through proliferation or not. Using a mouse model of CRC, the group revealed that about three-fourths of CAFs underwent proliferation during carcinogenesis. To identify the cellular source of proliferating CAFs, the authors performed lineage-tracing experiments that enable to track the fate of specific cell populations. The group identified colonic *Lepr*$^+$ stromal cells as a major origin of *Acta2*$^+$ CAFs. They also found that epithelial or bone marrow-derived cells were not a source of CAFs in the mouse CRC model.

Using comprehensive gene expression analysis, the team showed that *Lepr*-lineage CAFs actively express MCAM (melanoma cell adhesion molecule) protein. The group found that high MCAM expression was inversely associated with survival in patients with CRC. To delineate the mechanism by which MCAM accelerates CRC progression, the authors generated genetically engineered mice that lack the *Mcam* gene. In the mice devoid of *Mcam*, colorectal tumor growth was inhibited. This was accompanied by decreased infiltration of macrophages (a subtype of leukocyte). Fibroblast MCAM promoted macrophage recruitment and altered the immune microenvironment, thereby enhancing colorectal tumorigenesis.

Research Summary and Future Perspective

This study showed that *Lepr*-lineage colonic stromal cells are a major contributor to MCAM$^+$ tumor-promoting CAFs. Uncovering this stromal evolution paves the way for a better understanding of CAF biology. Furthermore, targeting these cancer-promoting CAFs could be a novel therapeutic strategy to treat CRC.

Publication

The origin and contribution of cancer-associated fibroblasts in colorectal carcinogenesis

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