News Release

Title

The balance of stromal BMP signaling mediated by *GREM1* and *ISLR* drives colorectal carcinogenesis

Key Points

- **It is known that fibroblasts, spindle-shaped non-malignant cells, proliferate within cancer tissues and could affect cancer progression.**
- **The research group found that there exist at least two different types of fibroblasts within colorectal cancer tissues:**
  ***GREM1*$^+$ cancer-promoting fibroblasts and *ISLR*$^+$ cancer-restraining fibroblasts.**
- **Altering the tumor microenvironment could be a novel therapeutic strategy to inhibit colorectal cancer progression**

Summary

Dr. Hiroki Kobayashi (Ph.D. student; International Collaborative Program in Comprehensive Medical Science between Nagoya University and the University of Adelaide/Joint Degree Program), Prof. Atsushi Enomoto (Department of Pathology, Nagoya University Graduate School of Medicine), Prof. Masahide Takahashi 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) found that colorectal cancer progression is regulated by heterogeneous fibroblasts called cancer-associated fibroblasts (CAFs). The group identified *GREM1*$^+$ cancer-promoting CAFs and *ISLR*$^+$ cancer-restraining CAFs within colorectal cancer tissues and showed that these could be potential therapeutic targets to inhibit colorectal cancer progression. This study has been published online in *Gastroenterology* on Nov 14, 2020.

Research Background

Cancer is not a homogenous mass of cancer cells, but also comprise non-malignant stromal cells. Fibroblasts within cancer tissues are an important constituent of the tumor stroma and are called cancer-associated fibroblasts (CAFs). Previous studies have revealed that CAFs are heterogeneous cell populations that could either promote or inhibit cancer progression. However, markers and mechanisms underlying the CAF heterogeneity remain unknown. As a result, the lack of understanding in CAF heterogeneity has hampered the development of effective therapeutics that target specific subtypes of CAFs.

Bone morphogenetic proteins (BMPs) are known to be a key regulator of intestinal homeostasis and cancer progression. Nonetheless, the exact role of BMPs in the tumor stroma is largely unknown.

Research Results

The research team found that *GREM1*$^+$ CAFs and *ISLR*$^+$ CAFs promote and inhibit colorectal cancer (CRC) progression, respectively, by modulating BMP signaling (**Figure 1**).

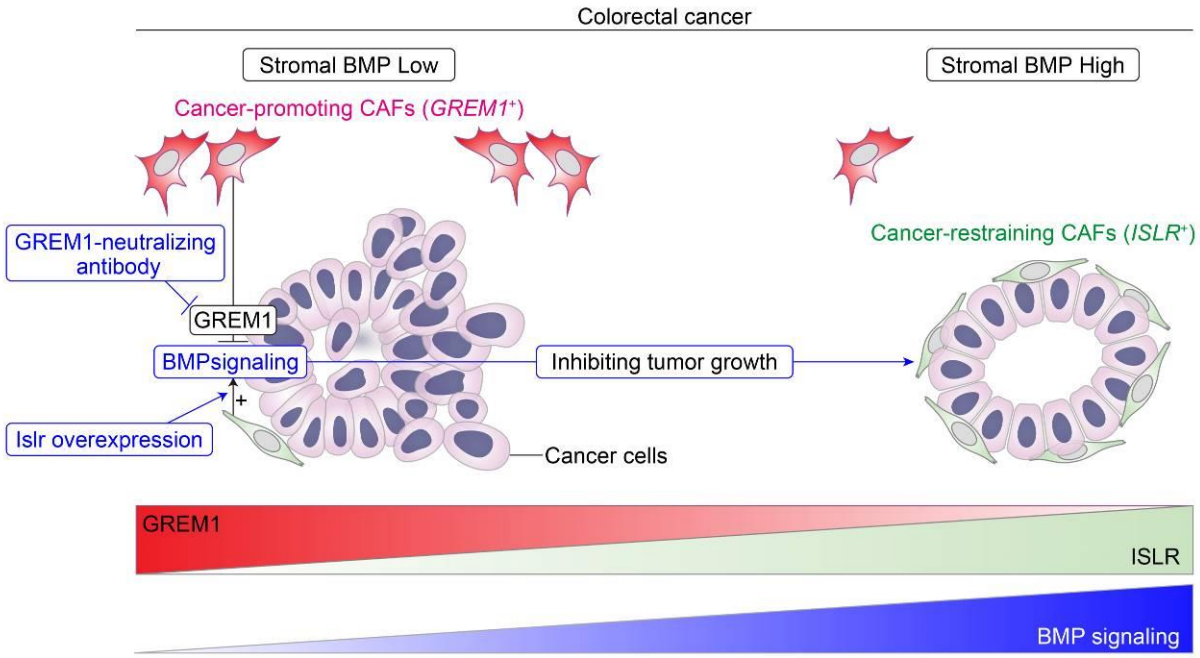

Figure 1: A working hypothesis for the role of BMP signaling mediated by stromal *GREM1* and *ISLR* in CRC. In the CRC stroma, *GREM1*$^+$ CAFs promote cancer progression by decreasing BMP signaling. In contrast, *ISLR*$^+$ CAFs restrain CRC growth via increased BMP signaling. Augmentation of stromal BMP signaling, either by a GREM1-neutralizing antibody or *Islr* overexpression, could represent an attractive therapeutic strategy to treat CRC.

Using comprehensive gene expression profiling data, the research team identified *GREM1* and *ISLR* (which codes Meflin) as BMP-related genes specifically expressed in colorectal CAFs. The Nagoya University group has previously shown that *ISLR* is a marker for cancer-restraining CAFs in pancreatic cancer and that *ISLR* augments BMP signaling. The group led by Dr. Daniel Worthley (South Australian Health and Medical Research Institute/The University of Adelaide) has a special research focus on the role of *GREM1*, a BMP inhibitor, in the intestine. Dr. Hiroki Kobayashi, a Ph.D. candidate in the Joint Degree Program between Nagoya University and the University of Adelaide, set out to study the role of *GREM1* and *ISLR* in colorectal cancer progression.

Interestingly, the group found that CRCs that highly express *GREM1* show dismal prognosis whereas high *ISLR* expression is associated with favorable prognosis. *GREM1* marked CAFs that were distinct from *ISLR*$^+$ CAFs in CRC tissues. In addition, the study showed that CRC proliferation could be attenuated using a *GREM1*-neutralizing antibody or *ISLR* overexpression in a CRC mouse model.

Despite advances in surgical techniques and medical treatment, hepatic metastasis is still a leading cause of CRC-related death. The group has found that hepatic metastasis progression

could be restrained using a special virus vector that induces *ISLR* overexpression in hepatocytes. This study is the first to use the special type of virus vector to treat hepatic metastasis.

Research Summary and Future Perspective

This study showed that CRC progression is promoted and restrained by cancer-associated fibroblast *GREM1* and *ISLR*, respectively. The finding that colorectal carcinogenesis is regulated by the *GREM1*/*ISLR* fibroblast dichotomy sheds new light on the vast diversity of CAFs. Furthermore, modulating BMP signaling by targeting *GREM1* or *ISLR* could be a novel therapeutic strategy to inhibit CRC progression.

Publication

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The balance of stromal BMP signaling mediated by *GREM1* and *ISLR* drives colorectal carcinogenesis

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