Targeting fibroblast diversity as a new avenue for cancer therapy

Center for Infectious Disease Education and Research

Specially Appointed Assistant Professor Akikazu Harada Researchmap https://researchmap.jp/akikazu_harada?lang=en

Specially Appointed Professor Akira Kikuchi Researchmap https://researchmap.jp/read0042908?lang=en

Abstract

Tumor tissues are composed not only of cancer cells, immune cells, and endothelial cells, but also of fibroblasts, which constitute the core of the tumor stroma. Recent studies have revealed that fibroblasts are not a uniform population of structural cells but consist of multiple subtypes with distinct functions. Understanding the molecular basis underlying this heterogeneity is crucial for developing therapeutic strategies that target fibroblasts, alongside cancer and immune cells. In this study, we aimed to elucidate the mechanisms that generate fibroblast diversity in colon cancer.

Through integrated analyses of single-cell RNA sequencing from human and mouse colon tumors, together with in vitro modeling, we identified a fibroblast subtype, Inflammatory fibroblast (InfFib), that is induced under hypoxic conditions and interacts with endothelial cells to sustain this hypoxic niche. Furthermore, InfFib acted on cancer cells, enabling tumors to continue growing even under hypoxic conditions. These findings reveal that fibroblasts maintain their heterogeneity through interactions with other stromal components, thereby exerting an influence on tumor progression.

Background & Results

Tumors comprise not only cancer cells but also a variety of stromal cells that dynamically interact within the tissue. Among these, fibroblasts represent the largest stromal population. Although once considered a homogeneous structural component, fibroblasts are now recognized to exhibit diverse subtypes and functions that significantly impact tumor development. However, the mechanisms by which fibroblast diversity is maintained remain unclear, hindering the rational design of therapeutic strategies that manipulate fibroblast states to suppress tumor progression.

To systematically define fibroblast subtypes, we analyzed single-cell RNA sequencing datasets from both human and mouse colon tissues under different pathological conditions, including normal colon, colitis, and colon cancer. Integrative analysis identified six conserved fibroblast subtypes shared between species. We focused on a distinctive subtype, InfFib, localized along the luminal side of tumors. InfFib displayed strong hypoxia-associated signatures and was enriched in hypoxic tumor regions. Mechanistically, InfFib was derived from BMPs fibroblasts of the normal colon through HIF2-mediated hypoxic signaling. InfFib secreted Wnt5a, which interacted with the Ryk receptor on adjacent endothelial cells, suppressing angiogenesis and thereby reinforcing local hypoxia. In parallel, InfFib secreted Epiregulin, promoting cancer cell proliferation even under low oxygen environment. Collectively, these findings delineate the molecular framework by which localized hypoxia induces and sustains the InfFib subtype, providing insight into how fibroblast heterogeneity emerges within the tumor milieu.

Significance of the research and Future perspective

Fibroblasts are widely distributed around various cell types, serving as central hubs for intercellular communication. Understanding how their diversity arises will open new avenues for therapeutic interventions that target fibroblasts to reshape the tumor microenvironment and control tumor progression.

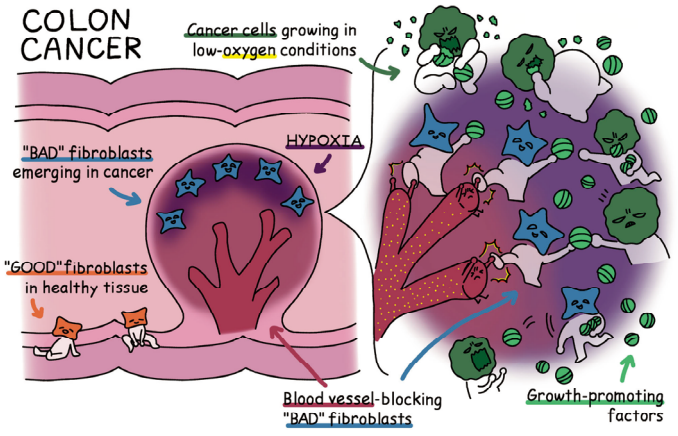

Figure 1

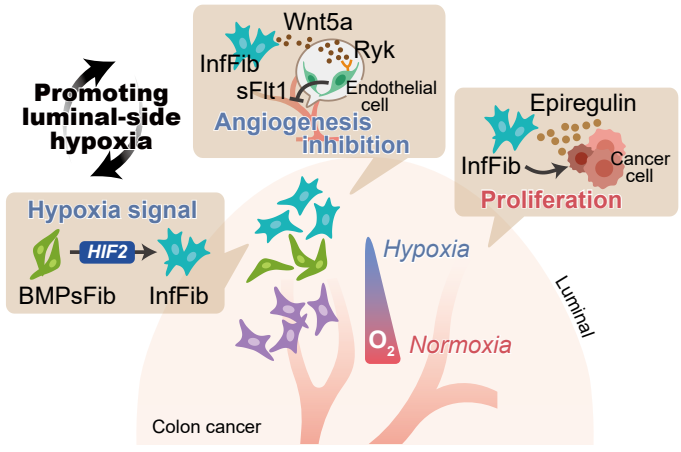

Figure 2

Patent

Treatise Harada, Akikazu et al. Hypoxia-induced Wnt5a-secreting fibroblasts promote colon cancer progression. Nature Communications. 2025, 16, 3653. doi: 10.1038/s41467-025-58748-9

URL https://www2.cider.osaka-u.ac.jp/bioreg/index_e.html

Keyword cancer, fibroblast, hypoxia, Wnt signaling