Social Cooperation Research Program

Project Division of Generative AI Utilization Aging Cells

生成 AI 活用加齢医学社会連携研究部門

Project Associate Professor　Teh-Wei Wang, Ph.D.　特任准教授　博士（理学）　王　　德　瑋

Aging and many age-related diseases are fundamentally linked to chronic inflammation. It is widely accepted that the accumulation of senescent cells in the body over time is one of the major contributors to chronic inflammation. However, our understanding of senescent cells in human tissues remains extremely limited. In our study, we utilized large-scale single-cell RNA sequencing data obtained from mouse models and integrated it with generative AI techniques to explore the characteristics of senescent cells. By applying these insights to human datasets, we aim to further elucidate the features of senescent cells in human tissues and identify potential strategies to target these cells, providing a clue for novel anti-aging therapeutic approaches.

1. Senescent hepatocytes promote liver fibrosis through activating LIFR pathway

Koji Nishikawa[1,2], Teh-Wei Wang, Satoshi Kawakami[1], Shota Tanimoto[1], Kiyoshi Yamaguchi[3], Taketomo Kido[4], Masamichi Kimura[2], Tsunekazu Hishima[5], Yuki T. Okamura[1], Satotaka Omori[6], Takumi Iritani[7], Toshikaze Chiba[8], Takehiro Jimbo[8], Michio Katano[7], Kansuporn Kamataki[7], Ryoichi Yokoyama[9], Eigo Shimizu[10], Kiminori Kimura[2], Satoshi Yamzaki[11], Seiya Imoto[10], Yoichi Furukawa[3], Atsushi Miyajima[4], Yoshikazu Johmura[12] and Makoto Nakanishi[1]

[1]Division of Cancer Cell Biology, IMSUT. [2]Department of Hepatology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital. [3]Division of Clinical Genome Research, IMSUT. [4]Laboratory of Cell Growth and Differentiation, Institute for Quantitative Biosciences, The University of Tokyo. [5]Department of Pathology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital. [6]Integrated Biosciences, Redwood City, CA, USA. [7]GMO Internet Group, Inc. [8]GMO Research Activity Support & Technology, Inc. [9]GMO Healthtech, Inc. [10]Division of Health Medical Intelligence, Human Genome Center, Center for Experimental Medicine and Systems Biology, IMSUT. [11]Division of Cell Regulation, Center of Experimental Medicine and Systems Biology, IMSUT. [12]Division of Cancer and Senescence Biology, Cancer Research Institute, Kanazawa University.

Liver fibrosis is a harmful outcome of the tissue repair process following chronic liver injury, predominantly thought to be initiated by hepatocytes. However, the specific hepatocyte subtypes and signaling pathways responsible for this activation remain poorly understood. Previous studies have demonstrated a strong correlation between the severity of fibrosis in cirrhotic patients and the prevalence of hepatocytes expressing high levels of $p16^{Ink4a}$ ($p16^{h}$ hepatocytes). Based on this observation, we hypothesized that $p16^{h}$ hepatocytes might play a key role in triggering fibrogenic responses upon liver injury.

In a long-term CCl_4-induced hepatitis model, a marked accumulation of $p16^{h}$ hepatocytes were ob-

served specifically in zone 3 of the liver. These cells displayed several hallmarks of cellular senescence, and their abundance was significantly associated with the extent of liver fibrosis. Remarkably, selective depletion of $p16^h$ hepatocytes alleviated CCl_4-induced liver fibrosis, likely by reducing the activation of hepatic stellate cells. Single-cell transcriptomic analysis of murine and human hepatocytes further identified the LIFR signaling pathway as a critical mediator linking $p16^h$ hepatocytes to the fibrogenic activation of hepatic stellate cells.

In addition, by using generative AI, we translated the gene signatures of $p16^h$ hepatocytes from mice into corresponding human genes, based on both gene sequences and protein sequences. Using these translated results, we investigated senescent hepatocytes in human cirrhotic samples. Our analysis revealed that the subset of hepatocytes with the highest similarity to the mouse $p16^h$ profile is likely associated with precancerous lesions.

Publication

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