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 age-related diseases are fundamentally associated with chronic inflammation. The accumulation of senescent cells widely regarded as a major driver of this process. However, senescent cells in vivo remain poorly characterized. Here, we integrate single-cell RNA sequencing and spatial transcriptomics from mouse models with AI approaches to identify senescent cell features and project these insights onto human datasets, aiming to determine conserved properties and potential therapeutic targets for anti-aging interventions.

1. Senescent hepatocytes promote liver fibrosis through activating LIFR pathway

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

Progressive fibrosis is a hallmark of organ aging and is observed in multiple tissues, including the liver. Liver fibrosis represents a particularly deleterious outcome of chronic liver injury and is thought to be initiated primarily by hepatocytes, yet the responsible cellular subtypes and signaling pathways remain unclear.

We identify a population of hepatocytes expressing elevated level of p16 (p16h hepatocytes) whose abundance correlates with fibrosis severity in human cirrhosis. Using a chronic CCl_4-induced hepatitis model, we show that p16h hepatocytes accumulate selectively in zone 3, exhibit canonical senescence features, and strongly associate with fibrosis progression. Selective elimination of p16h hepatocytes alleviates fibrosis, by suppressing hepatic stellate cell activation. Single-cell transcriptomic analyses in mouse and human livers identify LIFR signaling as a key mediator linking senescent hepatocytes to stellate cell fibrogenic activation. Furthermore, generative

AI–based cross-species gene mapping reveals a human hepatocyte population resembling mouse p16h hepatocytes, potentially associated with premalignant lesions, highlighting senescent hepatocytes as both fibrogenic drivers and therapeutic targets.

2. The role of senescent cells in driving inflammaging during the natural aging process in vivo

Yuki T. Okamura[1,2], Teh-Wei Wang[1,2], Takumi Iritani[3], Taiki Morimura[1,2], Xintong Zheng[1], Kiyoshi Yamaguchi[4], Satoshi Kawakami[1], Takehiro Jimbo[5], Michio Katano[3], Kansuporn Kamataki[3], Ryoichi Yokoyama[5], Miyuki Nakamura[5], Eigo Shimizu[6], Seiya Imoto[6], Yoichi Furukawa[4], Yoshikazu Johmura[7], and Makoto Nakanishi[1]

[1]Division of Cancer Cell Biology, [2]Project Division of Generative AI Utilization Aging Cells, The Institute of Medical Science, The University of Tokyo, 4-6-1, Shirokanedai, Minato-ku, Tokyo 108-8639, Japan. [3]GMO Internet Group, Inc., Shibuya-ku, Tokyo, Japan, [4]Division of Clinical Genome Research, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan. [5]GMO Research Activity Support & Technology, Inc., Shibuya-ku, Tokyo, Japan, [6]Division of Health Medical Intelligence, Human Genome Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan. [7]Division of Cancer and Senescence Biology, Cancer Research Institute, Kanazawa University, Kanazawa 920-1192, Japan

Senescent cells in vivo have been widely considered as a major driver of chronic inflammation. Over the past half century, biologists have observed serial passage accompanied by cell cycle arrest and defined such pro-inflammatory cells as senescent cells. Through biomarkers, aging researchers claim that numbers of senescent cells positively correlate with aging. Besides, eliminating senescent cells by senolytic approaches has been broadly demonstrated its therapeutic potential in age-related disorders. However, most of current knowledge about senescent cells has been built on studies of primary cultured fibroblasts or endothelial cells. It remains entirely unclear whether senolytic reagents designed on the basis of such platforms can truly target the highly heterogeneous senescent cells in vivo, and whether they cause off-target effects on other cell types. To identify senescent cells in vivo without relying on predefined biomarkers, we employed two orthogonal approaches to eliminate senescent cells, followed by scRNA-seq to comprehensively search for populations with consistent alteration. The transcriptomes of these cells were further confirmed to exhibit the inflammatory characteristics of senescent cells. Using this strategy, preliminary results revealed that a subset of fibroblasts located around the pulmonary arteries were senescent cells, and that they contributed to the formation of chronic inflammatory adventitial cuffs. We aim to expand this research framework across multiple models and organs to comprehensively investigate the importance of senescent cells in the aging process.

Publication

1. Zhang Y, Wang TW, Tamatani M, Zeng X, Nakamura L, Omori S, Yamaguchi K, Hatakeyama S, Shimizu E, Yamazaki S, Furukawa Y, Imoto S, Johmura Y, Nakanishi M. Signaling networks in cancer stromal senescent cells establish malignant microenvironment. **Proc Natl Acad Sci U S A**. 2025 Apr 8;122(14):e2412818122.
2. Wang TW, Nakanishi M. Immune surveillance of senescence: potential application to age-related diseases. **Trends Cell Biol**. 2025 Mar;35(3):248-257.