Advanced Clinical Research Center

Division of Advanced Genome Medicine
先端ゲノム医学分野

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The goals of our researches are to identify the mechanisms and to establish novel therapies especially for cancers and inflammatory diseases of the digestive system. One of the research fields is the inflammatory diseases, in which we investigated the molecular pathogenesis of gastritis, cholangitis and inflammatory bowel disease. Another research field is the malignancies. We specifically focus on the topics such as, differentiation of stem cells, proliferation and death of epithelium, interactions with immune cells or microbes, inter-organ interactions, and maintenance of tissue homeostasis. Using genetically engineered mice, we try to unveil the pathogenesis of various digestive diseases.

1. Role of IL-33 in the gastrointestinal homeostasis

Yoshihiro Hirata, Nobumi Suzuki[1], Yoku Hayakawa[1]. [1]Department of Gastroenterology, The University of Tokyo

Using several lines of gastric IL-33 overexpression mice, we found IL-33 is involved in the pathogenesis of gastritis, especially recruitment of specific immune cells into the stomach. Epithelium specific acetylcholine receptor knockout mice showed susceptibility to IL-33 mediated gastritis, suggesting the therapeutic potential of acetylcholine signaling in specific gastritis.

2. Analysis of primary biliary cholangitis mouse model

Jiaqi Zhang[4], Ryo Nakagawa[4], Hayato Nakagawa[3], Yoshihiro Hirata. [4]Department of Gastroenterology, Chiba University

Primary biliary cholangitis is a rare autoimmune cholestatic liver disease and its cause is not well understood. We found mice depleted of dendritic cells develop immune cell infiltration, bile duct destruction in the liver with elevated serum autoantibody, all of which are characteristics of human PBC. Serum from these mice induced T-cell dominant cholangitis in normal recipient mice, suggesting the critical role of autoantibody mediated immune reactions, as well as dendritic cell mediated immune tolerance in the pathogenesis of cholangitis.

3. Role of Sox9 in the gastric carcinogenesis

Hu Ke, Nobumi Suzuki[1], Yoku Hayakawa[1], Yoshihiro Hirata. [1]Department of Gastroenterology, The University of Tokyo

Sox9 is a multifunctional transcriptional factor which participates in development, stemness, as well as carcinogenesis of various tissues. To elucidate the role of Sox9 in gastric diseases, we established stomach specific Sox9 knockout mice (TFF1-cre; $Sox9^{f/f}$ mice) and found these mice developed gastritis and gastric tumor in the antrum. Recently we found combination of Sox9 deletion and CDH1 deletion showed aggressive malignant lesion in gastric antral epithelium, whose mechanism is currently under investigation.

4. Pathogenesis of squamo-columnar junction cancer of the stomach

Xu Qingpeng, Yoshihiro Hirata

Squamo-columnar junction (SCJ) is one of the transitional zones in body where two different cell types merge. The origin of SCJ tumors and the process of tumorigenesis are largely unknown. Using mouse models and lineage tracing, we try to identify cancer initiating cells as well as stem cells specific to gastric SCJ. Combination of Kras activation and TGFb signaling inactivation were found to be required for SCJ invasive tumor development. We are currently investigating the origin of this SCJ tumor.

5. Pathogenesis of eosinophil in the development and progression of colitis

Daisuke Kajimoto, Yoshihiro Hirata

Eosinophil is an immune cell derived from myeloid cell lineage, and the role in the development and progression of colitis is not fully understood. We have newly established an eosinophil specific cre expression mouse line (SigF-cre mouse), and eosinophil depleted mice (SigF-cre; Rosa-DTA mouse). We found eosinophil depleted mice showed exacerbated phenotype in DSS colitis, suggesting its protective role in colonic homeostasis.

6. Molecular mechanism of the development and the progression of sclerosing cholangitis

Ru Lin, Hayato Nakagawa[3], Yoshihiro Hirata. [3]Department of Gastroenterology, Mie University

Primary sclerosing cholangitis is a rare form of biliary inflammation which can progress to cirrhosis and cancer. We found infiltrated T cells have Th17 signatures, and damaged epithelium express stem cell markers. Antibiotics and UDCA treatment ameliorated immune cell infiltration and fibrosis of bile duct. We also found inactivation of Sox9 in bile duct cells led to amelioration of fibrosis, indicating critical role of Sox9 in the development of cholangitis.

Publications

1. Zhang J, Hirata Y. Response to "Which Cells Play a Protective Role in Primary Biliary Cholangitis: Dendritic Cells or Others?". Hepatol Res. 2025 Oct 11. doi: 10.1111/hepr.70053. Epub ahead of print. PMID: 41074730.
2. Zhang J, Nakagawa R, Xu Q, Hu K, Ru L, Nakagawa H, Hirata Y. Dendritic Cell-Depleted Mice Develop the Autoimmune Biliary Disease That Serologically and Pathogenically Models Human Primary Biliary Cholangitis. Hepatol Res. 2025 Nov;55(11):1471-1485. doi: 10.1111/hepr.70014. Epub 2025 Aug 6. PMID: 40767254.
3. Arai J, Hayakawa Y, Suzuki N, Kinoshita H, Hata M, Kurokawa K, Matsushita Y, Abe S, Oya Y, Tsuboi M, Ihara S, Iwata Y, Murakami K, Shiokawa T, Shiomi C, Uekura C, Yamamoto K, Fujiwara H, Kawamura S, Nakagawa H, Ikenoue T, Tateno H, Ushiku T, Ijichi H, Hirata Y, Kasuga M, Su GH, Wang TC, Fujishiro M. ARID1A mutation drives gastric tumorigenesis via activating type 2 immune dominant microenvironment. iScience. 2025 Jul 15;28(8):113117. doi: 10.1016/j.isci.2025.113117. PMID: 40761291; PMCID: PMC12319253.