

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 Suzuki¹, Yoku Hayakawa¹. ¹Department of Gastroenterology, The University of Tokyo

Using several lines of gastric IL-33 overexpression mice (TFF1-cre-LSL-IL33, Mist1creERT-LSL-IL33, TFF1pro-IL33), we found IL33 is involved in the pathogenesis of gastritis, especially recruitment of specific immune cells into the stomach. We have established SigF-cre-EGFP line to visualize SigF+ cells in vivo. Currently, role of acetylcholine signaling in IL-33 triggered gastritis is under investigation.

2. Role of Sox9 in the gastric carcinogenesis

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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^{fl/fl}

mice) and found these mice developed gastritis and gastric tumor in the antrum. We found Sox9 expression in antral UEA1+ mucous gland cells and GS2+ mucus neck cells in WT mice, suggesting the possible origin of SOX9 KO tumor. Now we investigate the tumor development mechanism focusing on RNA expression.

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

Ru Lin, Hisayoshi Natomi, Hayato Nakagawa³, Yoshihiro Hirata. ³Department of Gastroenterology, Mie University

Primary sclerosing cholangitis is a rare form of biliary inflammation which can progress to cirrhosis and cancer. We are currently investigating the role of intestinal microflora, on cholangitis using originally developed mouse biliary disease models. 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. Currently role of SOX9 in the development of inflammation and fibrosis in PSC model is under investigation using KO mice.

4. Analysis of primary biliary cholangitis mouse model

Jiaqi Zhang¹, Ryo Nakagawa¹, Naoya Kato¹, Hayato Nakagawa³, Yoshihiro Hirata. ¹Department of Gastroenterology, Chiba University

Primary biliary cholangitis is a rare autoimmune cholestatic liver disease and its cause is not well understood. We have generated transgenic mice which 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 could induce T-cell dominant cholangitis in normal recipient mice, suggesting the critical role of autoantibody mediated immune reactions in the development of cholangitis in this model.

5. 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. Barrett's adenocarcinoma and squamous cell carcinoma are two major tumors found in human gastric SCJ. 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.

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

Daisuke Kajimoto, Yoshihiro Hirata

Eosinophil is an immune cell derived from myeloid cell lineage. Its critical roles in allergy and parasite infection are well established, but the role in the development and progression of colitis is not fully understood. Using eosinophil depletion mouse line, we try to unveil the role of eosinophil in mouse colitis.

Publications

1. Matsubara Y, Ota Y, Denda T, Tanaka Y, Isobe M, Kato S, Konuma T, Takahashi S, Hirata Y, Ikematsu H, Baba K, Boku N. Both Th1 and Th2 CD4+ T-Cell Lineage Infiltrations Decrease in Post-hematopoietic Stem Cell Transplantation Colon Adenoma. *J Gastrointest Cancer*. 2024 Dec;55(4):1551-1558. doi: 10.1007/s12029-024-01097-5. Epub 2024 Aug 19. PMID: 39158838.
2. Murakami K, Arai J, Ihara S, Hirata Y, Tsuchida Y, Shoda H, Tsuboi M, Kurokawa K, Suzuki N, Kinoshita H, Hayakawa Y, Fujio K, Fujishiro M. Association Between Proton Pump Inhibitors and the Risk of Intestinal Behçet Disease. *J Rheumatol*. 2024 Dec 1;51(12):1193-1197. doi: 10.3899/jrheum.2024-0442. PMID: 39089843.
3. Arai J, Hayakawa Y, Tatenno H, Murakami K, Hayashi T, Hata M, Matsushita Y, Kinoshita H, Abe S, Kurokawa K, Oya Y, Tsuboi M, Ihara S, Nii-kura R, Suzuki N, Iwata Y, Shiokawa T, Shiomi C, Uekura C, Yamamoto K, Fujiwara H, Kawamura S, Nakagawa H, Mizuno S, Kudo T, Takahashi S, Ushiku T, Hirata Y, Fujii C, Nakayama J, Shibata S, Woods S, Worthley DL, Hatakeyama M, Wang TC, Fujishiro M. Impaired Glycosylation of Gastric Mucins Drives Gastric Tumorigenesis and Serves as a Novel Therapeutic Target. *Gastroenterology*. 2024 Aug;167(3):505-521.e19. doi: 10.1053/j.gastro.2024.03.037. Epub 2024 Apr 6. PMID: 38583723.