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Research Activities

Alimentary tract

1. FOXP3+ CD4+ regulatory T cells accumulate in areas of active inflammation, including granulomas in Crohn's disease, and retain potent regulatory activity ex vivo.
2. Visilizumab induces apoptosis of the lamina propria, but not peripheral blood T lymphocytes from patients with ulcerative colitis through activation of caspase-3-dependent and caspase-8-dependent pathways.
3. Plasmacytoid dendritic cells (DCs) regulate interleukin10 secretion from regulatory T cells and played a critical role in mucosal repair of colitis.
4. *Helicobacter* infection increased apoptosis in the livers of mice and might play a role in pathogenesis in the liver.
5. DCs engineered to secrete interleukin 12 derived from sarcoma promote the cross-priming of antitumor CD8 T cell responses against hemoglobin-beta.
6. Synergism between OK432-stimulated DCs and heat-treated tumor cells enhances the immunogenicity of DC/tumor fusion cells.
7. The gene mutations encoding inosine triphosphate pyrophosphohydrolase, which influences the metabolism of azathioprine/6-mercaptopurine, are closely related to thiopurine-induced adverse reactions in Japanese.
8. Treatment with cyclophosphamide, doxorubicin, and cisplatin removed both CD16+ and CD16− monocytes in all patients, and the dynamics of the CD16+ monocyte subset differed markedly between responders and nonresponders to treatment with cyclophosphamide, doxorubicin, and cisplatin.

Liver

1. Intrahepatic immunological reaction was studied by model mice of portal vein injection. It was demonstrated of activated CD8+ T cells in contact with Kupffer cells and undergoing apoptosis.
2. Intrahepatic expression of the co stimulatory molecule programmed death 1 in autoimmune liver disease: Programmed death 1 was expressed on more than half of the liver-infiltrating T cells within the portal tract.
3. Study of chronic hepatitis B and C virus: Natural killer cells target the hepatitis C virus (HCV) core protein in Cre/loxP-mediated naïve immune responses in HCV

transgenic mice. Natural killer cells have important roles in the initial recognition of HCV proteins and the later elimination of core-expressed hepatocytes. The interferon $\beta 2$ division dosage under treatment peg interferon $\alpha 2b$/ribavirin combination therapy was a predictor response rate of patients with intractable chronic HCV infection.

4. Clinical backgrounds and histological findings in autoimmune hepatitis: Liver biopsies should be done for both initial diagnosis and the assessment of therapy response in autoimmune hepatitis.

5. The relation of connective tissue growth factor and liver fibrosis: Connective tissue growth factor is a new marker of liver fibrosis with histological findings.

6. Necessity of nutritional evaluation before nutritional support in liver cirrhosis and nonalcoholic liver disease: More than 80% of cases showed excessive food intake. Patients with liver cirrhosis and nonalcoholic liver disease should be evaluated for nutritional imbalance before they receive nutritional support.

7. The expression of survivin during the early stages of hepatocellular carcinoma: In hepatocellular carcinoma tissues, the average survivin expression rate was 62%. The serum level of alanine aminotransferase was correlated with the survivin expression rate in specimens of hepatocellular carcinoma. Some clinical variables may be useful indicators for selecting patients for survivin-inhibiting treatment.

8. The mini-bioartificial liver was cultured with ^{13}C-glucose, and the amout of $^{13}CO_2$ in exhaust gas reflected the viability of an artificial organ or the damage to it.

9. Development of an implant-type bioartificial liver: A 3-dimensional tissue culture mimicking the liver (liver organoid) was established with an apatite-fiber scaffold in the bioreactor system.

Publications

Koido S, Hara E, Homma S, Mitsunaga M, Takahara A, Nagasaki E, Kawahara H, Watanabe M, Toyama Y, Yanagisawa S, Kobayashi S, Yanaga K, Fujise K, Gong J, Tajiri H. Synergistic induction of antigen-specific CTL by fusions of TLR-stimulated dendritic cells and heat-stressed tumor cells. *J Immunol* 2007; **179:** 4874–83.

Koido S, Hara E, Homma S, Fujise K, Gong J, Tajiri H. Dendritic/tumor fusion cell-based vaccination against cancer. *Arch Immunol Ther Exp* 2007; **55:** 281–7.

Kimura T, Amano K, Uehara H, Ariga H, Ishida T, Torii A, Tajiri H, Matsueda K, Yamato S. Urocortin I is present in the enteric nervous system and exerts an excitatory effect via cholinergic and serotonergic pathways in the rat colon. *Am J Physiol Gastrointest Liver Physiol* 2007; **293:** G903–10.

Oikawa T, Takahashi H, Ishikawa T, Hokari A, Otsuki N (Dept Mol Immunol, Grad Sch, Tokyo Med Dent Univ), Miyuki Azuma (Dept Mol Immunol, Grad Sch, Tokyo Med Dent Univ), Mikio Zeniya M, Tajiri H. Intrahepatic expression of the co-stimulatory molecules programmed death-1, and its ligands in autoimmune liver disease. *Pathol Int* 2007; **57:** 485–92.

Saito M, Matsuura T, Nagatsuma K, Tanaka K, Maehashi H, Shimizu K, Hataba Y, Kato F, Kashimori I, Tajiri H, Braet F. The functional interrelationship between gap junctions and fenestrae in endothelial cells of the liver organoid. *J Membr Biol* 2007; **217:** 115–21.

Mamori S, Nagatsuma K, Matsuura T, Ohkawa K, Hano H, Fukunaga M, Matsushima M, Masui Y, Fushiya N, Onoda H, Searashi Y, Takagi I, Tajiri H. Useful detection of CD147 (EMMPRIN) for pathological diagnosis of early hepatocellular carcinoma in needle biopsy samples. *World J Gastroenterol* 2007; **13:** 2913–7.

Mamori S, Asakura T, Ohkawa K, Tajiri H. Survivin expression in early hepatocellular carcinoma and post-treatment with anti-cancer drug under hypoxic culture condition. *World J Gastroenterol* 2007; **13:** 5306–11.

Kato M, Kaise M, Yonezawa J, Yoshida Y, Tajiri H. Autofluorescence endoscopy versus conventional white light endoscopy for the detection of superficial gastric neoplasia: a prospective comparative study. *Endoscopy* 2007; **39:** 937– 41.

Katada C, Muto M, Momma K, Arima M, Tajiri H,

Kanamaru C, Ooyanagi H, Endo H, Michida T, Hasuike N, Oda I, Fujii T, Saito D. Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae: a multicenter retrospective cohort study. *Endoscopy* 2007; **39:** 779–83.

Kaise M, Yamasaki T, Yonezawa J, Miwa J, Ohta Y, Tajiri H. CpG island hypermethylation of tumor-suppressor genes in *H. pylori*-infected non-neoplastic gastric mucosa is linked with gastric cancer risk. *Helicobacter* 2008; **13:** 35–41.

Koyama T, Tsubota A, Nariai K, Mitsunaga M, Yanaga K, Takahashi H. Novel biomedical imaging approach for detection of sentinel nodes in an experimental model of gastric cancer. *Br J Surg* 2007; **94:** 996–1001.

Tsubota A, Yoshikawa T, Nariai K, Mitsunaga M, Yumoto Y, Fukushima K, Hoshina S, Fujise K. Bovine lactoferrin potently inhibits liver mitochondrial 8-OHdG levels and retrieves hepatic OGG1 activities in Long-Evans Cinnamon rats. *J Hepatol* 2008; **48:** 486–93.

Odagi I, Kato T, Imazu H, Kaise M, Omar S, Tajiri H. Examination of normal intestine using confocal endomicroscopy. *J Gastroen Hepatol* 2007; **22**: 658–62.

Sakai A, Takikawa S, Thimme R, Meunier JC, Spangenberg HC, Govindarajan S, Farci P, Emerson SU, Chisari FV, Purcell RH, Bukh J. *In vivo* study of the HC-TN strain of hepatitis C virus recovered from a patient with fulminant hepatitis: RNA transcripts of a molecular clone (pHC-TN) are infectious in chimpanzees but not in Huh7.5 cells. *J Virol* 2007; **81:** 7208–19.

Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, Shiraishi K, Okuda H, Onji M, Kanazawa H, Tsubouchi H, Kato S, Kaito M, Watanabe A, Habu D, Ito S, Ishikawa T, Kawamura N, Arakawa Y. BCAA-enriched snack improves nutritional state of cirrhosis. *Nutrition (Burbank, Los Angeles County, Calif.)* 2007; **23:** 113–20.

Fukata M, Abreu MT. TLR4 signaling in the intestine in health and disease. *Biochem Soc Transac* 2007; **35:** 1473–88.

Fukata M, Chen A, Vamadevan AS, Cohen J, Breglio K, Krishnareddy S, Xu R, Harpaz N, Dannenberg AJ, Subbaramaiah K, Cooper HS, Itzkowitz SH, Abreu MT. Toll-like receptor-4 (TLR4) promotes the development of colitis-associated colorectal tumors. *Gastroenterology* 2007; **133:** 1869–81.

Saruta M, Yu QT, Fleshner PR, Mantel PY, Schmidt-Weber CB, Banham AH, Papadakis KA. Characterization of FOXP3+CD4+ regulatory T cells in Crohn's disease. *Clin Immunol* 2007; **125:** 281–90.

Fukata M, Abreu MT. Role of toll-like receptors in gastrointestinal malignancies. *Oncogene* 2008; **27:** 234–43.

Fukata M, Breglio K, Chen A, Vamadevan AS, Goo T, Hsu D, Conduah D, Xu R, Abreu MT. The myeloid differentiation factor 88 (MyD88) is required for CD4+ T cell effector function in a murine model of inflammatory bowel disease. *J Immunol* 2008; **180:** 1886–94.

Yu QT, Saruta M, Papadakis KA. Visilizumab induces apoptosis of mucosal T lymphocytes in ulcerative colitis through activation of caspase 3 and 8 dependent pathways. *Clin Immunol* 2008; **127**: 322–9.