

## Department of Internal Medicine

### Division of Gastroenterology and Hepatology

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Hisao Tajiri, *Professor*  
Toshifumi Okusa, *Professor*  
Yoshio Aizawa, *Associate Professor*  
Hisato Nakajima, *Associate Professor*  
Tomohiro Kato, *Assistant Professor*  
Tomohisa Ishikawa, *Assistant Professor*  
Mika Matsuoka, *Assistant Professor*  
Yasuyuki Searashi, *Assistant Professor*

Mariko Itsubo, *Professor*  
Ichiro Takagi, *Professor*  
Hirokazu Nishino, *Associate Professor*  
Tateki Yamane, *Assistant Professor*  
Shigeo Koido, *Assistant Professor*  
Atsushi Hokari, *Assistant Professor*  
Kazuhiko Koike, *Assistant Professor*

### Research Activities

#### *Alimentary tract*

1. Two-week triple antibiotic therapy is safe and produced remission in about 70% of patients with refractory ulcerative colitis. Mutation of the inosine triphosphate pyrophosphohydrolase gene is closely related to the adverse reactions to azathioprine/6-mercaptopurine in Japanese patients with inflammatory bowel disease.
2. The healing stage of dextran sodium sulfate—induced colitis was characterized by plasmacytoid dendritic cell (DC) subsets. These plasmacytoid DCs regulate the secretion of interleukin 10 from regulatory T cells. We conclude that colonic plasmacytoid DCs play a critical role in mucosal repair in colitis.
3. TLR8 is a X-linked inflammatory bowel disease susceptibility gene, with both common predisposing and protecting haplotypes. These associations further emphasize the importance of genetic variation in innate immunity as determinants of Crohn's disease and of ulcerative colitis.
4. Visilizumab induced apoptosis, predominantly of CD4<sup>+</sup> lamina propria T cells, whereas CD8<sup>+</sup> lamina propria T cells were largely resistant to apoptosis. Visilizumab induces apoptosis of lamina propria T lymphocytes, but not of peripheral blood T lymphocytes, from patients with ulcerative colitis through activation of caspase-3 and caspase-8—dependent pathways.
5. Assessment with the frequency scale for the symptoms of gastroesophageal reflux disease (GERD, FSSG) questionnaire identified young age, excessive intake of alcohol, and liver dysfunction as possible predictive factors. Treatment with 20 mg of rabeprazole for 4 weeks was effective for curing GERD. The results suggest that use of the FSSG questionnaire is an appropriate method for assessing the effect of treatments for GERD.
6. We found that *Helicobacter* infection increase apoptosis in the livers of C3H/He mice.

#### *Tumor immunology*

Local factors related to hepatocellular carcinoma (HCC) favor the generation of regulatory T cells through the inhibition of DC maturation; however, vaccination with

DC/HCC fusion cells in patients with HCC results in the recovery of DC function and the induction of antigen-specific cytotoxic T lymphocyte responses *in vitro*. DCs engineered to secrete interleukin 12 p70 delivered into sarcoma lesions promote the cross-priming of a protective CD8<sup>+</sup> T-cell response against hemoglobin beta.

### Liver

1. Regulatory T cells in the peripheral blood of patients with hepatitis C virus (HCV) infection might play a central role in the persistence of HCV infection and on the development of HCC. Infection of cells expressing the HCV replicon with an adenovirus expressing short hairpin (sh) RNA resulted in efficient vector delivery and expression of shRNA, leading to suppression of the replicon in the cells. A 4-week course of treatment with polyethyleneglycol-coupled interferon alpha 2a can achieve a high sustained virological response rate in “interferon-sensitive” patients with a low titer genotype 2a without negatively affecting outcome.
2. We found that the Sall4, a zinc-finger transcription factor, regulated cell-fate decision in fetal hepatic stem/progenitor cells. This molecule might have clinical applications.
3. Cases of autoimmune hepatitis in which multiple liver biopsies were performed were investigated for discrepancies between histological findings and the clinical course. Regulatory T cells, a subgroup of T cells, play an important role in the pathogenesis of autoimmune hepatitis in a mouse model.
4. Diffusion-weighted imaging and media enhancement in magnetic resonance imaging were useful methods for evaluating HCC. A study of the diagnostic efficacy of these methods is underway. In addition, we attempted to clarify the carcinogenic factors associated with non-B and non-C HCC compared with those associated with viral HCC.
5. A study of intrahepatic immunological reactions showed that between hepatic retention and apoptosis, the pool of retained activated CD8<sup>+</sup>T cells undergoes affinity high antigen by model mice with the portal vein injection method.
6. Validation of a food-frequency questionnaire based on food groups and indirect calorimetry was useful for estimating individual nutrient intake. We continue to study the imbalance of nutritional evaluation in chronic liver disease.
7. Results of our histological study suggest that a connective tissue growth factor might be used as a new marker of liver fibrosis.
8. We performed a study of target chemotherapy with a glutathione-doxorubicin (GSH-DXR) conjugate encapsulated in an anti-CD147 antibody—labeled liposome against carcinoma cells highly expressing CD147. This liposome-encapsulated GSH-DXR showed specific cytotoxicity against these carcinoma cells.

### Publications

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