

## Department of Internal Medicine

### Division of Gastroenterology and Hepatology

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### Research Activities

#### *Alimentary tract*

1. The Toll-like receptor (TLR) 8-mediated activation of human monocytes was shown to inhibit expression of tumor necrosis factor-like ligand 1A (TL1A), which is believed to be a key mediator of Crohn's disease. Immune complex-induced TL1A expression in monocytes was potently inhibited by a TLR8 or TLR7/8 ligand. Furthermore, TLR8 ligands inhibited TL1A production, resulting in the almost complete inhibition of interferon-gamma production by CD4(+) T cells. Our data suggest that TLR8 activation is an important, novel pathway for the targeted treatment of Crohn's disease. Diet therapy involving the use of an n-3 polyunsaturated fatty acid food exchange table altered the fatty acid composition of cell membranes and affected the clinical activity in patients with inflammatory bowel disease. Several types of enterobacteria enhanced secretion of corticotropin-releasing hormone in dendritic cells.
2. We analyzed the correlation between the symptomatic improvement of reflux esophagitis and quality of life (QOL) in patients with gastroesophageal reflux disease (GERD) by means of the Frequency Scale for Symptoms of GERD (FSSG). The QOL decreased as the symptoms worsened. In addition, the improvement in QOL after treatment with a proton-pump inhibitor was greater among subjects with more severe dysmotility symptoms. However, no correlation was observed between symptom improvement and the rate of QOL improvement. We concluded that the efficacy of treatment with a proton-pump inhibitor was associated with the severity of symptoms before treatment.
3. Predictive factors were identified and therapeutic effects were assessed among patients with GERD by means of the FSSG. Overall, 346 (25.9%) of the 1,335 subjects who underwent health checkups were found to have GERD according to the FSSG. The sensitivity and specificity of the FSSG were 34.7% and 72.7%, respectively. A young age, excessive alcohol intake, and liver dysfunction were possible predictive factors for GERD. The FSSG score was significantly decreased by treatment with rabeprazole (20 mg×4 weeks+10 mg×8 weeks). The FSSG was useful for detecting and assessing therapeutic effects in GERD.
4. A clinicopathologic study was performed to examine risk factors, particularly

vascular invasion, for metastasis of superficial esophageal cancers to lymph nodes. We carefully analyzed the risk factors of lymph node metastasis before surgical treatment in patients with esophageal superficial cancer. We examined 110 surgically resected lesions and detected metastasis to lymph nodes in 37 cases (33.6%). We evaluated vascular invasion using special staining procedures (D2-40, elastica-van Gieson, CD31, and CD34) and statistically analyzed these and other risk factors for lymph node metastasis; vascular invasion evaluation using special staining procedures was the strongest risk factor for lymph node metastatic. The negative predictive value was 94.6%.

### *Liver and Pancreas*

1. The clinical background and histological findings of patients with autoimmune hepatitis (AIH) were examined. Liver biopsy was useful for establishing a definitive diagnosis and evaluating treatment in patients with AIH. The blood sampling data were normalized with immunosuppressive drugs in more than 95% of the cases of AIH. A discrepancy between the clinical data and the histological activity was confirmed for some cases. The liver biopsy findings reflected the actual clinical course.
2. The relationship between the severity of sleep apnea syndrome (SAS) and liver damage was studied. We surveyed metabolic imbalances in patients with SAS. Twenty percent of patients with SAS had complications, such as obesity, dyslipidemia, and glucose intolerance. A relationship between the severity of SAS and liver metabolic imbalance under conditions of severe long-term hypoxia was suggested. Nonalcoholic fatty liver disease and SAS were thought to be associated with common metabolic imbalances.
3. Natural killer T (NKT) cells and dendritic cells in primary immunoreactions in a mouse model of AIH were analyzed. The results suggested that NKT and dendritic cells are involved in the pathogenesis of AIH. The number of intrahepatic activated NKT cells that secrete interferon- $\gamma$  increased during the inflammation phase. The expression of CD1d, which activates NKT cells, on intrahepatic Kupffer cells and dendritic cells also increased during the inflammation phase. These results indicate that activated NKT cells play a significant role in this AIH model.
4. The molecular mechanism of liver stem cells in fetal liver development was studied. The marker factor Sall4 was confirmed to regulate cell fate decisions in fetal hepatic stem/progenitor cells. This molecule may have novel clinical applications. Our results suggest that Sall4 plays a crucial role in controlling the lineage commitment of hepatoblasts, not only inhibiting their differentiation into hepatocytes, but also driving their differentiation toward cholangiocytes.
5. "Validation of a Food Frequency Questionnaire Based on Food Groups and Indirect Calorimeters" was a useful method for estimating the nutritional status of individual patients. We studied imbalances in the nutritional status of patients with chronic liver disease. Sixty-five percent of patients with liver cirrhosis exhibited excessive protein consumption. Thus, assessment of nutritional status was considered necessary for clinical care.
6. The relation between connective tissue growth factor (CTGF) and liver fibrosis was

studied. Consequently, CTGF was shown to be a peptide marker of fibrosis and angiogenesis. We measured plasma CTGF levels in patients with chronic liver disease. The plasma CTGF levels were higher in patients with liver cirrhosis than in patients with chronic hepatitis. A comparison of the plasma CTGF level and the pathological stage of liver fibrosis showed a good agreement. In addition, stellate cells positive for both lecithin:retinol acyltransferase and cellular retinol-binding protein 1 contributed to portal fibrosis in human liver disease.

7. The specific characteristics of liver dysfunction were examined at an annual company health checkup. We studied physical measurements, insulin resistance, and the characteristic liver damage pattern for the early identification of nonalcoholic fatty liver disease. Obese participants were found to have large liver fat stores and a high rate of liver dysfunction.

8. The effectiveness of magnetic resonance (MR) for visualizing hepatocellular carcinoma (HCC) was examined. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a new enhancement medium for the detection of HCC using MR. Detailed MR images obtained using Gd-EOB-DTPA and the clinical stage of HCC were analyzed. About 80% of the enhanced MR findings obtained with Gd-EOB-DTPA agreed with those obtained using hepatic artery angiography. This noninvasive enhanced MR technique was thus considered an effective imaging method.

9. A  $^{13}\text{C}$ -glucose breath test was established as a diagnostic test for insulin resistance and as a test of liver function.

10. We have developed a novel, quantitative, and specific assay for the degradation products of plasma latency-associated protein of transforming growth factor (TGF)  $\beta$  (LAP-D), which are produced during proteolytic TGF- $\beta$  activation. This assay has previously been validated as an *in vivo* marker of hepatic stellate cell activation during liver fibrosis. The plasma levels of LAP-D were significantly decreased in 24 cases 3 months after the start of successful combination therapy for hepatitis C virus (HCV) infection.

11. The relationship between regulatory T cells in the peripheral blood of patients with HCV infection and the progression of liver disease, including HCC, was studied. The apolipoprotein B level was found to be associated with the virological response in patients receiving treatment for chronic HCV infection.

12. Vaccination with Wilm's tumor protein 1 in combination with gemcitabine was examined for the treatment of patients with advanced pancreatic cancer. This therapy may be effective for patients with advanced pancreatic cancer.

## Publications

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**Ralf Kiesslich, Tajiri H.** Advanced Imaging in Endoscopy *Gastroenterological Endoscopy* Second Edition. GERMANY: Thieme; 2010. p. 21-35.