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Research Activities

Alimentary Tract

1. An antibody against tumor necrosis factor α is effective at preventing restenosis after endoscopic balloon dilatation therapy in patients with Crohn's disease

We enrolled 12 patients with Crohn's disease who had severe stenotic lesions. Seven patients had already been treated with infliximab or adalimumab before endoscopic balloon dilation (EBD), and 5 patients had started being treated with infliximab or adalimumab after EBD. No patients had symptoms of ileus, but 4 patients underwent EBD again because of mild restenosis. Endoscopic examination showed no restenosis in 4 patients. Our findings show that EBD is a useful treatment for stenosis in Crohn's disease and that an antibody against tumor necrosis factor α is useful for preventing restenosis after EBD.

The cell membrane fatty acid profile of patients with Crohn's disease at initial onset was significantly different from those of healthy subjects and patients with initial-onset ulcerative colitis (UC). This finding suggests that the lipid metabolism enzyme, i.e., delta 6-desaturase, is hyperactivated in Crohn's disease.

2. Development of optical molecular imaging for gastrointestinal cancers and image-guided phototherapy

We have developed photoimmunotherapy, a type of specific molecularly targeted phototherapy that uses monoclonal antibodies conjugated with near-infrared phthalocyanine dye. We have recently established a technique of specific molecularly targeted, fluorescence molecular imaging-guided phototherapy using a mouse model of human gastric cancer.

3. Endoscopic features of colorectal serrated lesions using image-enhanced endoscopy with pathological analysis

Sessile serrated adenoma/polyp (SSA/P) has recently been reported to have malignant potential. Color change on autofluorescence imaging, capillary dilatation, presence of a mucous layer on the tumor surface, and pit dilatation under narrow-band imaging were examined retrospectively. When magenta color, capillary dilatation, mucous cap, and pit dilatation were used for differentiating SSA/P from hyperplastic polyp, the sensitivity,

specificity, and accuracy were 43%, 68%, and 52%, respectively, for autofluorescence imaging; 10%, 96%, and, 41% for capillary dilatation; 94%, 40%, and 75% for mucous cap; and 80%, 72%, and 78% for pit dilatation. The findings of a mucous cap and a dilated pit might be helpful for differentiating SSA/P from hyperplastic polyp.

4. Elemental diet as preparation for colonoscopy in inflammatory bowel disease

We investigated the usefulness of an elemental diet as a bowel preparation regimen for colonoscopy in inflammatory bowel disease (IBD). One day before colonoscopy, patients with IBD received 1,200 ml of an elemental diet. A polyethylene glycol (PEG) lavage solution was used to cleanse the colon. The total amount of PEG solution used, the degree of colonic cleansing achieved, patient acceptance, and the safety of the regimen were evaluated. Bowel preparation with an elemental diet significantly reduced PEG volume for gut lavage before colonoscopy and was effective, safe, and suitable for patients with IBD.

5. Photodynamic diagnosis of colitis-associated dysplasia in a mouse model after oral administration of 5-aminolevulinic acid

Early and accurate detection of dysplastic lesions has become an important issue in the treatment of patients with chronic, extensive UC. We detected dysplastic lesions in mouse colonic tissue by determining the accumulation of the photosensitizer protoporphyrin IX induced by the oral administration of 5-aminolevulinic acid, a precursor of protoporphyrin IX. Photodynamic diagnosis with 5-aminolevulinic acid will be useful in detecting dysplastic lesions in the colon mucosa of patients with UC.

6. Efficacy of enemas with a zinc-containing compound, polaprezinc, in patients with UC

Polaprezinc enemas produced significant improvement, as assessed with endoscopic and clinical findings, in cases of moderate-to-severe UC. Significant improvements were detected with endoscopy in the rectum and sigmoid colon, which are areas reached by polaprezinc enemas. Polaprezinc enemas are a useful new add-on treatment to accelerate mucosal healing in UC.

7. Side effects of azathioprine

A pyrophosphohydrolase (thiopurine S-methyltransferase) gene mutation, 94C>A, was detected in most cases of leukopenia. However, this mutation might not definitively reflect the risk of adverse reactions to thiopurines.

8. Novel immunotherapy for pancreatic cancer

Fusions of dual Toll-like receptor-stimulated dendritic cells and ethanol-treated tumor cells induced efficient cytotoxic T lymphocytes through transforming growth factor β 1 blockade and interleukin 12p70 production.

Liver

1. Treatment response of antiviral analogue nucleic acids in chronic hepatitis B virus infection

Resistant viral mutations are an urgent remedial problem in chronic hepatitis B virus (HBV) infection treated with antiviral analogue nucleic acids. Analyses were performed of the viral gene sequence and the treatment response. We have considered the possibility of a new concurrent therapy for chronic HBV infection.

2. The relation histological findings and biochemical laboratory data of chronic hepatitis C virus infection

Histological activity and staging in some cases of chronic hepatitis C virus (HCV) infection did not match the biochemical data. We must weigh histological findings against biochemical data.

3. Clinical pathological study of primary biliary cirrhosis

We studied the clinical characteristics of primary biliary cirrhosis. We attempted to statistically analyze blood chemical variables and histological findings of liver biopsy. A comparison of clinical characteristics and micro-RNA expression in T cells was started this year.

4. Intrahepatic natural killer T-cell kinetics in a mouse model of autoimmune hepatitis

Natural killer T cell kinetics are significant reactions in autoimmune hepatitis. Natural killer T cells and cytokine profiles were examined in a mouse model of autoimmune hepatitis. Changes in immunoreactions were analyzed in a knock-out mouse model.

5. Nutritional imbalance in patients with liver cirrhosis

We are interested in the nutritional imbalance in patients with liver cirrhosis. The patients' nutritional background was analyzed with a food-frequency questionnaire based on food groups. We could easily evaluate the relation between nutritional imbalance and morbidity.

6. Nutritional evaluation in nonalcoholic fatty liver disease

The pathogenesis of nonalcoholic fatty liver disease is similar to that of metabolic syndrome. We evaluated nutritional conditions in detail in nonalcoholic fatty liver disease and metabolic syndrome. We have explored the possibility of a new nutrition supports system with accuracy.

7. A study comparing sleep apnea and nonalcoholic fatty liver disease

Sleep apnea syndrome seems to be closely related with an imbalance of hepatic metabolism. Sleep apnea syndrome is often complicated by severe hypoxia and liver dysfunction. We analyzed the respiratory quotient with indirect calorimetry.

8. Prognostic indices in hepatocellular carcinoma

The serum white blood cell count and the serum albumin concentration before treatment were independently associated with overall survival. We found that the values of these variables before treatment were associated with tumor progression and reduced liver function and were independent markers of poor prognosis in patients with hepatocellular carcinoma.

9. The features of dyslipoproteinemia in chronic HCV infection

The efficacy of PEG-interferon plus ribavirin combination therapy or telaprevir and PEG-interferon plus ribavirin triple therapy on chronic HCV infection was examined. In addition, the significance of interleukin (IL) 28B (rs8099917) single nucleotide polymorphism, HCV mutations, and dyslipoproteineima on the efficacy of antiviral therapy was determined. Of these factors, IL28B single nucleotide polymorphism was extremely important for predicting therapeutic outcome in patients with HCV genotype 1b. With triple therapy, almost all patients with genotype 1b carrying the IL28B major genotype achieved a sustained virological response. Meanwhile, almost all patients infected with HCV genotype 2 could achieve a sustained virological response with

response-guided therapy.

10. The fasting ^{13}C -glucose breath test

We attempted metabolic simulation with a computer to estimate *in vivo* glucose metabolism from the dynamics curve of the ^{13}C excretion rate on the fasting ^{13}C -glucose breath test. First, we established an *in vivo* metabolic model of glucose and adopted 5 compartment models. The dynamics curve of the exhalation of ^{13}C excretion in the 5 compartment models fitted well with that of actual values. In healthy subjects, the area under the curve until 360 minutes of the ^{13}C excretion dynamics curve in female subjects was greater than that in male subjects. The *in vivo* simulation suggested that glucose metabolism in the liver of female subjects is more efficient than that in male subjects. This simulation is also useful for judging the effects of drugs before and after treatment.

11. A novel, quantitative, and specific assay of plasma latency-associated protein of transforming growth factor degradates

The level of latency-associated protein of transforming growth factor β degradates (LAP-D) in blood and tissues would be novel markers reflecting fibrogenesis activity but not the amount of accumulated fibrosis in patients. We found that even if nucleotide analogs inhibited alanine aminotransferase release from livers infected with HBV, the plasma LAP-D level increased in some cases. Most likely, the effect of nucleotide analogs is not sufficient to inhibit fibrogenesis in the liver.

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