

Department of Pathology

Hiroshi Hano, *Professor*
Masaharu Fukunaga, *Associate Professor*
Masafumi Suzuki, *Associate Professor*
Satoru Chiba, *Assistant Professor*
Takako Kiyokawa, *Assistant Professor*
Hiroyuki Takahashi, *Assistant Professor*
Yukiko Kanetsuna, *Assistant Professor*

Yutaka Yamaguchi, *Professor*
Akihiko Sakata, *Associate Professor*
Masahiro Ikegami, *Associate Professor*
Yasushi Kikuchi, *Assistant Professor*
Takashi Nikaido, *Assistant Professor*
Koichi Nomura, *Assistant Professor*

General Summary

The research projects of our department have focused on studies of the pathogenesis, histogenesis, morphogenesis, and clinical pathology of nonneoplastic and neoplastic human diseases by means of light and electron microscopy, morphometry, immunohistochemistry, gene analysis, and other techniques.

Research Activities

Hepatology

We continued a histopathological study of nonalcoholic steatohepatitis. The additional cases of nonalcoholic steatohepatitis were examined. The results supported the previous conclusion that the pericellular fibrosis developing around the central veins and its terminal branches in one lobule expanded and connected in a band-like fashion to similar areas of fibrosis in adjacent lobules and that the fibrous band encircled the intact portal tract incompletely.

We studied chronic viral hepatitis histopathologically. Three-dimensional observation demonstrated that in the early stage the portal branches forming the framework of the liver lobules were damaged and were lost in part, with the consequences of portal-to-central fibrous bridging, subsequent widespread and progressive damage to the portal branches, distortion of the lobular architecture, and regenerative nodule formation. These changes indicate the process of self-assembly of histologic structures in a thermodynamic nonequilibrium system.

Damage and repair of the DNA of hepatocytes caused by oxidative stress in liver cirrhosis and chronic hepatitis were investigated immunohistochemically. The expression of 2 markers of oxidative stress, 8-hydroxy-2'-deoxyguanosine and thymidine glycol, were examined. The results showed that 8-hydroxy-2'-deoxyguanosine was expressed mainly by hepatocytes and that thymidine glycol was strongly positive in various cells, including hepatocytes, epithelial cells of bile ducts, endothelial cells, sinusoidal cells, and lymphocytes.

The development and distribution of lymphatic channels were examined immunohistochemically using D₂40 and CD34 in normal liver, chronic hepatitis, and liver cirrhosis. Lymphatic channels increased in number and tended to be dilated in chronic hepatitis and liver cirrhosis. These lymphatic channels were distributed preferentially in the capsule and subcapsular portal areas. The development of lymphatic channels was

considered to be correlated with fibrosis.

The 3-dimensional structure of cystic lesions in polycystic disease of the liver was examined with serial histologic sections. The results indicated that proliferating ductules changed to von Meyenburg complexes, which continued to grow and became large cysts lined with ductular epithelium. Some von Meyenburg complexes were connected to preexisting bile ducts, but others were not. These cystic structures were nourished by the arterial blood supply.

Renal pathology

We continued our histologic examination of mitochondrial nephropathy. Tubular cells with cytoplasmic granular swelling were removed by means of laser microdissection. Electron microscopic examination revealed abnormal mitochondria, which were considered to have caused histologic changes of the cells.

Fifteen kidneys obtained at autopsy after bone marrow transplantation were subjected to histologic examination. Thrombotic microangiopathy was detected in 9 cases. However, the relationship between thrombotic microangiopathy and calcineurin inhibitor was obscure.

Histologic examination in cases of chronic rejection of renal transplants revealed peritubular capillaritis and thickening of the capillary basement membrane. Endothelial cells positive for caveolin-1 increased in number. These findings were correlated with the severity of chronic rejection.

New criteria for the prognosis of IgA nephropathy were established on the basis of the results of histologic examination of specimens collected nationwide.

A new disease concept, glomerular deposition disease, was proposed.

Histologic examination of biopsy specimens obtained from transplanted kidneys indicated that patchy tubular injury was correlated with local circulatory disturbance of the transplanted kidney. Also it might be an unknown marker suggesting vascular rejection.

Specimens of renal cell carcinoma collected in the department were re-evaluated histologically with revised general rules for clinical and pathological studies of renal cell carcinoma. We found that cystic renal cell carcinoma with cystic lesions comprising more than 50% of the cut surface of the kidney had a better prognosis than did cases with cystic lesions comprising less than 50% of the cut surface.

Gastrointestinal pathology

Risk factors for metastasis were examined in 136 surgically resected specimens of colorectal cancer with submucosal invasion. Lymphatic channels were immunohistochemically stained with D2-40, and blood vessels were stained with Elastica-van Gieson stain and immunohistochemical stains for CD31 and CD34. Multivariate statistical analysis showed that both lymphatic invasion and blood vessel invasion were closely related to lymphatic metastasis.

Gynecologic pathology

Uterine cervical adenocarcinoma was examined with special reference to human papil-

loma virus (HPV) infection. We found that that the development of cervical adenocarcinoma with common histologic subtypes was closely related to HPV infection. On the other hand, cervical adenocarcinoma with uncommon subtypes were unrelated to HPV infection.

The pathogenesis of ovarian borderline malignancy derived from the müllerian duct was studied. The relationship of reserve cells of cervical gland-like cells to the development of ovarian borderline tumor was noted.

The distribution of reserve cells of cervical gland-like cells was examined in ovarian borderline tumor of müllerian type.

Urogenital pathology

Clinicopathological studies of prostatic carcinoma were continued. Histologic changes during the treatment of prostatic cancer were examined, and the response to treatment was evaluated.

Frequency of loss of heterozygosity was studied in prostatic cancers with special reference to tumor volume.

Soft-tissue tumor

Borderline vascular tumors, including composite hemangioendothelioma and perivascular epithelioid cell tumors, were examined clinicopathologically. The histologic characteristics and prognosis of epithelioid trophoblastic tumor was studied.

Oncology

Whole base sequences of mitochondrial DNA and genomic instability-related genes were examined with the polymerase chain reaction — single-strand conformation polymorphism method in gastric, colonic, and renal cancers. The results indicated that genomic instability was not involved in the development of these cancers.

The loss of heterozygosity in the short arm of chromosome 8 was analyzed in 86 specimens of liver cell cancer obtained at autopsy. The 8p22-23 loci were frequently lost. This finding indicates that the loss of these loci play important roles in carcinogenesis and, especially, in the metastasis of liver cell cancer.

Publications

Lu T, Hano H. Identification of minimal regions of deletion at 8p23.1-22 associated with metastasis of hepatocellular carcinoma. *Liver Int* 2007; **27**: 782-90.

Miki J¹, Furusato B (AFIP), Li H¹, Gu Y¹, Takahashi H, Egawa S, Sesterhenn A¹, McLeod GD (Walter Reed Army Med Cent), Srivastava S¹, Rhim SJ¹ (¹Uniformed Services Univ). Identification of putative stem cell markers, CD133 and CXCR4, in hTERT-immortalized primary nonmalignant and malignant tumor-derived human prostate epithelial cell lines and in prostate cancer specimens. *Cancer Res* 2007; **67**: 3153-61.

Joh K. Pathology of glomerular deposition diseases and fibrillary glomerulopathies associated with paraproteinemia and haematopoietic disorder. *Nephrology* 2007; **12**: S21-4.

Mamori S, Nagatsuma K, Matsuura T, Ohkawa K, Hano H, Fukunaga M, Matsuura 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.

Wakui S, Akagi Y¹, Muto T¹, Yokoo K¹, Hirono S¹, Kobayashi Y¹, Kamei Y¹, Shiota K¹, Akahori F¹,

- Suzuki Y¹, Hano H, Endou H¹, Kanai Y¹ (¹Azabu Univ).** Testicular toxicology of pubescent and adult rats prenatally exposure to 3,3',4,4',5-pentachlorobiphenyl. *J Toxicol Pathol* 2007; **20**: 133-40.
- Setoguchi K¹, Ishida H¹, Shimmura H¹, Shimizu T¹, Shirakawa Y¹, Omoto K¹, Toki D¹, Setoguchi S¹, Tokumoto T¹, Horita S¹, Nakayama H¹ (¹Tokyo Women's Med Coll), Yamaguchi Y, Tanabe T.** Analysis of renal transplant protocol biopsies in ABO-incompatible kidney transplantation. *Am J Transplant* 2008; **8**: 86-94.
- Yamamoto I, Horita S¹, Takahashi T (Vanderbulit Univ), Tanabe K¹, Fuchinoue S¹, Teraoka S¹ (¹Tokyo Women's Med Coll), Hattori M, Yamaguchi Y.** Glomerular expression of plasmalemmal vesicle-associated protein-1 in patients with transplant glomerulopathy. *Am J Transplant* 2008; **7**: 1954-60.
- Aita K¹, Yamaguchi Y, Horita S², Ohno M², Tanabe K², Fuchinoue S², Teraoka S², Toma H² (²Tokyo Women's Med Coll), Nagata M¹ (¹Tsukuba Univ).** Thickening of the peritubular capillary basement membrane is a useful diagnostic marker of chronic rejection in renal allografts. *Am J Transplant* 2008; **7**: 923-9.
- Takao M, Okamoto A, Nikaido T, Urashima M, Takakura S, Saito M, Okamoto S, Takikawa O, Sasaki H, Yasuda M, Ochiai K, Tanaka T.** Increased synthesis of indoleamine-2,3-dioxygenase protein is positively associated with impaired survival in patients with serous-type, but not with other types of, ovarian cancer. *Oncol Rep* 2007; **17**: 1333-9.
- Ueda K, Yamada K, Urashima M, Ishibashi Y, Shirai M, Nikaido T, Takahashi H, Okamoto A, Saito M, Yasuda M, Ohkawa K, Tanaka T.** Association of extracellular matrix metalloproteinase inducer in endometrial carcinoma with patient outcomes and clinicopathogenesis using monoclonal antibody 12C3. *Oncol Rep* 2007; **17**: 731-5.
- Fukunaga M, Mistuda A¹, Shibuya K¹, Honda Y¹, Shimada N¹, Koike J¹ (¹Toho Univ), Sugimoto M.** Retroperitoneal lymphangioliomyomatosis associated with endosalpingiosis. *APMIS* 2007; **115**: 1460-5.
- Kanayam R¹, Oka K¹, Fukunaga M, Tomisawa H¹, Takahashi Y¹ (¹Mito Saiseikai General Hosp), Okano M, Hakozaki H (Fukushima Rosai Hosp).** Spindle cell carcinoma arising in the pharynx, with granulocytosis and high serum granulocyte colony stimulating factor titer. *J Laryngol Otol* 2007; **121**: 597-600.
- Sakai K, Takatsu A, Shigeta A, Abe S, Ikegami M, Takagi K.** Sudden death due to undiagnosed acute promyelocytic leukemia: a case report. *Int J Legal Med* 2008; **121**: 311-4.
- Wakui S, Takagi F¹, Muto T¹, Yokoo K¹, Hirono S¹, Kobayashi Y¹, Shiota K¹, Akahori F¹, Suzuki Y¹, Hano H, Endou H¹, Kanai Y¹ (¹Azabu Univ).** Spermatogenesis in aged rats after prenatal 3,3',4,4',5-pentachlorobiphenyl exposure. *Toxicology* 2007; **238**: 186-91.
- Komeda M¹, Yamaguchi Y, Yamamoto I, Ogura M, Utsunomiya Y, Sanaka T¹ (¹Tokyo Women's Med Coll), Hosoya T.** Histological investigation of renal pathological changes in MPO-ANCA-related nephritis using repeat renal biopsies (in Japan). *Nippon Jinzo Gakkai Shi* 2007; **49**(4): 438-5.