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REVIEW

Current status of basic and clinical research in the field of gastroenterology in China

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This article discusses the major scientific advances in the field of gastroenterology in China, including some investigations into the mechanisms of diseases, new clues and new approaches to treatment.

ESOPHAGUS

An atlas of esophageal motility was published at the end of 1994 in which more than 160 typical manometric graphs were selected from a total of 2500 graphs of various esophageal motility disorders and the perioperative period, which is useful and practical for clinicians[1]. 24 h esophageal pH monitoring has been carried out in many hospitals among healthy Chinese adults and peptic ulcer patients. In the former, the obtained values were different from healthy Western adults reported in the Western medical literature. Among those with pH < 4, the total fraction time was 3.4%, upright fraction time 4.3%, supine fraction time 4.3%, the number of reflux episodes > 5.0 min less than two, the longest reflux episode 16 min and the number of reflux episodes 60, giving a composite score of 12.7. These might be due to racial differences, LES function, living habits and dietary composition[2]. Recently, an esophageal manometric study was conducted in asymptomatic esophageal diabetic patients that showed the following abnormalities: Diminution of resting LES pressure and amplitude of contraction of the lower segment of the esophageal body, increase of tertiary and segmental contractions and frequent double peak and multi peak contractions[3].

STOMACH

The gastric and gallbladder emptying time was reduced after long term acid inhibition by omeprazole in the treatment of reflux esophagitis combined with concomitant reduction of postprandial release of pancreatic polypeptides and normal serum VIP and CCK. It was suggested that the diminished vagal tone was responsible for the long term use of omeprazole in reflux esophagitis patients[4]. *Helicobacter pylori* (*Hp*) is now also a subject of emphasis in China and has become a rapidly expanding specialty. In 43 strains of *Hp*, an analysis of the expression of *CagA* and *VacA* virulence factors was carried out. According to their gastric and phenotypic properties, type Ⅰ bacteria had the gene coding for *CagA* and expression of protein together with vacuolating cytotoxins, whereas type Ⅱ bacteria did not. There was an intermediate phenotype expressing *CagA* independently of *VagA* or vice versa and the authors concluded that *CagA* is not necessary for the expression of vacuolating cytotoxins[5]. On differentiation of *Hp* isolated from recrudescence and reinfection after dual or triple therapy, some used PCR and single strand conformation polymorphism analysis was also found to be useful in the epidemiological study of *Hp* infection[6]. On a study of local humoral immunity of gastric *Hp* infection, research in the Shanghai Institute of Digestive Diseases studied the immunoglobulin antibodies to *Hp* immunoblot analysis in 167 patients with various gastroduodenal diseases. Protein bands 138, 71 KDa and 100.31 KDa were most frequently found (92%-100%) and 64.67 KDa protein was found in 72.5% of duodenal ulcers, 64.2% of gastric ulcers and 92.9% of gastric cancer. The author concluded that 64.67 KDa protein band might be a marker for predicting and assessing the severity of gastric disease[7]. Among IgG, IgA and IgM bands in children, the IgM bands were more numerous than those in adults, indicating an early stage of *Hp* infection[8]. Another basic study was conducted on hydrophobicity changes of the gastric mucosal surface to search for the influence of *Hp* in patients with erosive gastritis and peptic ulcer and the contact angle was found to be decreased in *Hp* positive patients, which reflected hydrophobicity changes and phospholipase levels in the mucosa. It suggests weakening of the mucosal barrier and disturbed mucosal phospholipid metabolism[9].

In *Hp* infection, the levels of ascorbic acid and copper zine superoxide dismutase in gastric juice were significantly lower in *Hp* positive than in *Hp* negative patients and the lipoperoxide level was the highest. In patients with gastric cancer, the CuZnSOD levels in gastric juice and plasma were much lower than in those with chronic gastric or peptic ulcers. The degree of decrease in ascorbic acid and CuZnSOD level in gastric juice was in decreasing order in patients

with CSG, CAG and gastric cancer[10]. Electromicroscopic features of *Hp* infection of gastric mucosa revealed *Hp* aggregation on the epithelial cell membrane in the form of hairy sticks or pseudopodia-like protrusions. Transmission electromicroscopy also showed that mucus granules aggregated at the inner side of the cell membrane. Scanning electromicroscopy disclosed a nibbling phenomenon of *Hp*, adhering beside the ulcerative area of the cell membrane and some island-like granules floating on the surface[11]. Investigating the pathogenesis of *Hp* infection showed that the tissue TNF-α and gastrin production were increased but both were diminished after *Hp* eradication, which might be an important mechanism of gastrin linked hypothesis in patients with *Hp* infection. With regards to the relationship between *Hp* and gastric cancer, several articles focused on the molecular aspects. It was found that the mutation rate of H-ras oncogene was higher in *Hp* infected groups than in those without infection, showing that the *Hp* infection was associated with an increased expression of ras p21 protein which increased the risk of ras oncogene activation, DNA damage and S-phase cells, indicating the rapid turnover of cells from injury[12]. Another experimental study showed DNA damage in gastric mucosal cells in *Hp* infection of an animal model, manifested as a decrease in the percentage of double strand DNA, chromaticity, fluorescent intensity of DNA EB complex, with EB as a fluorescence probe, and its resistance to hydrolysis by DNase Ⅰ. This indicates *Hp* infection may play a causative role in gastric cancer[13]. Clinically, transmission of *Hp* is probably from human to human, from patients to medical staff. In a survey of one hospital, the overall prevalence of *Hp* among medical staff was 70% compared to 41.7% of the general population ($P < 0.01$). Among endoscopists, its prevalence was 82.4%, higher than medical doctors in general (66.4%) and nurses 65% ($P < 0.05$)[14]. To assess the therapeutic efficiency of single, dual and triple therapy for eradication of *Hp* infection, ^{14}C and ^{13}C breath tests are presently used in large medical centers. A capsule-based modified microdose ^{14}C urea breath test proved to be more simple, accurate and economical than the conventional ones. Its sensitivity and specificity were 93.3% and 92.3%, respectively, and the positive and negative prediction values were similar[15]. In a newly discovered test, ^{15}N-urea excretion, which is devised here and can be used as a tracer for detection of clinical *Hp* infection, the ^{15}N-excretion rate in urine ammonium was much higher in *Hp* positive than in *Hp* negative subjects. A single dose of ^{15}N was taken orally and urine samples were collected every 30 min for two hours. The normal value was < 5%, its sensitivity was 96% and specificity 97%, indicating it was simple, accurate and non invasive[16].

Basic research of gastric cancer inclines towards the molecular level. Point mutation of c-Ha-ras at codon 12 and 61, N-ras at codon 12 and K-ras at codon 12 and 13 were observed in formalin fixed paraffin embedded specimens of 43 cases of gastric cancer by using PCR-RFLP. Mutation of c-Ha-ras at codon 12 in 33.3% and K-ras at codon 12 in 4.8% was found. Only one case with mutation of ras gene survived five years, about 50% without this point mutation survived five years or more. With ras gene point mutation, local lymph nodes metastases were present in 100% and lymph node involvement was only 69% in those with no point mutation. Furthermore, there were much fewer stage Ⅰ and Ⅱ cases of ras gene mutation, indicating that point mutation of ras oncogene in cancer tissue signifies a poor prognosis[17]. Another advance was the study of the plasma and intracellular concentrations of vitamin A, C, E, β carotene, folic acid and B12 in gastric precancerous lesions and gastric cancer patients with a status of DNA methylation. It was found that folic acid was most effective for atrophy and intestinal dysplasia, natural β carotene could ameliorate the histological changes and the total genomic DNA methylation was enhanced. As we know, human EGF plays an important role in the growth of gastric cancer. EGF is found to be increased in serum and saliva of patients with gastric cancer but not in urine[18] and it is higher in stage Ⅲ and Ⅳ than in stage Ⅰ and Ⅱ, according to the TNM classification. A new treatment advance has been made, successful local adjuvant therapy in experimental gastric cancer, *i.e.* the parvovirus[19]. The parvoviral NS gene expression was studied in human gastric cancer cells transfected with a plasmid carrying MVMPNS gene which showed the following effectiveness: Nucleus/cytoplasm ratio decreased, cancer cell replication time was prolonged, rate of cloning diminished, intracellular adhesion ability increased and tumor formation in nude mice suppressed as some of the cancer cells died. In another study, expression of ras and myc oncogenes of gastric cancer cells were suppressed by the above-mentioned NS gene with augmentation of expression of IL-1α, IL-1β, IL-6 and TGFβ. It is anticipated that the parvoviral NS gene can influence the expression of many important intracellular genes and interfere with differentiation and proliferation of cancer cells, in which the direct cytotoxic effect or induction of apoptosis might be its mechanism. In the diagnosis of gastric and colorectal cancer, a 40 KDa glycoside oligosaccharide structure glycoprotein was found to be a tumor associated antigen, its rapid ELISA kit showed positive rates in gastric, colonic and rectal cancer of 64%, 67.7% and 60%, respectively, and 41.4% in benign gastric diseases[20]. For detection of micrometastasis of bone marrow in patients with gastric cancer, an anti-epithelial cell membrane antibody examined in the marrow blood was performed by immunohistochemical staining and its positive rates were found to be correlated to the degree of cell differentiation, location of gastric cancer, the TNM staging and age of patients. The positive cells of the epithelial cell membrane antibody in the marrow blood were significantly higher than CEA positive cells ($P < 0.01$). The five year survival rate was much lower and the cause of death was mainly due to dissemination[21]. An experiment of estradiol in human gastric cancer cell lines showed the number of cells in various stages and proliferative indices increased and its stimulative effect could be inhibited by tamoxifen, which should be combined with chemotherapy in gastric cancer patients[22]. Furthermore, LAK cells when given together with anti-gastric cancer monoclonal antibody MGb2 increased the killing effect and the combined use of the two is more promising[23].

SMALL AND LARGE INTESTINE

Enteroclysis, angiography, radionuclide scanning and enteroscopy were used to diagnose gastrointestinal bleeding of obscure origin, confirmed by surgery and pathology. Among these, 70% were diagnosed solely by enteroclysis and leiomyoma was the most common finding, the nonspecific inflammation of the ileum and Meckel's diverticulum was the next, followed by angiodysplasia. Jejunal mucosal biopsy could be complementary in certain difficult to diagnose small intestinal lesions. Enteroclysis is also helpful to diagnose chronic idiopathic pseudo intestinal obstruction[24]. An experimental transplantation of human colonic tubular adenocarcinoma into BALB/C nu/nu mice was conducted, with five generations of transplanted mice showing xenograft cancer in each generation of nude mice manifesting the same ploidy status, DNA content (mostly aneuploid), distribution of estrogen and progesterone receptors and cell kinetics as human colorectal cancer[25]. Another study on the somatostatin level of carcinoma and precancerous tissue showed that the mean somatostatin level in well differentiated cancerous tissues was higher than that in poorly differentiated and that in distant mucosa (5.10 cm from the cancerous tissue) it was lower than that in the adjacent mucosal area (< 2 cm). This indicates that the somatostatin level is correlated to the differentiation of cancer and the presence of some sort of host defense reaction to delay its growth[26].

LIVER

The three main targets of research in hepatology are hepatitis C, hepatic fibrosis and hepatic cancer, mainly the aspects of pathogenesis and approaches in treatment. By immunohistochemical staining with monoclonal antibody of HCV-Ag (NS4) in patients with hepatitis C (acute, chronic and severe types), it was shown that HCV-Ag granules were distributed sporadically or in clusters in the cytoplasm of liver cells in acute and chronic hepatitis patients but was different in severe hepatitis. Cases with both seropositive HCV RNA and anti-HCV had HCV-Ag detected in contrast to cases with seropositive anti-HCV only. This shows that the expression of hepatic HCV-Ag is closely related to the presence of serum HCV RNA[27]. Cloning and sequencing of c-DNA of C33c protein gene in the NS 3 region of HCV from Shanghai and Jiangsu Province showed that the two isolates were homologous and this homology was higher than 99% at the nucleotide level. If compared with other isolates, the homology (94%-97.7%) at the amino acid level was much higher than the homology (81.4%-94.5%) at the nucleotide level. It suggests that C33c protein is suitable for diagnostic use[28]. In another study, the NS4 antigen of HCV in liver tissue from 9 patients treated with IFN-α was studied immunohistochemically using the LAB method of HCV NS4 McAb. The pattern of HCV-Ab staining was the same in pre and

post therapy liver specimens and less HCV-Ag positive cells were seen in those with a beneficial response to INF-α. This shows that the pattern of HCV-Ag staining and the histological activity index are more useful to predict and assess the therapeutic response to IFN-α than serum ALT and HCV RNA[29]. In a nationwide epidemiological survey of 67, 153 subjects, the infection rate of HCV was 3.2%, with about 40 million people infected. Analysis of HCV in Chinese patients showed most strains were Okamoto type Ⅱ and Ⅲ (Simmond type 1b and 2a) and only some strains were type Ⅰ (1a). Most of the strains in northern, western and southern China were type Ⅱ but in northwestern and northeastern areas, predominantly HCV strains were type Ⅲ. The difference of HCV genotypes was not correlated with clinical severity and course of illness. The histopathological characteristics of chronic hepatitis C and B were somewhat different with most HCV specimens showing mild to moderate hepatitis, steatosis 61% *vs* 29% ($P < 0.001$), bile duct damage 75% *vs* 29% ($P < 0.01$), lymphocyte aggregation/follicle 43% *vs* 21% ($P < 0.01$), increase of mononuclear cells in sinusoids 49% *vs* 27% ($P < 0.05$) and less frequent ground glass hepatocytes, 14% *vs* 53% ($P < 0.01$). The major ultrastructural changes were shown in the endoplasmic reticulum and mitochondria[30]. In another report, the pathological picture of hepatitis C in Chinese adult acute hepatitis patients was the same as in Westerners and steatosis was prominent despite mild necrosis and inflammation. Dense lymphoid aggregates and fibrosis in the portal tract were frequent, most cases exhibited cytoplasmic positivity in the form of diffuse or inclusion body. Electromicroscopy showed some intercellular and perisinusoidal fibrosis and the latter in the hepatic lobules and portal tracts was an indication of a trend toward chronicity. Significant pathological discrepancies were present between hepatitis C and B[31]. Regarding a treatment regimen, a randomized control study was carried out comparing 3Mu IFN-α 2α t.i.w. regimen for 6 mo and 6Mu IFN t.i.w. for 3 mo followed by 3Mu t.i.w. for another 3 mo. The complete response rate at the end of 6 mo was 67.6% and 62% respectively, and the clearance rate of serum HCV RNA was 71.4% and 72%, respectively. The normalization of serum ALT was also similar in the two groups (67.6% and 62.1%). The recommended dosage in most Chinese patients is 3Mu t.i.w. for 6 mo and for those with a poor response, an escalating dosage and prolonged schedule is necessary[30]. Until December 1992, there were 602 cases of hepatitis D coexisting with hepatitis B, with a seropositive HDAg marker in 6773 cases of hepatitis B, and the positive rate varied in different regions of the country, 1.73% and 37.5%, with an average of 8.89%. In 2797 hepatic specimens of hepatitis B, 223 were positive for HDAg, the average positive rate was 33%. A positive HDAg marker was most frequently seen in chronic hepatitis B with moderate activity[32].

Chronic hepatitis B treated with domestic recombinant human interferon alpha-1 was conducted in a randomized double blind sequential clinical trial of 225 cases in matched pairs. This domestic product is a medical engineering product. The serum HBeAg, HBV DNA and both HBeAg and HBV DNA were 40.5%, 57.1% and 39.3% in 37 pairs of the treated group and 57.6%, 64% and 45.3% in the extended treated group, compared with controlled group ($P < 0.01$). In the 6 mo follow up, the seronegative conversion rate of HBeAg and HBV DNA remained at 54% and 50.9%, respectively, and for 12 mo, they were 59.8% and 56.9%, respectively. The seropositive conversion rates of anti HBe were 29.7%, 2.7% and 33.3% in the 3 allocated groups. These demonstrated that the domestic product of recombinant human IFNα-1 at a dosage of 40 μg/d for three months has a similar effect as the Western product[33]. Another series of the therapeutic vaccine of viral hepatitis B was conducted in infected one day old ducklings as an animal model. The DHBs was complexed to anti DHBsAg and attached to staphylococcus aureus Conan 1 strain, then serum viral DNA was converted to negative in 60%-80% of treated ducks, DHBsAg was converted to negative in 40% and in some, anti DHBs could be detected. This is the result of complexing DHBsAg with anti DHBs which is immunogenic[34].

Hepatic fibrosis is another topic focused on with the consensus that the cirrhotic stage is irreversible and therapy should be aimed at the early stage of hepatic fibrosis as chronic hepatitis B and C are prevalent in this part of the world and alcoholic liver disease is rising.

Separation and cultivation of rat Ito cells was successfully established ten years ago in the Shanghai Institute of Digestive Disease. Collagen Ⅰ, Ⅲ, Ⅳ, Ⅴ and various components of extracellular matrix (ECM), such as fibronectin (FN), la minin (LN), undulin, integrin, hyaluronic acid (HA) *etc.*, were all evolved from Ito cells, playing an important role in hepatic fibrosis. Collagen Ⅲ is more abundant in early cirrhosis, whereas collagen Ⅰ is predominant in advanced cirrhosis. Expression of the HBV genome and its effect on the modulation of ECM was studied in Changzhen Hospital of the 2nd Military Medical University with fruitful results. Hormones such as insulin and glucagon and growth factors such as EGF and FGF all stimulate the growth of fibroblasts[35]. Many Chinese medicinal herbs with remarkable effectiveness, homologous to colchicine, have been developed to revolutionize treatment. Collagenolytic enzymes are being investigated at present and many medicinal herbs and herbal mixtures have been found to be effective in promoting the activity of matrix metalloproteinase. The intrahepatic deposition of collagen was found to have a corresponding increase of collagenase activity at the early stage of hepatic fibrosis and the increase of degradation paralleled the abnormal collagen synthesis by a feedback mechanism which led to the formation of the continuation of sinusoidal basement membrane, *i.e.* the capillarization of sinusoids, forming the pathological basis of progression to cirrhosis. The activities of lysosomal and microsomal enzymes such as β N-acetyl glucosamidase (β-NAG) and glycylproline dipetidyl aminopeptidase (GPDA) were also found to be increased significantly at the early stage of fibrosis. All this indicated that degradation of collagen metabolism was very active in the active stage of chronic hepatitis. P Ⅲ P, PC Ⅲ, HA, FN, LN, Collagen Ⅳ and Ⅵ are the principal markers used in certain medical centers in Shanghai. The 7S segment of collagen Ⅳ was found to be increased and paralleled with the increment of collagen Ⅳ mRNA, which is considered to be a better marker than P-Ⅲ-P in hepatic fibrosis[36]. On culture of lipocytes, IFN-γ and tocopherol were found to have an inhibitory action on ^{3}H hydroxyproline incorporation, whereas IL-2, IL-6 promoted proliferation of lipocytes and synthesis of collagen. Furthermore, IL-6 had a bidirectional effect, it increased expression of a2 macroglobulin to inhibit the collagenase activity and thereby the degradation of collagen. Tocopherol is a co-repressor enzyme and inhibits replication of lipocyte DNA and selectively inhibits the synthesis of collagen[37]. pHGF derived from fetal liver promoted the hepatocyte proliferation and has an anti-hepatic fibrosis effect, as seen by the reduction of hyaluronic acid. It also increases the immunological function of macrophages, T and NK cells activities and diminishes the peripheral blood mononuclear cells to produce TNF[38]. Tetrandrine had an inhibitory effect on ^{3}H-proline incorporation at a concentration of 10 μg/mL-50 μg/mL in an experimental study of DNA and collagen synthesis of 3T3 cells and was considered antifibrotic[39]. Another drug, cinnarizine was found to have the effect of blocking the G_1 phase cells of 3T3 fibroblasts from progressing to the S-phase and diminished the DNA content and mitosis, as demonstrated by flow cytometry[40]. Retinoic acid when co-cultured with 3T3 fibroblasts and Ito cells was shown to inhibit the procollagen Ⅲ mRNA expression at the same time, which was the mechanism of action of its antifibrogenic effect[41]. In the nutritional therapy for post-hepatic cirrhosis patients, a high calorie vegetarian diet can provide a daily intake of 2263 Kcal and 95 g protein with 2/3 of vegetarian origin. By a ^{15}N-glycine tracer kinetic study, 24 h urinary creatinine output increased, that of urea nitrogen decreased, serum albumin and transferrin increased and the body nitrogen balance became positive[42]. In portal hypertension, transjugular intrahepatic portosystemic stent shunts were performed in Beijing and Nanjing PLA General Hospital in over two hundred cases, with the rates of success of 92.2% and 94.5%, respectively, and the mortality rates of 0% and 5.5%, respectively. The velocity of portal blood flow increased, esophageal varices disappeared and only a few developed stenosis and occlusion of the shunt but angioplasty and stent reinstitution resulted in secondary patency. Hepatic failure and rebleeding were rare[43,44]. Recently, an experimental study was conducted on the role of nitric oxide in arterial vasodilatation of cirrhotic rats. It was believed that endogenous nitric oxide could increase mean arterial pressure, reduce peripheral vascular resistance and cardiac index, leading to hyperdynamic circulatory status, but correct treatment awaits further investigation[45].

With the advances of molecular biological technology and genetic effects, the study of molecular events in hepatocarcinogenesis is

rapidly progressing in China. In addition to the seven oncogenes, namely, N-ras, C-myc, c-ets2, IGF Ⅱ, IGF Ⅱ R, IGF Ⅰ R and CSF-Ⅰ R, activated in human hepatic cancer, Gu found that transthyretin was deleted in the gene structure and suppressed in mRNA expression in primary hepatic cancer. When it was transfected into human hepatoma cells, cell growth was retarded, indicating that this might be a novel candidate as a cancer suppressor gene for primary hepatoma[46]. Studies at the molecular level also included methylation of c-myc oncogene, expression of BCL-2 oncoprotein, the interacting site of hepatitis B virus X gene and tumor suppressor gene *p*53, alterations of *p*16 gene, expression of *IL-2* gene, expression of chimeric anti-HBx antibody, retroviral vector mediated gene, transfer of TNF gene, *p*53 mutational point dimorphism, ras and *p*53 gene mutation, *etc.*[47]. The precise pathogenesis is still not completely elucidated. More recently, the HBxAg gene has been suspected to link HBV infection and HCC, which might inhibit the function of tumor suppressor gene *p*53. Detection of the expression of HBxAg was shown by using anti recombinant HBV X protein antibody and an immunohistochemical method, LSAB. The HBxAg was localized primarily in the cytoplasm with some in the nucleus in cancerous and precancerous tissues in all 38 cases. Detection rate of HBsAg in cancer was even higher than HBsAg in both serum and cancerous tissue. This indicates that HBxAg is closely related to hepatic cancer and might be used as a carrier in targeted therapy in the future[48]. Also by immunohistochemical staining, the positive signals of HBsAg and HBcAg were observed in 10.9% (9/43) and 14.54% (8/55) of hepatic cancer cells, the latter appeared as fine brown granules in the cytoplasm and only one was in the pattern of the inclusion body. The relationship of HBcAg and HBsAg in the induction of hepatocellular carcinoma remains unknown[49]. HCV RNA by a non-radioactive in situ hybridization and immunohistochemical method could also be demonstrated in the cytoplasm, nucleus or both. HCAg molecules were found and expressed in both cytoplasmic and inclusion types. HCV infected cells, including hepatic cancer cells and hepatocytes, were in diffuse, clustered or discrete forms in both cancer and precancerous tissues[50]. In another study, in 102 liver cancer specimens by immunohistochemistry, HCV antigen C33c and HBxAg were found to be positive in 81.4% and 74.5%, respectively, both were positive in 61.8% and when added together, 94.1%. In the precancerous tissue of 50 cases, the aforementioned antigens were 63% and 92%, respectively. HCV C33c antigen was localized intra-cytoplasmically in cancer cells and distributed in focal or diffuse form, some were accessible to the nucleus and C33c antigen positive cells were scattered or focal in cancer cells and diffuse in precancerous tissue[51]. Expression of EGF and EGFR was found to be positive in noncancerous tissue and less were found in cancer tissue, indicating that during the cancerous process, with EGFR a loss of normal membranous structures[52]. EGFab, EGFR-McAb and somatostatin all exerted an inhibitory effect on the growth of hepatic cells. Somatostatin was shown to antagonize the growth stimulating effect of EGF and cause down regulation of EGFR[53].

Experimental gene therapy is best exemplified by introducing *IL-2* gene into the mouse hepatoma cell line by means of a retroviral vector. The transfected cells showed diminution of tumorigenicity when *IL-2* gene transfected cells were inactivated with mitomycin and inoculated several times, antitumor activity was apparent and growth of tumor nodules were retarded and more vulnerable to liquefaction and necrosis, which might open a new avenue to the treatment of hepatic carcinoma[54]. Another study of human *IL-2* gene transduced into a hepatoma cell line of mice by lipofectamine DNA complex showed IL-2 secreted by these cancer cells and necrosis at the tumor center and inflammatory cells infiltrating along the tumor border, which indicates that a direct transfer of *IL-2* gene into cancer cells produced an antitumor effect[55]. Expression of *p*53 and PCNA in hepatocellular carcinoma was found to have close relationship with portal vein tumor thrombogenesis. The PCNA labeled index was higher in positive than negative *p*53 expression. This indicates that *p*53 mutation may result in highly proliferative and invasive potentials which might be one of the mechanisms of genesis of portal vein tumor thrombus[56]. Regarding sensitivity and specificity, ten tumor markers were compared in the diagnosis of hepatoma. It was found that AFP-variant LCA reactive AFP, des-gamma carboxyprothrombin and GGT-Ⅱ were superior to α L-fucosidase, α-1-AT, ALP-Ⅱ, aldolase isoenzyme and acidic ferritin. The sensitivity of the aforementioned markers was 84.4%, 72.3% and 79.7% and their specificity was 89.4%, 97% and 96.4%. The sensitivity of serum pyruvate kinase M2, hepatic cancer specific protein and HAg 18.1 was 95.3%, 91.6% and 86.7%, respectively. The best screening procedures in the detection of primary hepatoma are AFP and ultrasound plus one of the three and this combination will cover AFP negative or low level of AFP patients to obtain an early diagnosis[57]. Serum soluble TNFR Ⅰ level in liver cancer patients was found to correlate well with staging of the disease and response to chemotherapy. The frequency of increase of sTNFR Ⅰ was 89.16%, greatly exceeding that of serum AFP (54.22%), and its determination could serve as a diagnostic aid in the detection of cancer and in the assessment of prognosis[58]. A high level of PC Ⅲ was also seen in patients with hepatic carcinoma, PC Ⅲ could be demonstrated within carcinoma cells by an immunofluorescence technique and carcinoma cells could produce PC Ⅲ directly, hence its high level might also be taken as a marker of hepatic carcinoma.

BILIARY SYSTEM

In a study of the phagocytic function of hepatic and pulmonary macrophages, 12 h after the onset of acute cholangitis caused by ^{14}C labeled living B. Coli, the phagocytic function of Kupffer cells decreased progressively and in contrast, the function of pulmonary alveolar macrophages increased continuously. The TNF secretion was increased in both cases. Another study on the effect of somatostatin on the sphincter of Oddi through endoscopic manometry found that somatostatin had significant inhibitory effect on the activity of the sphincter of Oddi and is beneficial to biliary and pancreatic flow. Epithelial tumor markers for extrahepatic bile ducts have been studied, 54.0% (22/42) were found to be positive for epithelial membrane antigen and 76.2% (32/42) positive for cytokeratin. The well differentiated adenocarcinoma had higher positive rate than the poorly differentiated. The two antigens were slightly more frequently present in precancerous than cancerous tissues but was lower in those with metastasis than those without. The absence of these markers in bile duct carcinoma signifies a poor prognosis. In another study using polyclonal antibody against C-erbB-2 protein by an immunohistochemical method, 26/41 cases of adenocarcinoma of the extrahepatic bile duct exhibited overexpression of C-erbB-2 on the cell membrane, indicating amplification of this gene in these cancers, and overexpression of this gene was also correlated with metastasis. Microvessels were found more abundantly by an immunohistochemical method of factor Ⅷ related antigen in poorly differentiated gallbladder carcinoma than in well differentiated ones and in those with metastasis than those without. This indicates angiogenesis in gallbladder carcinoma is related to the histological pattern, the degree of differentiation and presence of metastasis. Therapeutic endoscopy is now widely used all over the country and sphincterotomy, dilatation and stent placement for stenosis of bile duct have all been performed.

PANCREAS

In experimental acute hemorrhagic necrotizing pancreatitis, there was alteration of platelets and fibrinolytic function, the plasma granular membrane protein (GMP-140) and plasminogen activated inhibitor activity were found to be increased, platelet electrophoretic time much prolonged and tissue plasminogen activator activity much lower compared to sham operated dogs after induction of the disease. With treatment with Chinese herbal medicine tetramethylpyrazine, all the aforementioned alterations were absent, indicating that platelet activation and decreased fibrinolytic function play an important role in pancreatic microcirculatory disturbance and possible pancreatic microthrombosis. Tetramethylpyrazine has beneficial effects in correcting these disturbances, providing a therapeutic basis for its clinical use. Aside from the above, another herb, rhubarb (Da Huang) has been used in China for years in acute pancreatitis, including both the edematous and necrotizing forms, with great success before the advent of octreotide. In acute edematous pancreatitis, the cure rate is 100% and the time of the disappearance of abdominal pain, subsidence of fever and recovery of urinary amylase to normal were much shorter compared to the conventional Western therapy. In acute hemorrhagic necrotizing pancreatitis, rhubarb plus conventional

Western therapy without octreotide, atropine and gastrointestinal decompression resulted in the operative and mortality rates being much lower, 22.2% *vs* 66.6% and 3.3% *vs* 22.8%, respectively ($P < 0.01$). The mechanisms of the actions of rhubarb are: Inhibiting trypsin, pancreatic lipase, elastase, kininogens, *etc.*; a broad spectrum antibiotic action for both aerobes and anaerobes; increasing the level of SOD; inhibiting absorption of endotoxins; lowering the blood viscosity, elevating the osmotic pressure and decreasing TXB2, improving the ratio of TXB2/PGF-1α and pancreatic microcirculation; a hemostatic action; and in animal models, the intercellular tight junction and nuclear structure of the cells are restored to normal. Nowadays, we treat acute hemorrhagic necrotizing pancreatitis with either octreotide or a rhubarb mixture or both. This Chinese herbal medicine can also abolish intestinal paralysis and restore gastrointestinal tract function.

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