JSPS Asian CORE Program Seminar
-Helicobacter pylori infection and gastric cancer prevention -
Kobe University Graduate School of Medicine

Time & Date : 14:30-17:30pm, Friday, February 22, 2013
Venue: Shinryoku Hall, Kobe University School of Medicine

【 Program 】
◆ 14:30 – Introduction
-Takeshi Azuma, MD, PhD.
Professor, Department of Gastroenterology,
Kobe University Graduate School of Medicine

◆ 14:40 – Helicobacter pylori infection and gastric cancer in the eastern region of Shandong Province China
-Jing Xue
Department of Gastroenterology, The Affiliated hospital of medical college
Qingdao University

◆ 15:00 – Helicobacter pylori research: The Philippine experience
-Maria Cristina C. Africa, MD.
Institute of Digestive and Liver Disease, St. Luke’s Medical Center

◆ 15:20 – The development mechanism of gastric MALT lymphoma after Helicobacter suis infection
-Yang Lin, MD
Division of Gastroenterology, Department of Internal Medicine,
Kobe University Graduate School of Medicine

◆ 15:40-16:00 Break

◆ 16:00 – Omega-3 orchestrated Helicobacter pylori-induced gastric carcinogenesis
-Ki Baik Hahm, MD, PhD
Professor and Director, CHA University Medical School CHA Medical Center and CHA cancer prevention research Center

◆ 16:45 – Molecular epidemiology of Helicobacter pylori
-Yoshio Yamaoka, MD, PhD.
Professor, Department of Environmental and Preventive Medicine,
Oita University Faculty of Medicine Graduate School of Medicine

◆ 17:30 – Closing
-Takeshi Azuma, MD, PhD.
Helicobacter pylori infection and gastric cancer in the eastern region of Shandong Province China

Jing Xue, M.D.
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Gastric cancer (GC) remains one of the most common cancers worldwide. It is considered as the second leading cause of cancer-related mortality worldwide. The incidence and mortality of gastric cancer in China is high, but significant geographical variation in incidence exists. Especially, Linqu County of Shandong Province is one of the regions with highest incidence in northern Chinese population.

The report includes three parts:

First part: we evaluated Helicobacter pylori infection in Linqu County and perform an intervention study for blocking gastric precancerous lesions by eradicating H. pylori.

Eight years after eradicating H. pylori, compared with the control group, the incidence of gastric lesions more than severe CAG in treat group was significantly reduced, the regression proportion was increased, the progression proportion of gastric lesions was decreased and there had a tendency to reduce the incidence of gastric cancer.

Second part: The investigation of the current infection rate of H. pylori and the correlation study of virulent genotype of H. pylori and gastric cancer in Qingdao.

The current infection rate of H. pylori among people of Qingdao according to UBT was 49.4%. CagA, VacAsI/i1/m1, VacAsI/i1/m2 and iceA1 were dominant genotypes of bacterial strain of H. pylori in Eastern China. The existence of virulent genotypes of CagA, VacAs1, VacA1 and iceA1 had no correlation with the incidence of gastric cancer. Further studies were required to investigate the potential genes affecting the virulence of bacterial strains of East Asia.

Third part: Research on antibiotic resistance of H. pylori and efficacy analysis of rescue therapy in Qingdao.

In Qingdao, H. pylori was resistant to metronidazole, levofloxacin and clarithromycin, compared with traditional sequential therapy. The improved therapy of adding bismuth and replacing antibiotics with moxifloxacin was an efficient and safe scheme in improving the eradication ratio of H. pylori infection and can be used as rescue therapy after the failure of first-line therapy.

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Graduated from the Medical college of JiaMusi University in 2004 and received the M.D. degree from Jilin University in 2007 in China. Then, worked at the Affiliated hospital of medical college Qingdao University Speciality: H. pylori and Gastric cancer
The incidence of Helicobacter pylori infection in the Philippines has been reported to be high. However, there have been few published studies on the characterization and genotyping of local isolates of this pathogen.

H. pylori at St. Luke's Medical Center, Quezon City started in 1997, when a clinical trial on the efficacy of Lansoprazole containing dual and triple therapy in patients with duodenal ulcer associated with H. pylori was conducted in the hospital. This marked the establishment of the St. Luke’s H. pylori Study Group, in order to promote multidisciplinary research efforts on H. pylori. The group conducted several projects using molecular methods to characterize and genotype of H. pylori isolated from Filipino patients with gastroduodenal diseases, including establishing a culture collection.

For vacA, the most common genotype was s1a/m1, while the least common was s2/m2. cagA was detected in more than half of the isolates. Sequencing of some culture-positive cagA isolates revealed that these were mostly of the Western cagA type. Clarithromycin resistance was also documented in some isolates.

With regards treatment regimen, we follow the standard H. pylori eradication therapy of PPI + Amoxicillin + Clarithromycin or Metronidazole given for 10-14 days. Some patients have been given Levofoxacin instead of Clarithromycin or Metronidazole. Follow up with Urea Breath Test showed high eradication rate. Only a few resistant cases were reported and proper antibiotic regimen were given after culture and sensitivity tests were done.
The development mechanism of gastric MALT lymphoma after Helicobacter suis infection

Division of Gastroenterology,
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Lin Yang, Koji Yamamoto, Takeshi Azuma

Helicobacter (H.) suis, which belongs to the Helicobacter family just like H. pylori, is spiral-shaped gram-negative bacterium, and is found in the stomachs of various animals including cats, dogs, pigs, and humans. Long-term H. suis infection can induce gastric MALT lymphoma in 100% of mice, which is preceded by the formation and development of gastric lymphoid follicles. Recently, we revealed that H. suis derived from pigs could also colonize in the stomach of mice and induce the development of gastric lymphoid follicles with infiltrated immunocompetent cells. Peyer's patches (PPs) play an important role in the development of H. pylori-induced chronic gastritis. However, PPs were not essential for the formation of gastric lymphoid follicles induced by H. suis infection, suggesting the different pathogenic mechanism between H. suis and H. pylori.

In addition, the chemokine CXCL13 and Th1 cytokine IFN-γ were significantly up-regulated in the stomach of H. suis-infected mice compared with other chemokines and cytokines. CXCL13 is essential for the formation and maintenance of B lymphocyte follicles and Germinal centers (GCs) in PPs and lymph nodes. We showed that anti-CXCL13 antibody administration efficiently inhibited the formation of gastric lymphoid follicles after H. suis infection. The infiltration of various immunocompetent cells, the development of germinal center and the expression of lymphoid follicle formation associated genes were also effectively suppressed by anti-CXCL13 antibody treatment. These results indicated that CXCL13 was deeply involved in the development of gastric lymphoid follicles after H. suis infection.

On the other hand, at 3 months after H. suis infection, the formation of gastric lymphoid follicles was observed in IL-4-deficient mice similar as wild-type mice but not in IFN-γ-deficient mice, suggesting that the induction of IFN-γ was essential for the formation of gastric lymphoid follicles after H. suis infection. The expression of CXCL13 in H.suis-infected stomach was strongly induced in wild-type mice but not in IFN-γ-deficient mice. Recently it has been reported that recombinant IFN-γ significantly induced the activation of CXCL13 in immune-related cells. Therefore, we speculated that the up-regulation of IFN-γ after H. suis infection might evoke the formation of gastric lymphoid follicles via the induction of CXCL13.

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Helicobacter pylori (H. pylori) infection has been associated with diverse clinical entities beyond gastric cancer, in which perpetuating gastric inflammation and resulting cytotoxicity plays fundamental pathogenesis. In this Kobe symposium, the recent result that n3-polyunsaturated fatty acids (n3-PUFA) can prevent H. pylori-associated gastritis and cancer through attenuation of cytotoxicity will be introduced. n3-PUFA had been prescribed for diverse clinical conditions including IBD, cardiovascular diseases including atherosclerosis, and even general health promoting purpose as well as cancer prevention based on potent antioxidative and anti-inflammatory action. Although increasing levels of arachidonates (AA) and prostaglandins through COX-2 had been responsible for H. pylori-cytotoxicity and associated carcinogenesis, there is no clear result whether the n3-PUFAs rich in fish oils can be solving strategy to rescue H. pylori-cytotoxicity. Using fat-1 transgenic mice, which can generate n3-PUFA through genetic overexpression of 3-desaturase, the influence of n3-PUFA on H. pylori-cytotoxicity was investigated. At 16 weeks, the inflammatory cytokines as well as angiogenic factors were significantly increased in wild type littermates, whereas these changes were significantly attenuated in fat-1 transgenic mice and in 24 weeks, tumorous and nodular changes of stomach were noted in WT control mice, whereas no apparent changes were noted in fat-1 transgenic mice, Molecular changes relevant to H. pylori-cytotoxicity were significantly decreased in fat-1 transgenic mice, on the other hand, anti-inflammation and anti-apoptosis were significantly enhanced. Lipid rafts were responsible for these protections of fat-1 transgenic mice against H. pylori infection. Conclusively, the modulation of H. pylori cytotoxicity can be prime strategy to protect from H. pylori-associated cancer in high risk patients.

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Molecular epidemiology of Helicobacter pylori

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Helicobacter pylori infection is linked to various gastroduodenal diseases; however, only approximately 20% of infected individuals develop severe diseases. Despite the high prevalence of H. pylori infection in Africa and South Asia, the incidence of gastric cancer in these areas is much lower than in other countries. Such geographic differences in the pathology can be explained, at least in part, by the presence of different types of H. pylori virulence factors, especially cagA and vacA. The genotype of the virulence genes is also useful as a tool to track human migration utilizing the high genetic diversity and frequent recombination between different H. pylori strains. Multilocus sequence typing (MLST) analysis using 7 housekeeping genes can also help predict the history of human migrations. MLST analysis provides more detailed information on human migration than does the analysis of human genetics. Although approaches by MLST are effective, the method focuses on a small number of genes and may miss information conveyed by the rest of the genome. Genome-wide analyses using next generation sequencing technology, which can read DNA sequences in less time and at lower costs than Sanger sequencing, enabled us to efficiently investigate the evolution of H. pylori as well as to search the novel virulence factors of H. pylori. H. pylori infections are rapidly declining due to improvements in personal hygiene and quality of life. The molecular epidemiology of H. pylori infection should be studied before it disappears.

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