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World J Gastroentero, 2000; 6(3):440-441
World Journal of Gastroenterology
 ISSN 1007-9327

The effect of mast cell on the induction of Helicobacter pylori infection in Mongolian gerbils

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Subject headings diseases models, animal; Mongolian gerbils; *Helicobacter pylori*; mast cell; *Helicobacter* infections

Chi J,Lu M,Fu BY, Nakajima S, Hattori T. The effect of mast cell on the induction of Helicobacter pylori infection in Mongolian gerbils. ***World J Gastroentero***, 2000;6(3):440-441

INTRODUCTION

Since 1982, Helicobacter pylori (Hp) has been successfully isolated and cult ured[1], and the fact many diseases such as gastritis, peptic ulcer, gas tric carcinoma and gastric lymphoma were related to *Hp*, and *Hp* as an etiological organism, has attracted much attention. In 1991 Yokata *et al*[2] first induced the *Hp* infection in Mongolian gerbils. From then on researches on *Hp* infection and its eradication exploded worldwide.Nakajima *et al*[3] reported that mast cells were increased in gastric mucosa and submucosa of patients with *Hp* infection and found degranulated mast cells in these tissues. Now it is known that high affinity IgE and Fc segment receptors exist on the mast cell surface. When IgE bound to these receptors, mast cells degranulated and then many kinds of bioactive mediators were secreted so that the inflammatory process could be effected. Therefore it is extremely important to understand the relationship between degranulation of mast cells in the mucosa infected with *Hp* and the inflammatory response, and to conjecture of the effect of mast cells on the pathogenesis of *Hp* infection. This study observed the inflammation of gastric mucosa and the morphology, density, distribution and degranulation of mast cells in the infected gerbils using the histochemical or immunohistochemical methods and electron microscopy to elucidate the effect of mast cells on the pathogenesis of *Hp* infection.

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Received 2000-01-16 **Accepted** 2000-02-28

MATERIALS AND METHODS

Animals

Thirteen male Mongolian gerbils infected with *Hp* for 1mo to 3 mos were allocated to the experimental group, while 5 male Mongolian gerbils with out *Hp* infection to the control group.

The induction of animal models

Six-week-old specific pathogen-free/sea male Mongolian gerbils and *Hp* ATCC 43504 were used. The gerbils were subjected to ATCC 43504 and ethanol treatment according to the method described by Hirayama *et al*[4]. Normal subjects were treated with the same amount of Brucella Broth. The gerbils infected with *Hp* were injected with BrdU subcutaneously one hour before sacrifice. A portion of the stomach was fixed in MFAA[5] and embedded in paraffin, and cut in sequential 3 μm-4 μm section for light microscopy; the remainder was fixed in 25 g/L Glutaldehyde ,serially dehydrated in ethanol, postfixed in 10 g/L osmi um acid, embedded in Epon, and cut in 60 nm ultrathin sections for electron microscopy.

Staining of mast cells

Alcian blue (AB1.0)/ PAS staining The immunohistochemical staining of anti-mast cell monoclonal antibody, MSRM4 (produced by Moredum Scientific Iimited Co. Britain, diluted 200 folds) by LsAB method was applied.

Double-staining AB staining was followed by anti-Brdu Ab and anti-CD3 lymphatic Ab complex staining to observe the cellular marking rate of mast cells in S-phase and their relationship with T lymphocytes.

Staining for electron microscopy with uranyl acetate and lead citrate

Bactericidal treatment Positive group was defined at 6 mos after *Hp* infection and then was cured with triad treatment (Lansoprazole, Ampicillin, Clarithromycin) for 2 wks continuously. At wk 4, wk 8 and wk 12 after withdrawl of medication, the gerbils were sacrificed to observe the changes in distribution, amount and degranulation of mast cells before and after bactericidal treatment.

Counting of mast cells At the magnification employed (× 400), the positive mast cells in the mucosa and the epithelial layer in gastric antrum and body in 5 consecutive areas were counted and

their mean values represented the density of positive cells in this particular area. All the data according to different areas were divided into different groups for further statistic treatment and analysis compared with the normal subjects.

RESULTS

Light microscopy

Mast cells appeared blue stained with AB/ PAS and brown when immunohistochemic al staining was used. Positive mast cells, filled with granules in cytoplasm, dispersed in epithelium, lamina propria and submucosa and also commonly in muscular layer, having a close relationship with the vessels and nerves in submucosa and muscular layer. All of the above picture rarely appeared in the gastric tissues of normal gerbils. At 2 wk after *Hp* infection, the mast cells began to increase in amount with a tendency of inflammatory-dependence, significantly different from the normal group ($P<0.001$). On the double staining section, there existed varied amounts of blue heterophilic granules in the cytoplasm and the nucleus was brown. The mast cells with these morphologic characteristics corresponded to the cells in S-phase. The increase of cells in S-phase signified the active hyperplasia in the progression of inflammation. The double staining of CD3 and mast cells indicated that a great deal of mast cells were around the lymphatic follicles in which CD3 existed. The amount of mast cells decreased 1 mo after bactericidal treatment and recovered to the normal level 3 mos after treatment.

Electron microscopy

Under the normal circumstances, the specific high-electron density granules in cells were stable and existed independently, while in inflammatory state the mast cells were activated to degranulate and form vacuoles and tended to be vacuolated after the fusion of vacuoles.

DISCUSSION

It is well known that mast cells exist widely in trachea, digestive tract, skin and many other organs and play an important role in the pathogenesis of allergic reaction characterized by bronchial asthma and urticaria. Recent studies on mast cells found direct or indirect evidences to reveal the close relationship between the mast cells and the injury of gastric mucosa[6]. The mast cells located in human gastroenteral tract and induced by pathogen or some antigens, may secrete bioactive substances such as histamine and prostaglandin, which increase the secretion of gastric acid, and then trigger a series of events: the injury of tissues and the inflammation of mucosa. The rapid development in recent years on the cell culture and molecular biology provides the possibility of explaining that various cytokines can cause the activation and proliferation of mast cells and mast cells can produce and secrete these cytokines. TNFα, GMCSF, IL-6 an d IL-x can act as the precursor in the local inflammatory reaction which leads to the infiltration of inflammatory cells, and at the same time modulates the development and proliferation of themselves-the autoregulative process. The results of this study showed that the mast cells in gastric mucosa with infection of *Hp* increased significantly, the infiltration of lymphatic cells depended on the appearance of mast cells and the conspicuous increase of degranulation of mast cells in inflammatory areas was related to the degree of gastritis. All of the above supported the fact that mast cells play a role in the occurrence and development of the pathogenecity of *Hp*. It has been reported that some of the mast cells have the function of extending and movement so that the mast cells can penetrate the basal membrane and move toward the interepithelial space. During the moving process, degranulation appears gradually, which results in the phenomena of vacuolation. Therefore, some researchers believe that mast cells of mucosa-type are the active state of mast cells of conjugated-type. At present, the mechanis m of the degranulation of mast cells remains unclear. The relationship between m ast cells and *Hp* infection and the effect of the mediator secreted by mast c ells on the pathophysiology of *Hp* infected gastric diseases need further in vestigation.

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