Models for gastric cancer in mice

INTRODUCTION:

While incidences of stomach cancer have decreased over the past several decades, the disease remains an important public health problem. A variety of experimental animal models have been established in order to recognize pathological and molecular biochemical mechanisms (Tetsuya Tsukamoto, 2007).

As a result, experimental efforts have focused on identifying chemical, infectious or genetic means to induce gastric cancer in animals (Yoku Hayakawa, 2013).

Still, most inbred strains of mice have proven resistant to gastric carcinogenesis. Mice have a different gastric anatomy compared to humans, in mice the gastric fundus equivalent is lined by squamous, rather than oxyntic glandular epithelium, the squamocolumnar junction does not normally estimated the gastroesophageal junction as it does in normal human anatomy.

By the discovery of H. pylori, studies showing a strong association with gastric cancer (Songhua Zhang, 2012).

To set up useful models which imitate human gastric cancer phenotypes, investigators have utilized animals infected with Helicobacter species and treated with carcinogens, including mice. Mice are the animal model of choice for cancer research, Because of the ability to control their genome (Yoku Hayakawa, 2013).

Though the most concern has been in mouse models, only a limited number of H. pylori strains have been known that effectively colonize in the mouse stomach. The most useful models to date have been H. pylori SS1-infected mice, and H. felis firstly isolated from the stomach of cats and dogs. Both of these gastric Helicobacters are able of long-term colonization and have the ability to influence chronic gastritis and precancerous lesions in mice. Chronic H. felis infection has been shown to induce severe inflammation, atrophy, metaplasia, dysplasia and gastric cancer in C57BL/6 mice.

However, despite the important advances made utilizing diverse mouse models, these models have all shown some limitations, including modest gastric pathology, slow time course, and the absence of invasive or metastatic tumors (Yoku Hayakawa, 2013)

Mouse models

Although there is no particular model that is the best for all applications, on the basis of cost and accessibility of immunological reagents and genome in order, the mouse is incontestably the most well-situated and suitable today. It is significant to note that the morphology of the gastric neoplasia in mice is similar to but not identical to that in human. C57BL/6 mice—this strain has been widely studied for investigating Helicobacter pylori’s role in gastric carcinogenesis, due in part to the many genetically engineered knockouts available on this background. (Songhua Zhang, 2012).

Helicobacter Infection Models

As Helicobacter pylori (H. pylori) is now recognized as a most important risk factor for chronic gastritis and stomach cancer, the function of Helicobacter pylori infection in the etiology and pathogenesis of gastric cancer, pursued researchers to the development of animal models of gastric Helicobacter infection. (Songhua Zhang, 2012) (Yoku Hayakawa, 2013).

The variety of H. pylori strain is essential for establishing the infection in a mouse model. A choice of H. pylori strains gave special outcome in different strains of mice. (Xin Wang)

Along with H. pylori mouse adapted strains reported up to know, the Sydney strain of H. pylori (SS1) has been the best characterized and most functional in murine model systems.

While the H. pylori SS1 strain was primarily reported to have an whole Cag-PAI, the SS1 strain used in following studies does not appear to express CagA, which may be clarify the limited virulence of SS1 in mice. Systemic expression of CagA in transgenic mice has led to the development of gastrointestinal and hematological malignancies. Amusingly, the C57BL/6 strain in particular is proved to be astonishingly resistant to colonization with various H. pylori strains. C57BL/6 mice infected with SS1 and fed a high-salt diet developed more obvious gastric atrophy and foveolar hyperplasia. H. pylori eradication has been shown to markedly decrease stomach cancer incidence in C57BL/6 mice. (Yoku Hayakawa, 2013)

Chemical Carcinogenesis Models of Gastric Cancer

Gender

Mouse models of Helicobacter infection have been used to study the role of other co-factors in gastric carcinogenesis, such as sexual category, diet, and co-infection. Gender may be important, since gastric cancer is much more common in men compared to women. Some studies of Helicobacter infection in mice point to those female C57BL/6 mice are more at risk to gastric disease. (Yoku Hayakawa, 2013)

Diet

High salt diets, and diets wealthy in nitrates and nitrites, have been linked with an increased gastric cancer risk.

Treatment with N-nitroso compounds, such as MNU, prior to H. pylori infection caused more severe preneoplastic changes and improved gastric cancer.

To explore the mechanisms of gastric cancer progress and found a useful animal model of gastric tumorigenesis, investigators examined the efficacy of a variety of chemical carcinogens. They explored the function of N-methyl-N-nitrosourea (MNU) as a gastric carcinogen in mouse models. The efficiency of tumor generation by MNU was found to depend on its concentration rather than total intake, and MNU in the drinking water at 240 ppm on alternate weeks (total exposure; 5 weeks) was effective in inducing gastric cancer in 6 strains of mice that were studied. MNU-induced tumors in mice are located mainly in the gastric antrum, and pathologically are uniformly well- or moderately-differentiated adenocarcinomas. The tumors are loaded in stromal cells, and occasionally attack into the submucosa. Synergy between N-methyl-N-Nitrosourea (MNU) or N-methyl-N’-nitro-N-nitrosoguanidine

(MNNG) and H. pylori has been revealed to increased gastric tumor rate in Mongolian gerbils and in mice. (Yoku Hayakawa2013)

Conclusions

The expansion of murine and Mongolian gerbil models to investigate the effects of Helicobacter infection has allowed investigators to examine the worth of host factors, environmental factors and bacterial strain virulence in the outcome of gastric diseases. These rodent models are also being explored to expand new therapeutic strategies against H. pylori infection and accordingly bound the related diseases. Concern of the host, the Helicobacter strain and environmental microbial and chemical co-factors are all significant for best translation of these results to the clinic.

In fact, H. pylori infection has only been shown to be connected with preneoplastic or neoplastic disease in mouse strains with a predisposition to gastric cancer.

Cag A

Gastric intestinal metaplasia (IM) and gastric cancer are connected with Helicobacter pylori, but the bacterium often is untraceable in these lesions. To unravel this detectable disagreement, IM, H. pylori presence, and the expression of H. pylori virulence genes were quantified parallel using histologic testing, in situ hybridization, and immunohistochemistry. H. pylori was detected inside metaplastic, dysplastic, and neoplastic epithelial cells, and cagA and babA2 expression was co localized. (Cristina Semino-Mora2003)

The virulence factor that has received the most attention is the cytotoxin-associated gene A (cagA), which encodes the CagA protein and is occupied in the increased risk of PUD. CagA is a 120-145 kDa protein with a carboxy terminal variable region. Length polymorphism observed at the 3’ end of cagA gene of H. pylori, which results in variation in the number of phosphorylation sites of the encoded protein (CagA), is of immense notice in recent times since higher number of phosphorylation sites in CagA was described to be associated with stronger biological function and disease symptom. Cag A is translocated into the host cell, where it is phosphorylated, binds to SHP-2 tyrosine phosphatase, leading to cytokine production by the host cell, phosphorylation-dependent cytoskeletal rearrangement, and transcriptional activation of host’s targets. The cellular effects of CagA may explain why patients infected with CagA+ strains usually have a higher inflammatory response and production of pro-inflammatory cytokines. (A. K. Mukhopadhyay)

Since the various host and bacterial factors that find out the final outcome of H. pylori infection are known to vary in unlike populations, researcher suggest that the direct determination of cagA transcription in situ provides a quantity of the combined effect of these factors together.

FISH method is highly specific for H. pylori 16S rRNA as it uses a probe (biotin-labeled 5′- TACCTCT CCCACACTCT AGAATAGTAGT TTCAAATGC-3′) that is 100% homologous with over 150 H. pylori strains published in the GenBank database. The FISH cagA probe (5′-CTG CAA AAG ATT GTT TGG CAG A-3′-NH2 digoxigenin labeled) 20 completely matched the cagA sequence of 128 H. pylori strains published in the GenBank database, with only one

mismatch between the probe and the cagA sequence of 34 additional strains. (James R. Rick, 2010)