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IL-8 СВЯЗЫВАЕТ ПУТИ NF-κB и Wnt/β-КАТЕНИН ПРИ ПЕРСИСТЕНТНОМ ВОСПАЛИТЕЛЬНОМ ОТВЕТЕ, ВЫЗВАННОМ ХРОНИЧЕСКОЙ ИНФЕКЦИЕЙ *Helicobacter pylori*[1]

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Инфекция *Helicobacter pylori* (*H. pylori*) иногда вызывает стойкий воспалительный ответ в эпителиальных клетках слизистой оболочки желудка человека, что может приводить к возникновению рака. Однако основной механизм канцерогенеза пока не выяснен. Нами разработаны модели хронической инфекции *H. pylori* в клетках GES-1 и на мышах C57BL/6J. Для определения уровня интерлейкина-8 (IL-8) использовали иммуноферментный анализ. Экспрессию мРНК и белков NF-κB p65, IL-8, Wnt2 и β-катенина определяли методами ПЦР в режиме реального времени, иммуноблотинга, иммунофлуоресцентного окрашивания и иммуногистохимии. Инфекцию *H. pylori* у мышей оценивали с помощью экспресс-теста на уреазу, окрашивания гематоксилином–эозином и серебрения по Вартину–Старри. Исследование морфологических изменений в слизистой оболочке желудка проводили методом электронной микроскопии. Выявлено, что в клетках слизистой оболочки желудка, инфицированных *H. pylori*, наряду с активацией сигнального пути NF-κB и повышением концентрации IL-8, значимо повышалась экспрессия Wnt2. На основании этих результатов можно предполагать, что IL-8 позитивно регулирует экспрессию гена *Wnt2*. При исследовании хронической инфекции *H. pylori* на модели мышей C57BL/6J показано, что у экспериментальных животных повышена частота предраковых поражений в ткани слизистой оболочки желудка. При сравнении ультраструктурных изменений в клетках слизистой оболочки желудка и анализе взаимосвязи между сигнальным путем NF-κB и экспрессией Wnt2 обнаружено, что инфекция *H. pylori* активирует сигнальные пути NF-κB, а массивное высвобождение IL-8 положительно коррелирует с высокой экспрессией белка Wnt2. Как следствие, активация сигнального пути Wnt/β-catenin может быть вовлечена в злокачественную трансформацию клеток слизистой оболочки желудка. Таким образом, хроническая инфекция *H. pylori* может приводить к персистентному воспалительному ответу: активировать путь NF-κB, способствовать высвобождению IL-8 и тем самым активировать путь Wnt/β-catenin. IL-8, по-видимому, играет роль линкера в сцеплении этих двух сигнальных путей.

Ключевые слова: *Helicobacter pylori*, интерлейкин-8, Wnt2, NF-κB, сигнальные пути, воспаление, рак желудка

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IL-8 Links NF-κB and Wnt/β-Catenin Pathways in Persistent Inflammatory Response Induced by Chronic *Helicobacter pylori* Infection

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Helicobacter pylori (*H. pylori*) infection can cause persistent inflammatory response in human gastric mucosal epithelial cells, which may result in the occurrence of cancer. However, the underlying mechanism of carcinogenesis has not been elucidated yet. Herein, we established the models of chronic *H. pylori* infection in GES-1 cells and C57BL/6J mice. Interleukin 8 (IL-8) level was detected by ELISA. The expression of NF-κB p65, IL-8, Wnt2 and β-catenin mRNA and proteins was evaluated by real-time PCR, Western blotting, immunofluorescence staining, and immunohistochemistry. The infection of *H. pylori* in mice was evaluated by rapid urease test, H&E staining and Warthin–Starry silver staining. The morphological changes of gastric mucosa were observed by electron microscopy. Our results showed that in *H. pylori* infected gastric mucosal cells along with activation of NF-κB signaling pathway and increase of IL-8 level, the expression of Wnt2 was

also increased significantly, which preliminarily indicates that IL-8 can positively regulate the expression of *Wnt2*. Studies in chronic *H. pylori* infected C57BL/6J mice models showed that there was an increased incidence of premalignant lesions in the gastric mucosa tissue. Through comparing changes of gastric mucosal cell ultrastructure and analyzing the relationship between NF-κB signaling pathway and Wnt2 expression, we found that *H. pylori* infection activated NF-κB signal pathways, and the massive release of IL-8 was positively correlated with the high expression of Wnt2 protein. Subsequently, the activated Wnt/β-catenin signal pathways may be involved in the malignant transformation of gastric mucosal cells. Collectively, *H. pylori* chronic infection may continuously lead to persistent inflammatory response: activate NF-κB pathway, promote IL-8 release and thereby activate Wnt/β-catenin pathway. IL-8 probably plays an important role of a linker in coupling these two signal pathways.

Keywords: *Helicobacter pylori*, interleukin 8, Wnt2, NF-κB, signaling pathway, inflammation, gastric cancer