




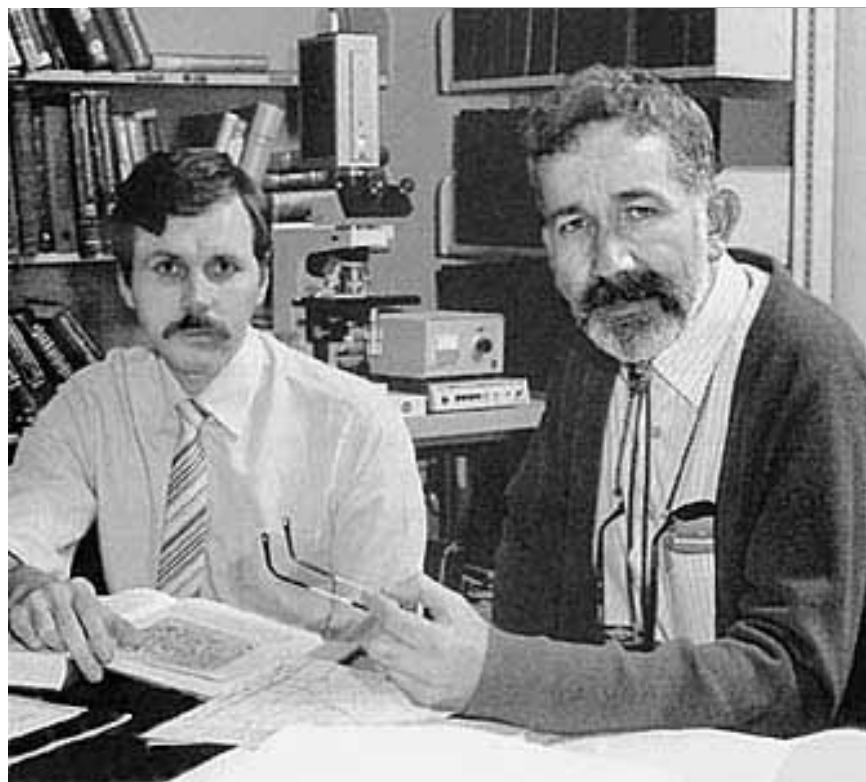
ХЕЛИКОБАКТЕРИОЗЫ

СПбГУ
2015г.



**Хеликобактериоз –
хроническая инфекция,
вызываемая *Helicobacter
pylori* и отличающаяся
преимущественной
локализацией возбудителя на
слизистой ЖКТ и 12-перстной
КИШКИ.**

Б.Маршалл (слева) и Р.Уоррен (1984)



2005г. Нобелевская премия по медицине

Helicobacter pylori (*helix* - спираль, *bacter* – палочка, *pylorus* - привратник желудка, перекрывающий проход из желудка в двенадцатиперстную кишку).

Название заболевания	Частота выделения <i>Helicobacter pylori</i> , %
Гастрит А	20
Гастрит В	80
Язвенная болезнь желудка	70-100
Язвенная болезнь 12-перстной кишки	100
Неязвенная диспепсия желудка	45
Рак желудка	84

Helicobacter pylori and cancer

Figure 7.1: Stomach cancer age-standardised incidence per 100,000 population



Особенности строения и функционирования желудка

Отсутствие пищи



- Поступление пищевого комка в желудок
- Расслабление дна и тела желудка

Наполнение пищей



- Сокращение дна желудка (частота 0,31 сокращений в минуту)
- Продвижение содержимого в дистальную часть желудка

Эвакуация пищи



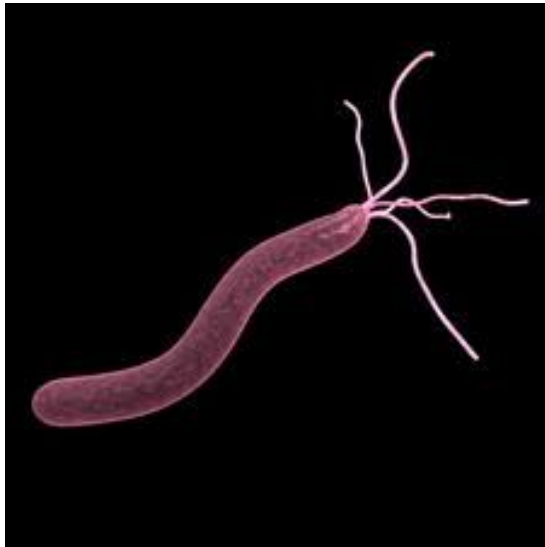
- Перемешивание, измельчение и эвакуация пищи
- Координация-синхронизация перистальтики желудка с открытием пилорического сфинктера

Сем. *Helicobacteraceae*

р. *Helicobacter* состоит из 24 видов,
патогенны для человека :

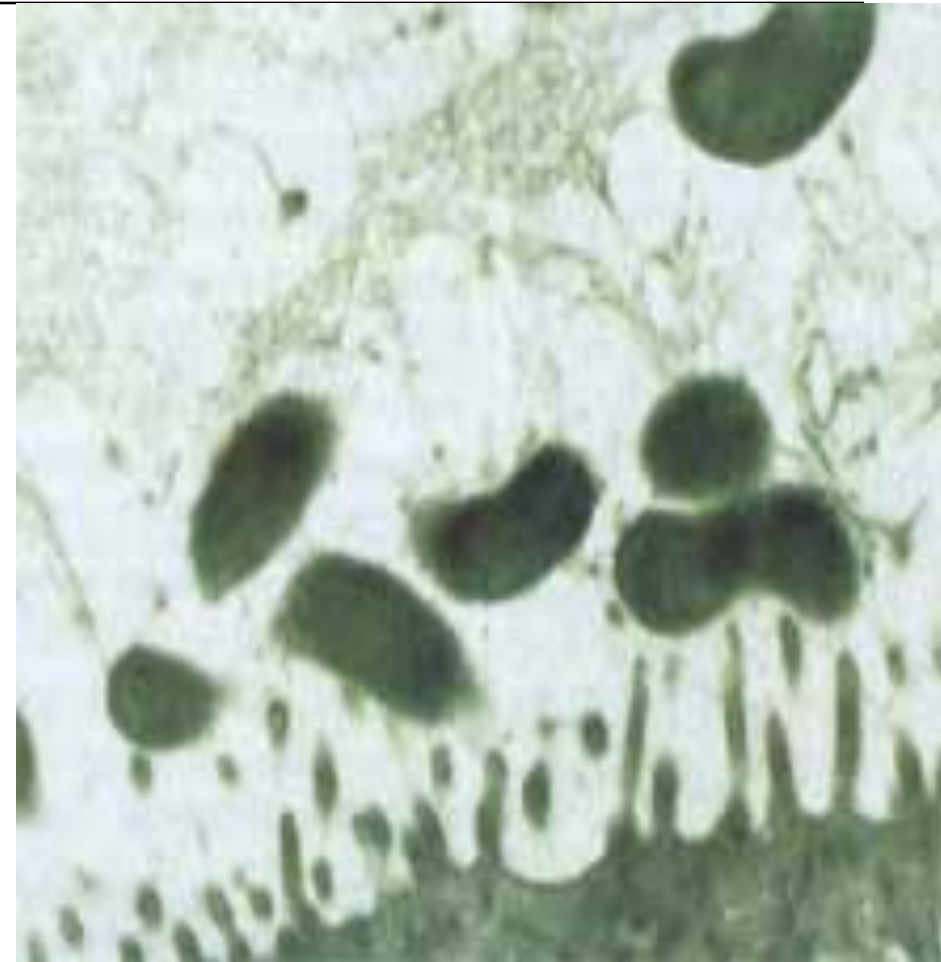
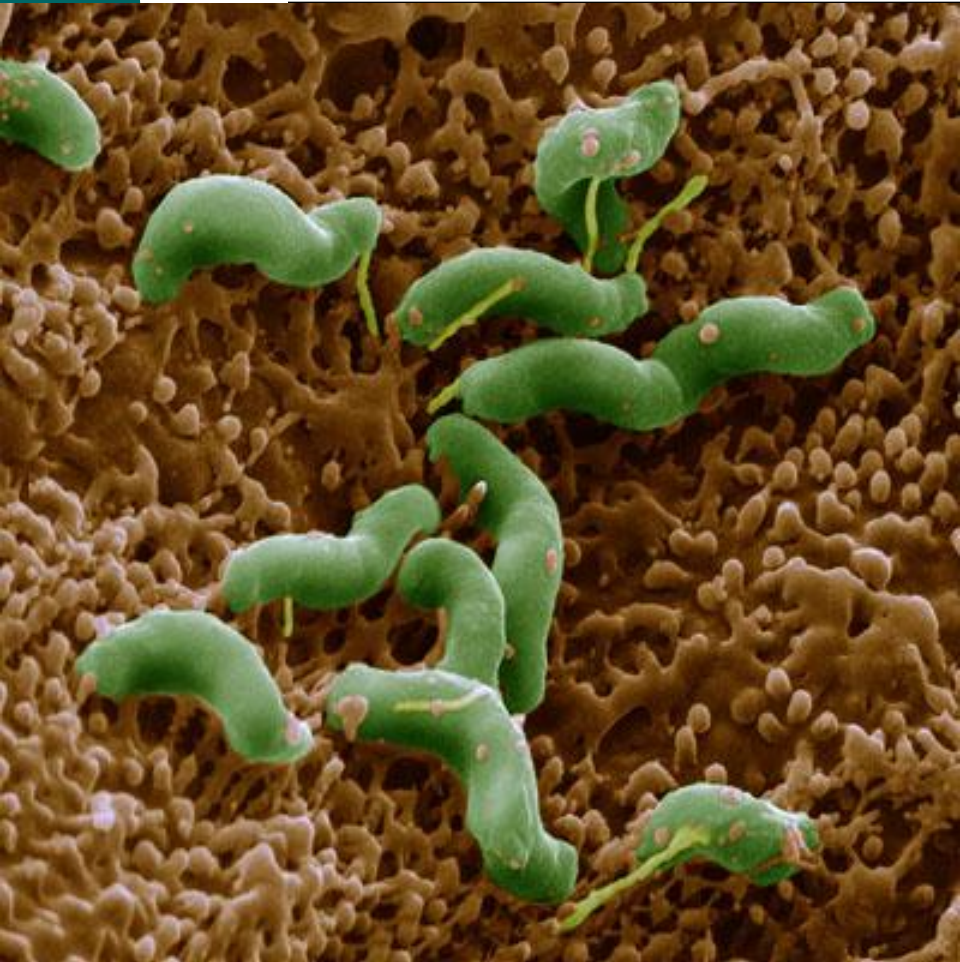
- *Helicobacter heilmannii* – вызывает гастрит
- *Helicobacter pylori* – гастрит, язва
- *Helicobacter cinaedi* - энтерит, септицимия
- *Helicobacter fennelliae* - энтерит, септицимия
- *Helicobacter rappini* - энтерит, септицимия
- *Helicobacter bilis* – роль не ясна

Морфология *Helicobacter pylori*



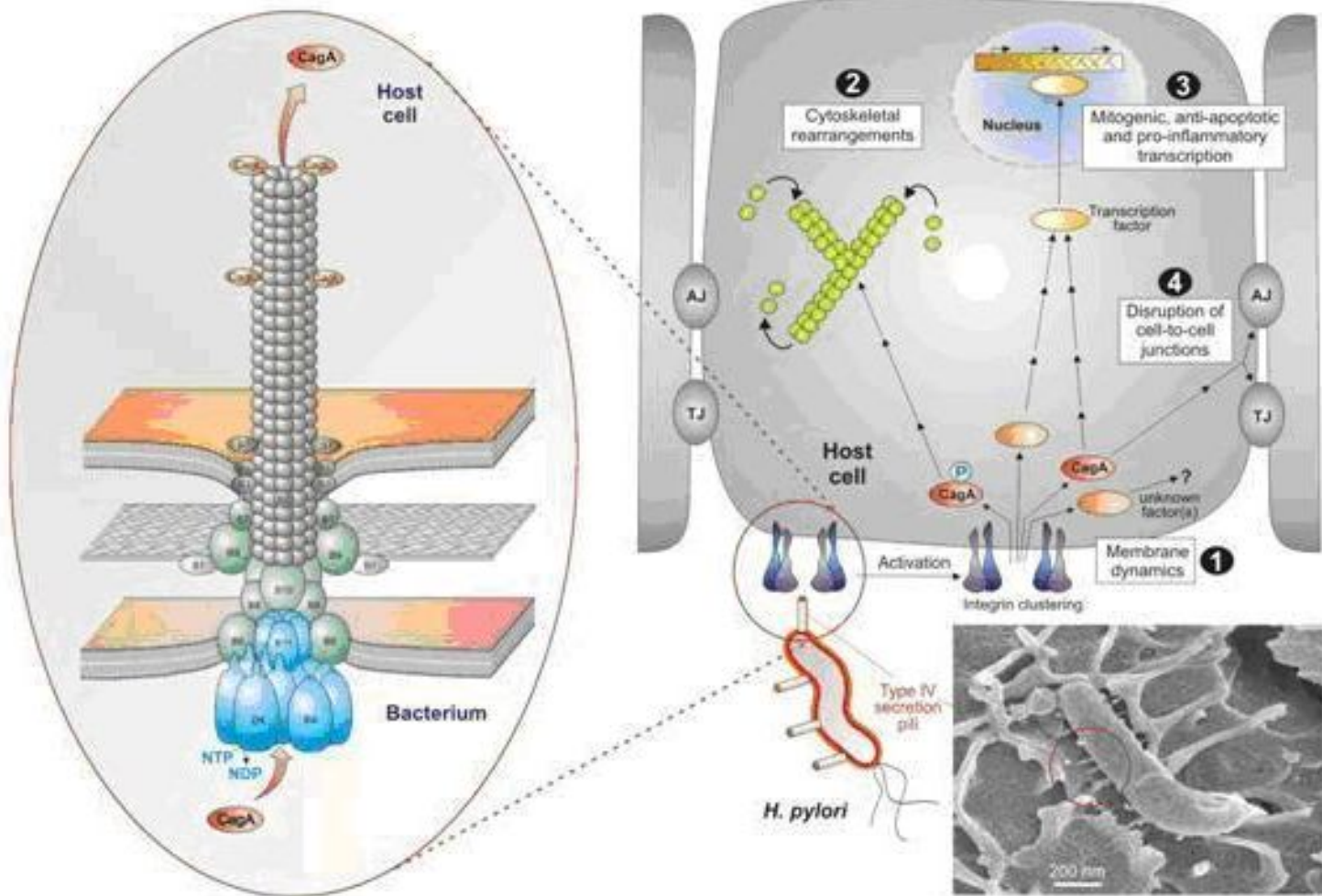
Электронная микроскопия

Колонизация *Helicobacter pylori* на слизистой желудка



Культуральные свойства

- Микроаэрофилы (менее 5% O₂)
- pH 4-7
- Каталаза –
- Оксидаза +
- Не окисляет и не ферментирует сахара
- Окисляет органические кислоты



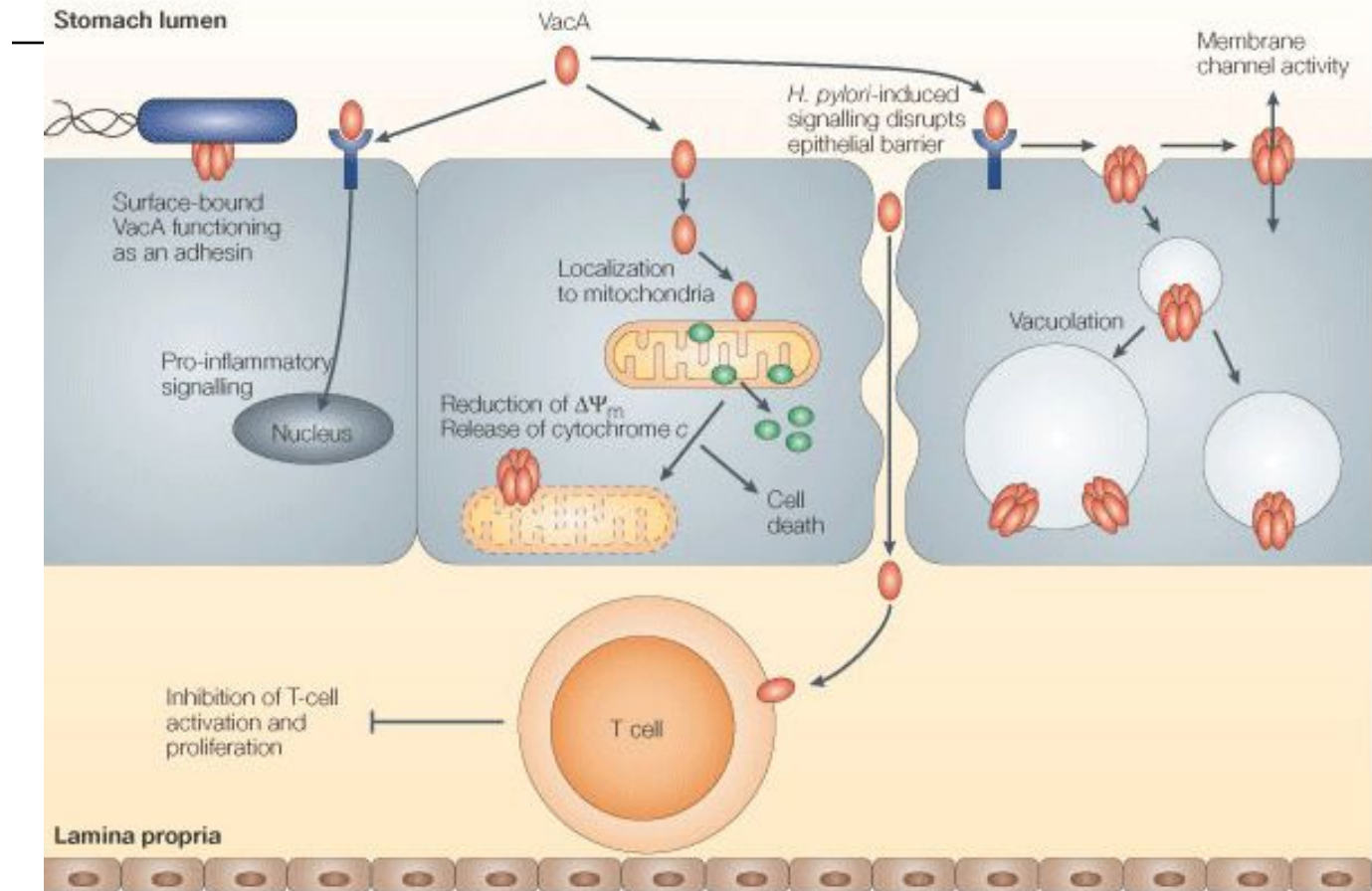
Model for the assembled type IV secretion machinery and its role in *Helicobacter pylori*-induced cell signalling

(image courtesy of Prof. Steffen Backert, SBBS)

Факторы патогенности *Helicobacter pylori*



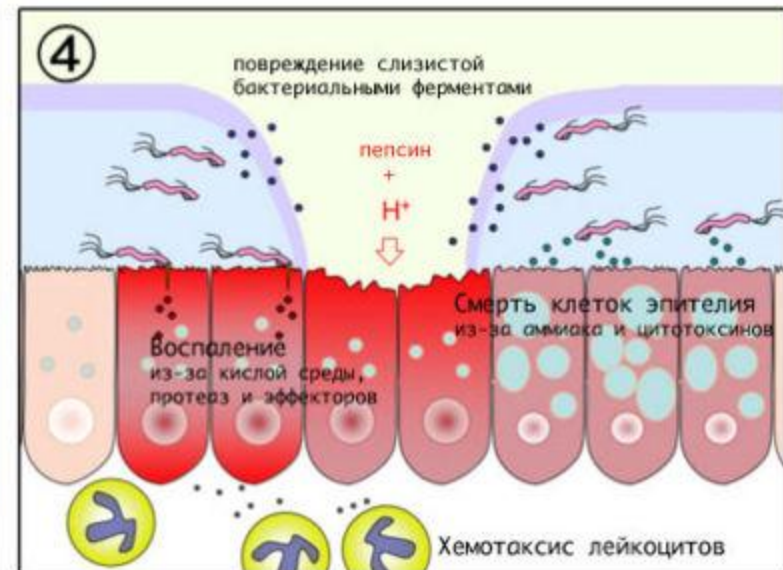
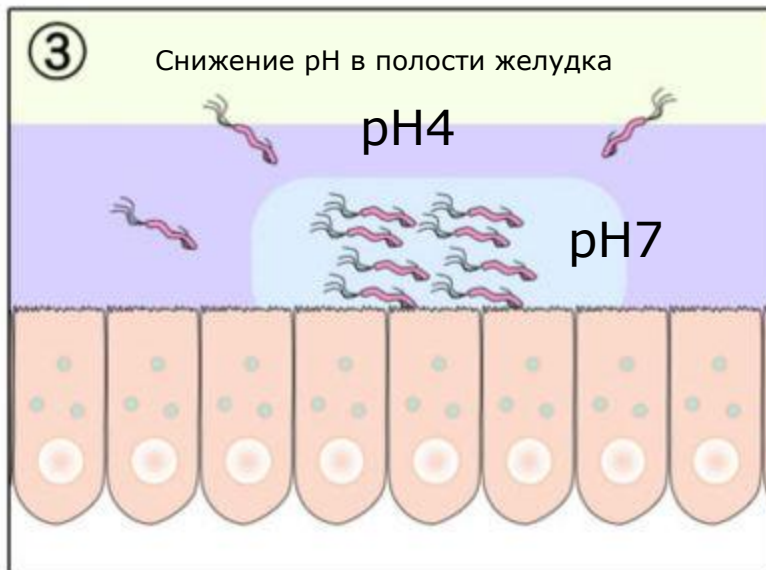
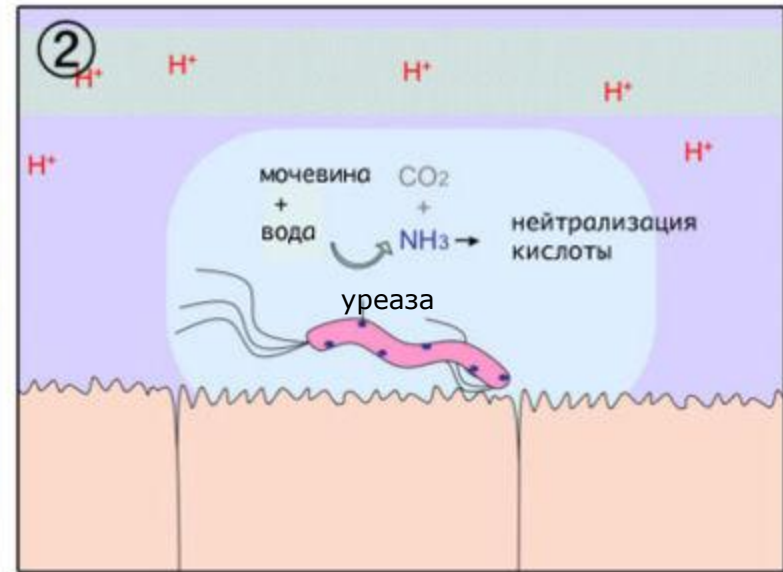
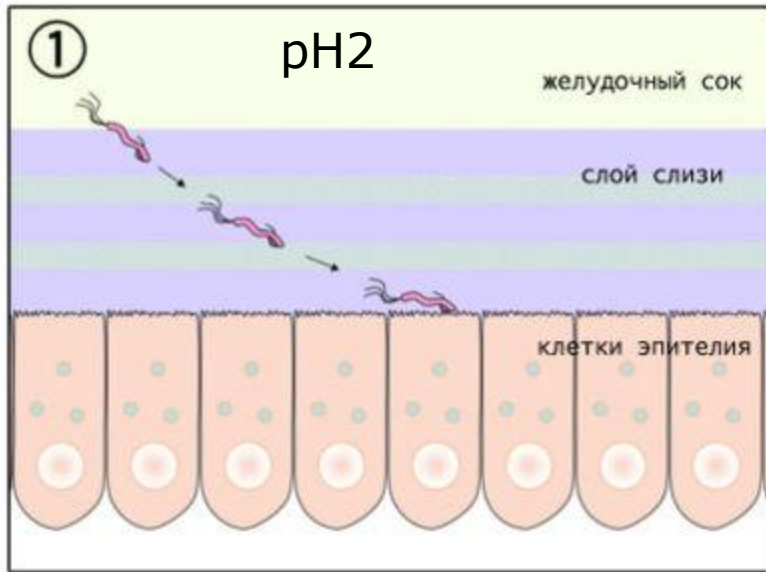
Механизм действия экзотоксина VacA



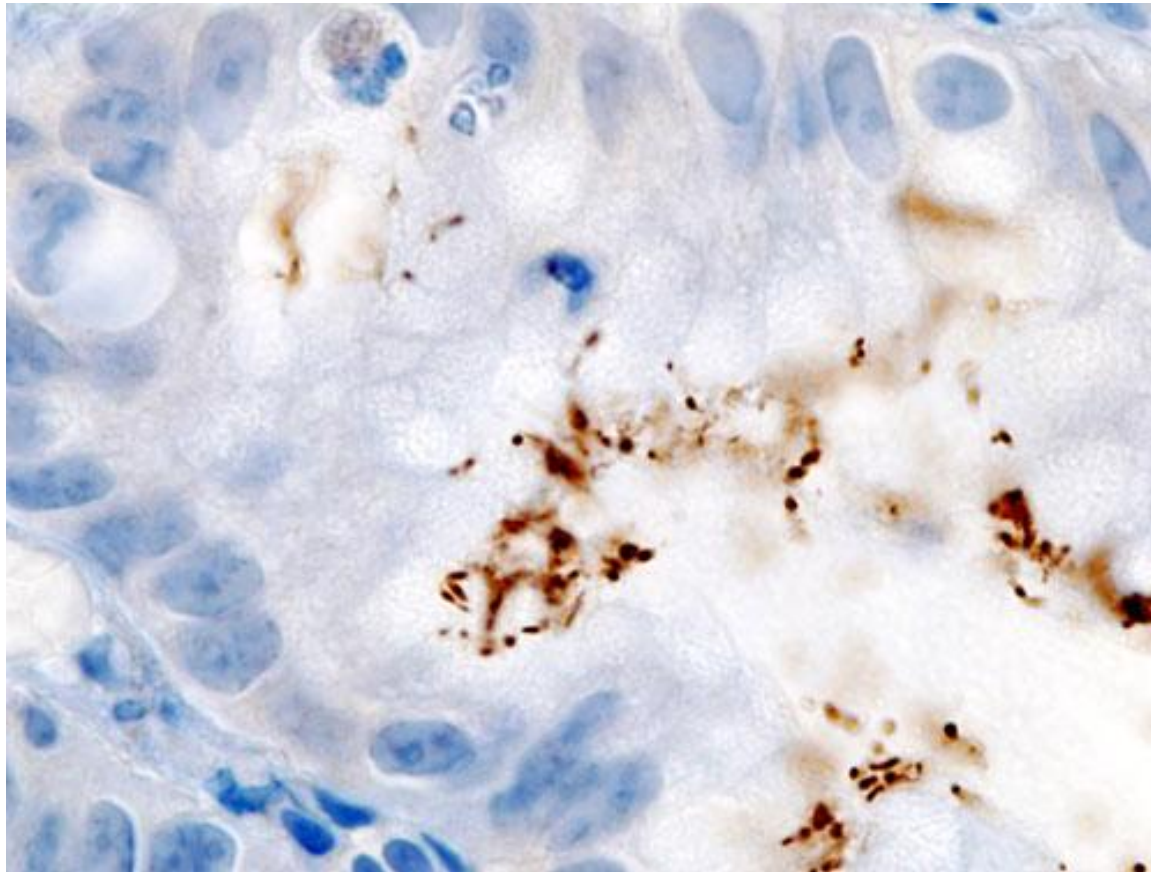
Nature Reviews | Microbiology

Effects of VacA on gastric epithelial cells include alterations in mitochondrial membrane permeability and apoptosis, stimulation of pro-inflammatory signalling, increased permeability of the plasma membrane and alterations in endocytic compartments. Multiple *H. pylori* factors, including CagA, disrupt the gastric epithelial barrier and might thereby facilitate passage of VacA through the epithelial layer^{148, 149}. Within the lamina propria, VacA interferes with the activation and proliferation of T lymphocytes. Many of these effects of VacA are attributable to the formation of VacA membrane channels. $\Delta\Psi_m$ indicates mitochondrial transmembrane potential.

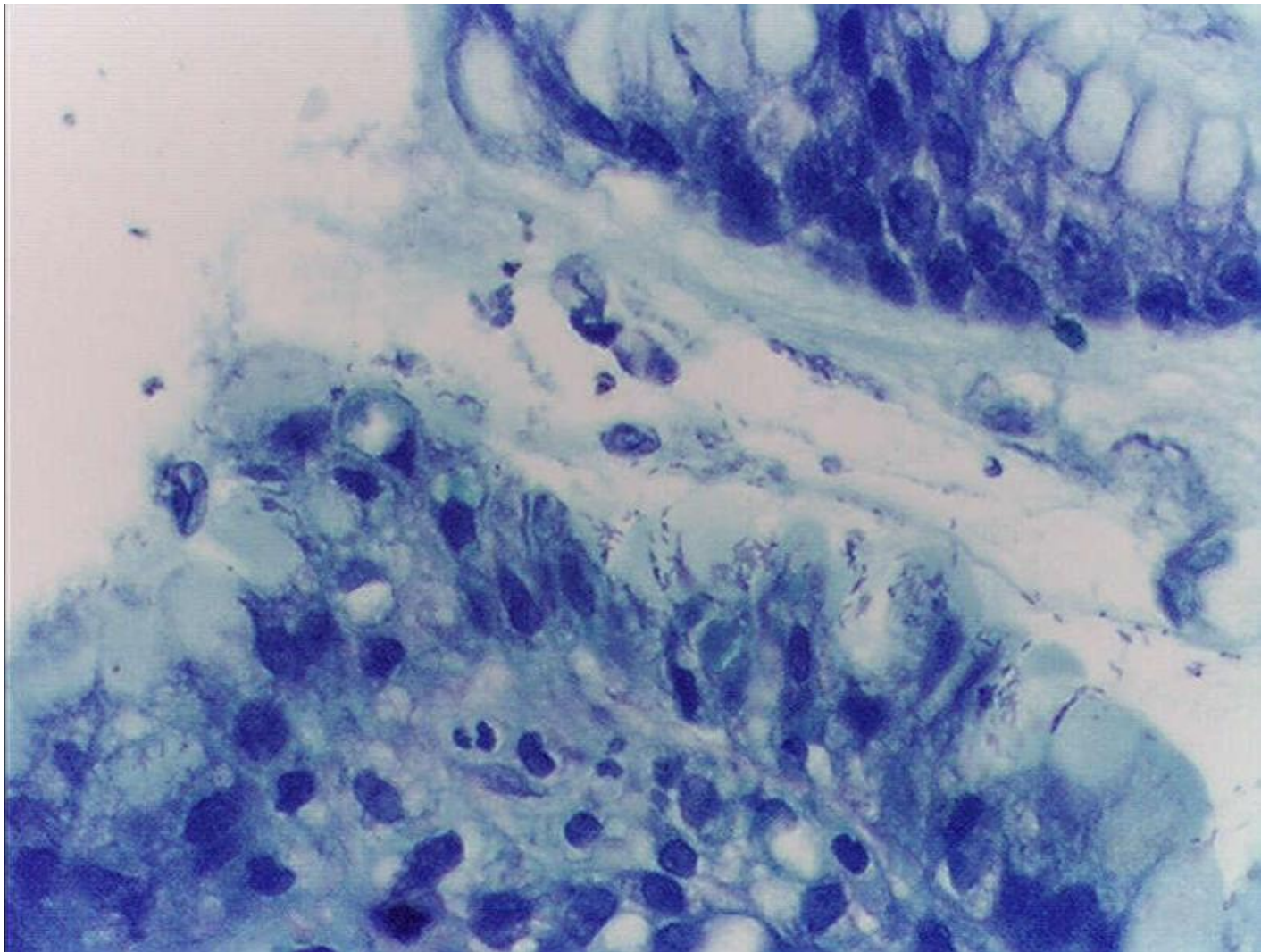
Патогенез *Helicobacter pylori*



Иммуногистохимическая окраска *H. pylori* в биоптате слизистой желудка

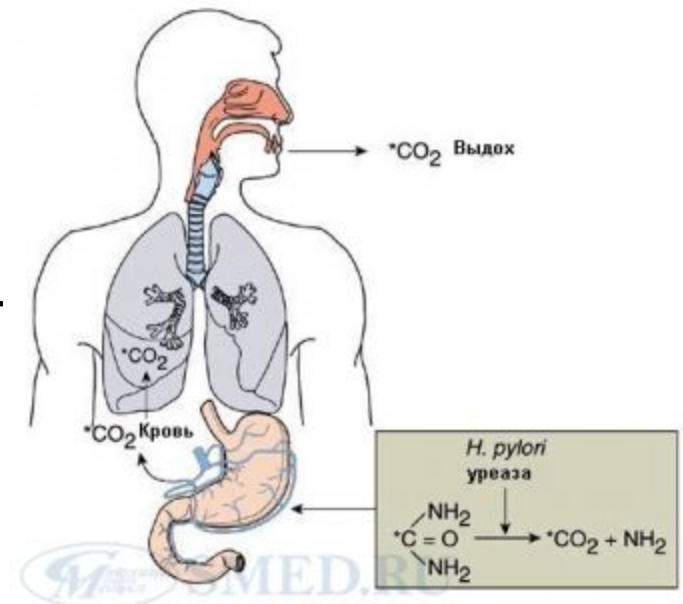


H. pylori в слизистой желудка.
Окраска по Романовскому-Гимзе.

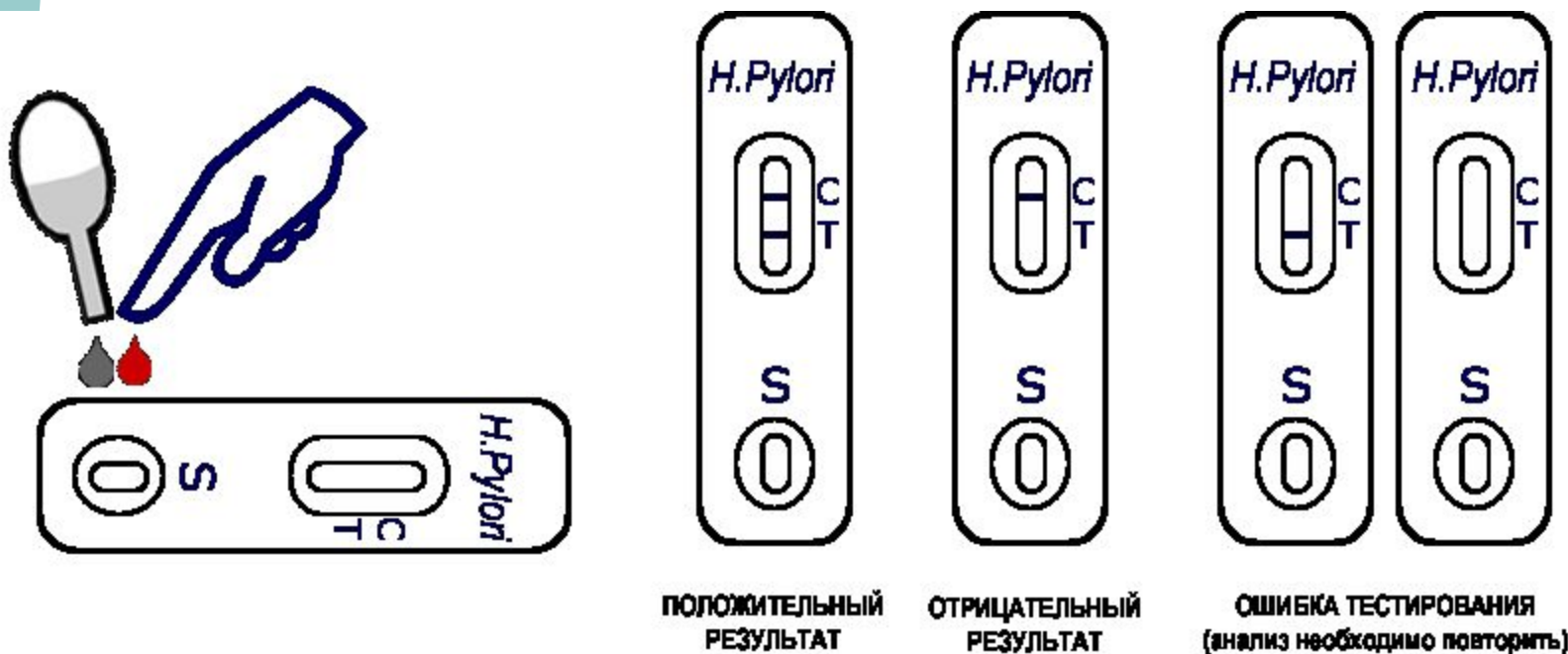


Лабораторная диагностика

- Инвазивные методы:
 - Микроскопия нативного материала
 - Бактериологический метод
 - ИФА
 - ПЦР
 - Гистология
 - Уреазный тест
- Неинвазивные методы:
 - Уреазный дыхательный тест



Набора реагентов «КреативМП – H.Pylori» для выявления антител к Helicobacter Pylori иммунохроматографическим экспресс-методом



Набор реагентов «КреативМП-H.Pylori» для выявления Helicobacter Pylori иммунохроматографическим экспресс-методом ТУ 9398-002-83178876-2010 предназначен для качественного одноэтапного быстрого выявления всех изоформ (IgG, IgM, IgA) антител к Helicobacter Pylori в сыворотке, плазме или цельной крови человека. Набор предназначен для использования в клинической практике, а также для самостоятельного использования потребителем

Прибор BreathMAT PLUS
для определения инфицированности
организма человека бактериями
Helicobacter pylori

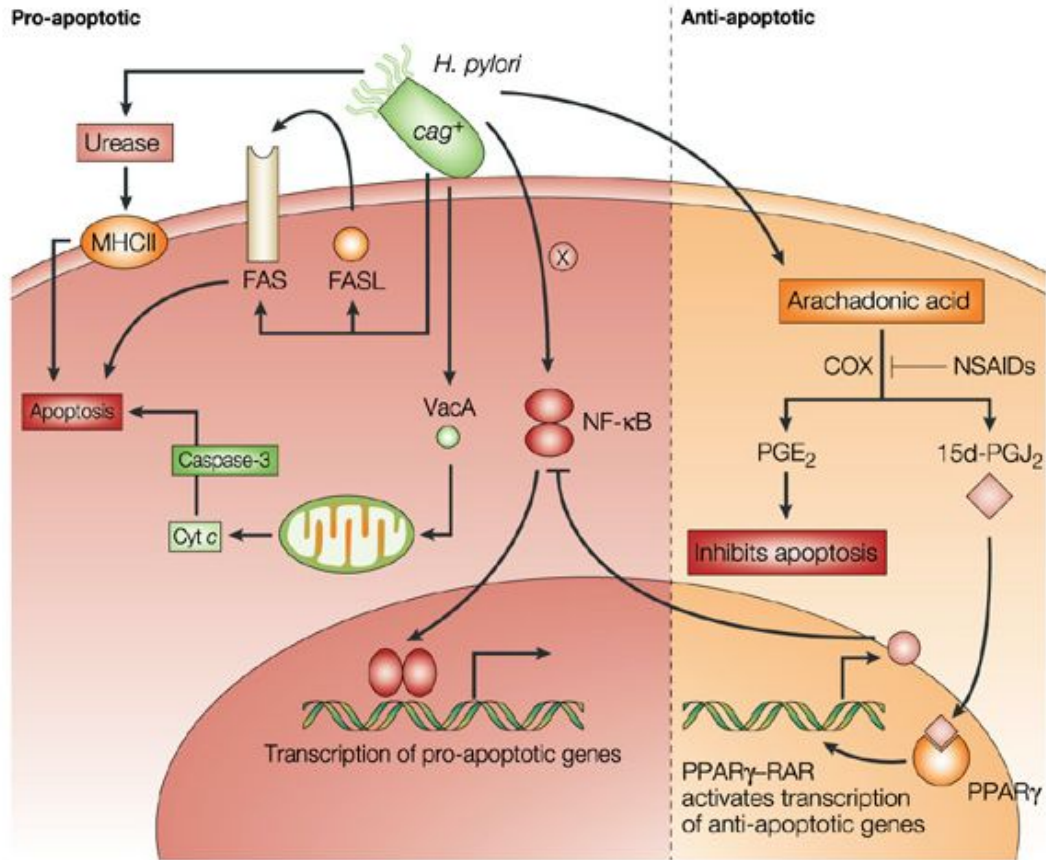


Лечение хеликобактериозов

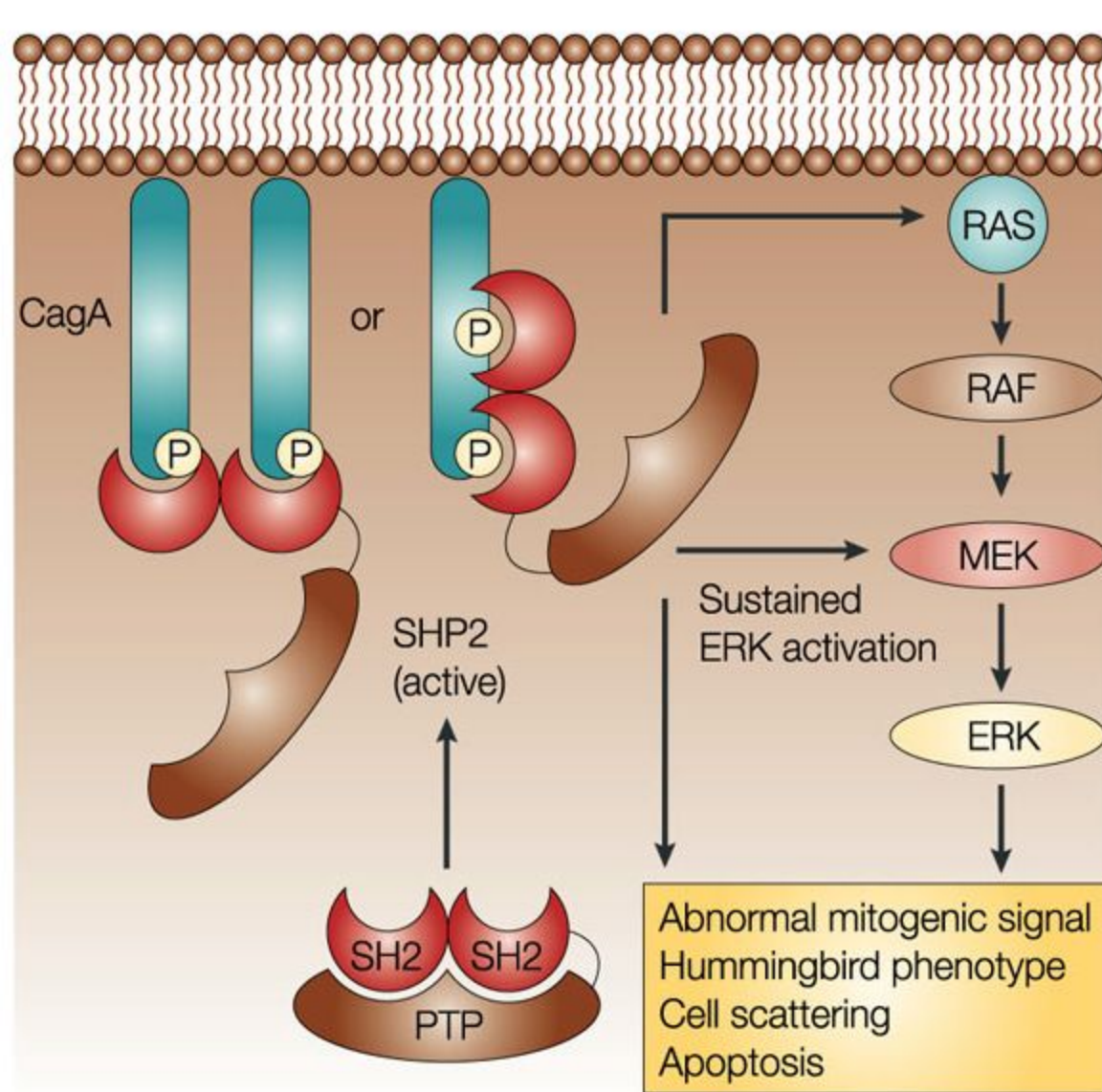
- **Антибиотики:** амоксициллин, кларитромицин, азитромицин, метронидазол, тинидазол, тетрациклин, фуразолидон.
- **Препараты висмута** – лечение язвы и гастрита

Доказана связь развития заболеваний из-за отсутствия в организме *Helicobacter pylori*

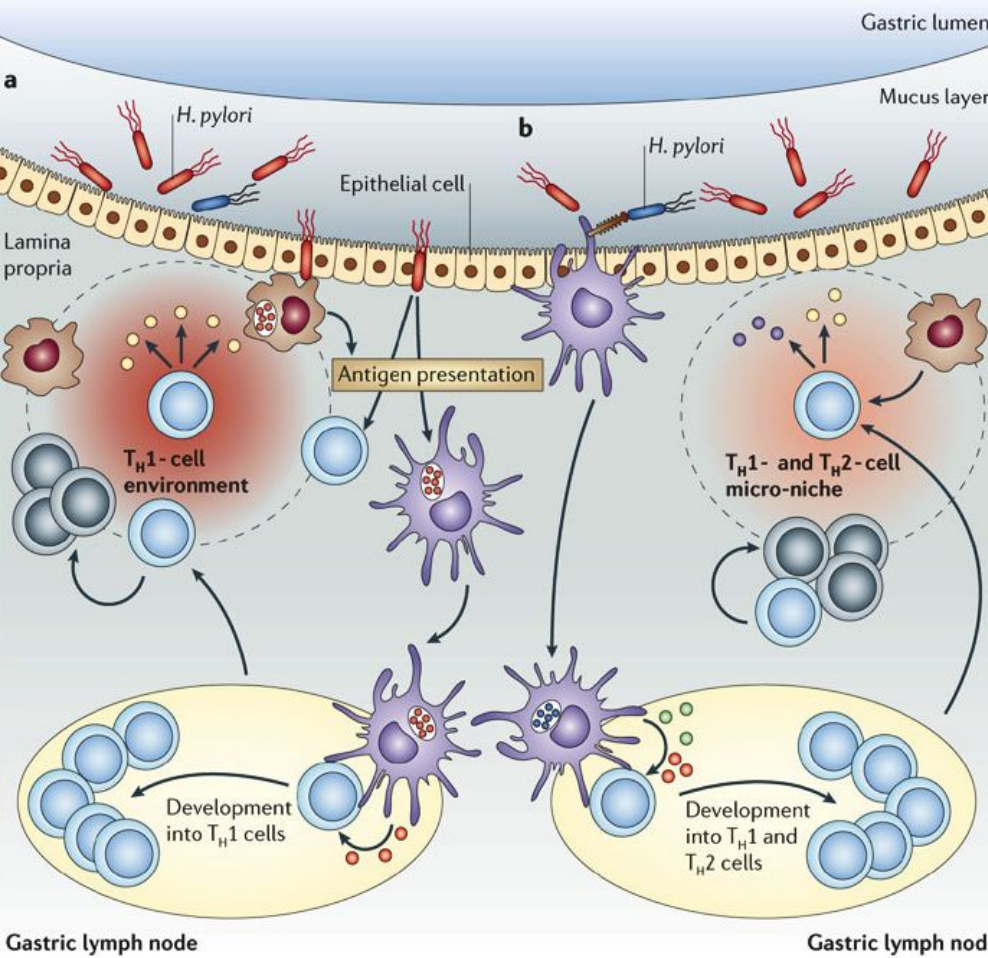
- нарушения энергетического гомеостаза (ожирение)
- бронхиальная астма
- аллергический ринит
- атопический дерматит
- сахарный диабет
- -системная иммуномодулирующую активность *H.pylori*



H. pylori can regulate gastric epithelial apoptosis through several mechanisms. Following adherence, signalling by the cag secretion system (but not CagA per se) leads to activation of an unknown factor(s) X that leads to activation of nuclear factor- κ B (NF- κ B). NF- κ B translocates to the nucleus to activate transcription of pro-apoptotic genes. *H. pylori* can also induce apoptosis by stimulating expression of FAS and its ligand (FASL). The *H. pylori* vacA gene product causes mitochondrial release of cytochrome c (cyt c), which leads to activation of caspase-3 and apoptosis. *H. pylori* also activates pathways that downregulate apoptosis. *H. pylori* binding to the epithelial-cell surface generates arachadonic acid, which is metabolized to prostaglandin E₂ (PGE₂) and prostaglandin 15-deoxy12,14-J₂ (15d-PGJ₂) by cyclooxygenase (COX) enzymes. These enzymes are inhibited by non-steroidal anti-inflammatory drugs (NSAIDs). 15d-PGJ₂ is an endogenous ligand of peroxisome proliferator-activated receptor- γ (PPAR γ), a nuclear hormone receptor that heterodimerizes with the retinoid (RAR) family of nuclear receptors to activate transcription of target genes. These gene products inhibit NF- κ B activation, however, preventing apoptosis. The COX-generated metabolite PGE₂ also attenuates apoptosis. So, *H. pylori* has the capacity to stimulate and inhibit gastric epithelial-cell apoptosis, which might influence the risk of gastric carcinogenesis.



Cytotoxin-associated antigen A (CagA) is phosphorylated by SRC, which allows it to specifically interact with the SRC-homology 2 (SH2) domains of the protein tyrosine phosphatase (PTP) SHP2. This interaction induces SHP2 to undergo a conformational change, which stimulates its phosphatase activity. Activated SHP2 can induce extracellular signal-regulated kinase (ERK) signalling through RAS-dependent and -independent mechanisms. Sustained deregulation of this pathway eventually leads to apoptosis in gastric epithelial cells. MEK, mitogen-activated protein kinase/ERK kinase.



a | In susceptible hosts, *Helicobacter pylori* colonizes the stomach and induces upregulation of expression of MHC class II molecules and co-stimulatory molecules by epithelial cells, facilitating the presentation of *H. pylori* antigens by epithelial cells to gastric mucosal T cells^{84, 85}, which are mainly of the T helper 1 (TH1)-cell type (for further details, see main text). In addition, *H. pylori* antigens are presented by professional antigen-presenting cells such as macrophages and dendritic cells (DCs), which might acquire antigens as a result of epithelial-cell turnover.

Development of *H. pylori*-associated peptic-ulcer disease is associated with the chronic predominance of effector TH1 cells in the gastric mucosa³⁵. b | In infected patients with asymptomatic chronic gastritis, *H. pylori*-specific T cells are mainly of the TH0-cell type, which secrete both interferon- (IFN-) and interleukin-4 (IL-4). This indicates that most infected people switch from an acute gastric *H. pylori*-specific response that is mediated by TH1 cells to a response that is mediated by TH1 and TH2 cells³⁶. The mechanisms that are involved in the switch from a TH1-cell response to a TH1- and TH2-cell response are unknown at present, but *H. pylori* phase variants that bind DC-SIGN to suppress the development of TH cells into TH1 cells, through IL-10 (Ref. 39), might facilitate this switch and be selected for by the host. DC-SIGN-binding variants of *H. pylori* (blue) are selectively bound by DC-SIGN-expressing DCs that protrude from the gastric epithelium⁵⁴, and these cells subsequently migrate to gastric lymph nodes, where they suppress the development of TH cells into TH1 cells. DC-SIGN-mediated uptake of *H. pylori* is a rapid process, leaving non-DC-SIGN-binding bacteria (red) behind in the mucus layer. Even when, after a certain time, all DC-SIGN-binding *H. pylori* would have been removed from the gastric mucosa, new DC-SIGN-binding variants, which continually arise during bacterial replication, might maintain a certain level of suppression of development into TH1 cells. *H. pylori*-specific TH1 and TH2 cells home to the gastric mucosa, where they establish TH1- and TH2-cell micro-niches. In asymptomatic chronic gastritis, TH1-cell microenvironments might coexist with TH1- and TH2-cell microenvironments (see also the T-cell clones depicted in Fig. 1). In TH1-cell microenvironments, the *H. pylori* population might be partially killed by T cells, through IL-12- and possibly IFN--dependent mechanisms^{29, 86, 87}. However, the TH1-cell response also increases gastritis⁸⁷ and might free nutritious compounds for *H. pylori*. In TH1- and TH2-cell micro-niches, gastric damage is less severe, and *H. pylori* might thrive and persist in the absence of a strong TH1-cell response.