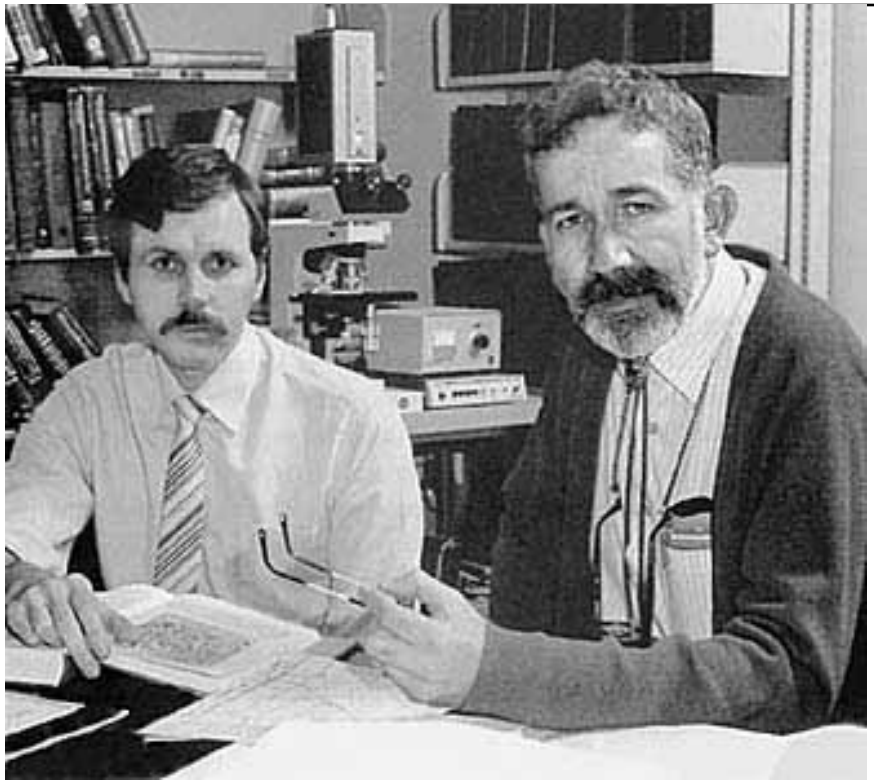
ХЕЛИКОБАКТЕРИОЗЫ

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)

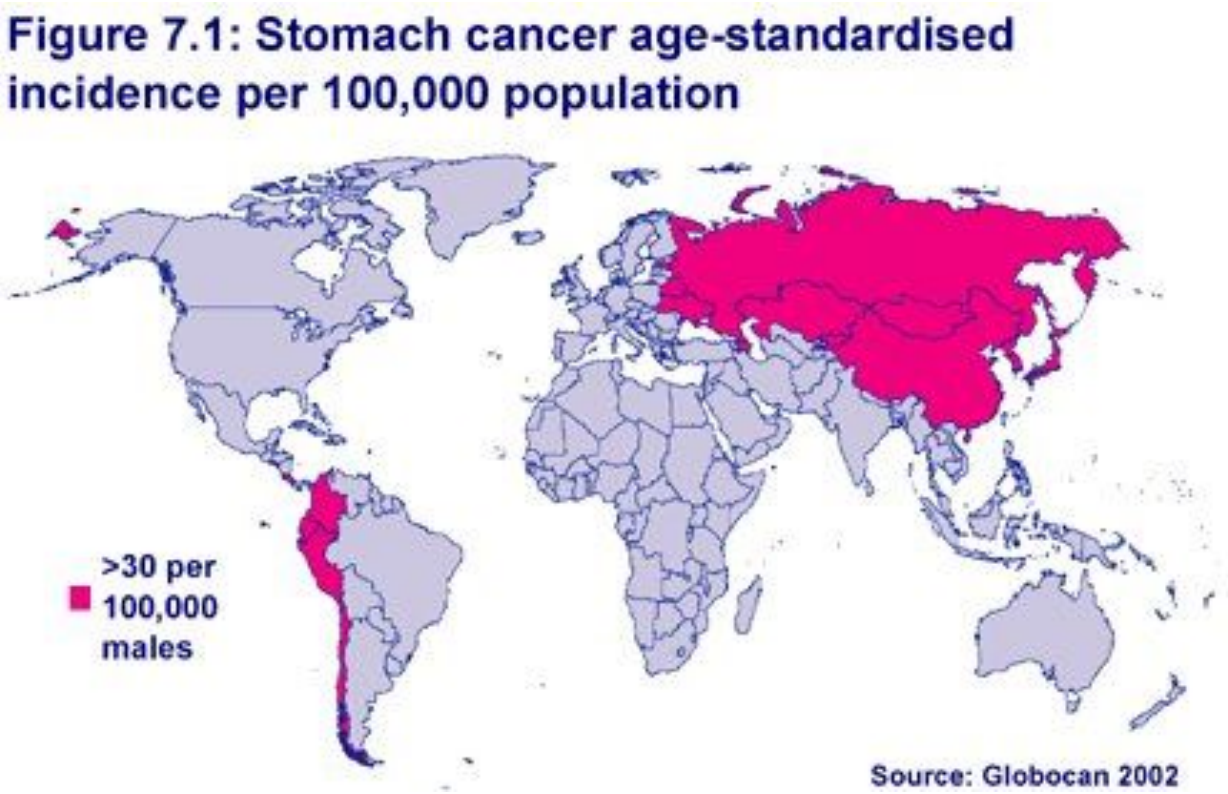


2005г. Нобелевская премия по медицине

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

Название заболевания	Частота выделения *Helicobacter pylori*,%
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



http://info.cancerresearchuk.org/cancerstats/causes/infectiousagents/helicobacterpylori/helicobacter-pylori2

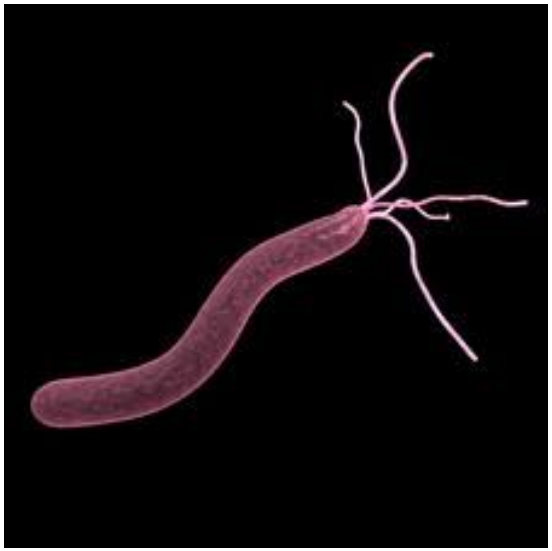
Особенности строения и функционирования желудка

Сем. *Helicobacteraceae*

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

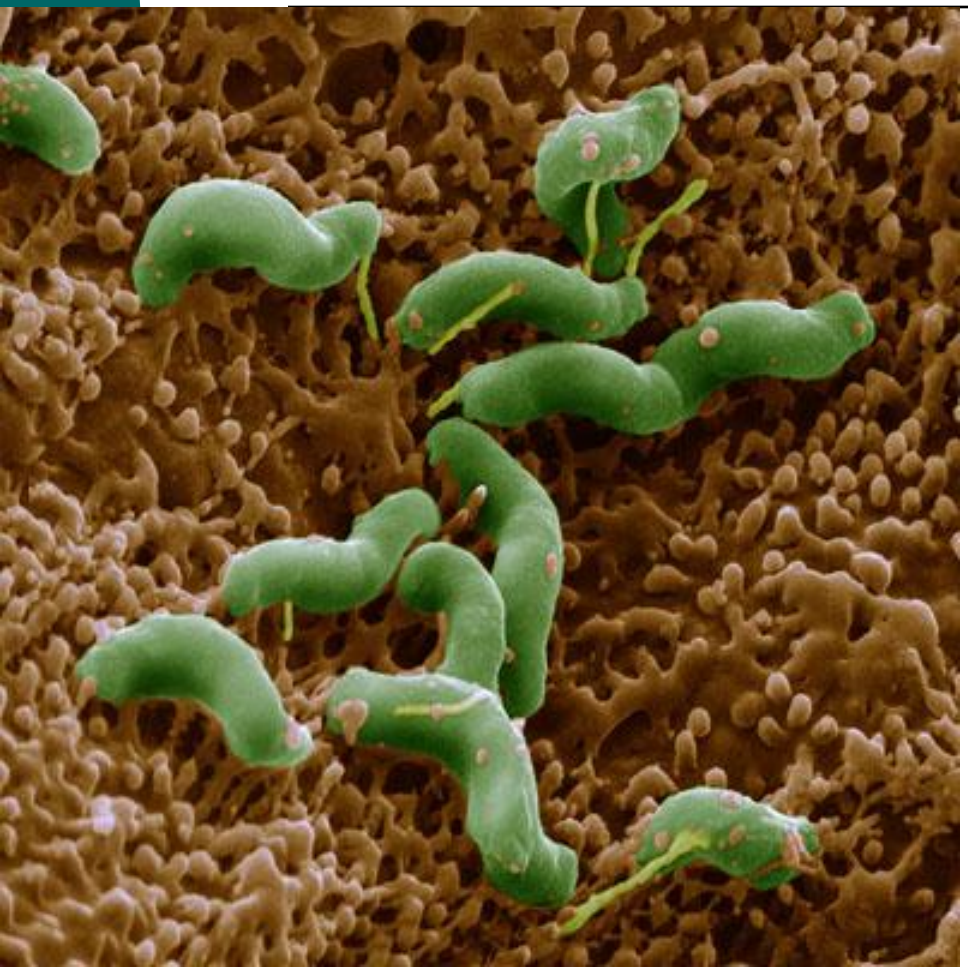
- *Helicobacter heilmannii* – вызывает гастрит
- *Helicobacter pylori* – гастрит, язва
- *Helicobacter cinaedi* - энтерит, септицимия
- *Helicobacter fennelliae* - энтерит, септицимия
- *Helicobacter rappini* - энтерит, септицимия
- *Helicobacter bilis* – роль не ясна

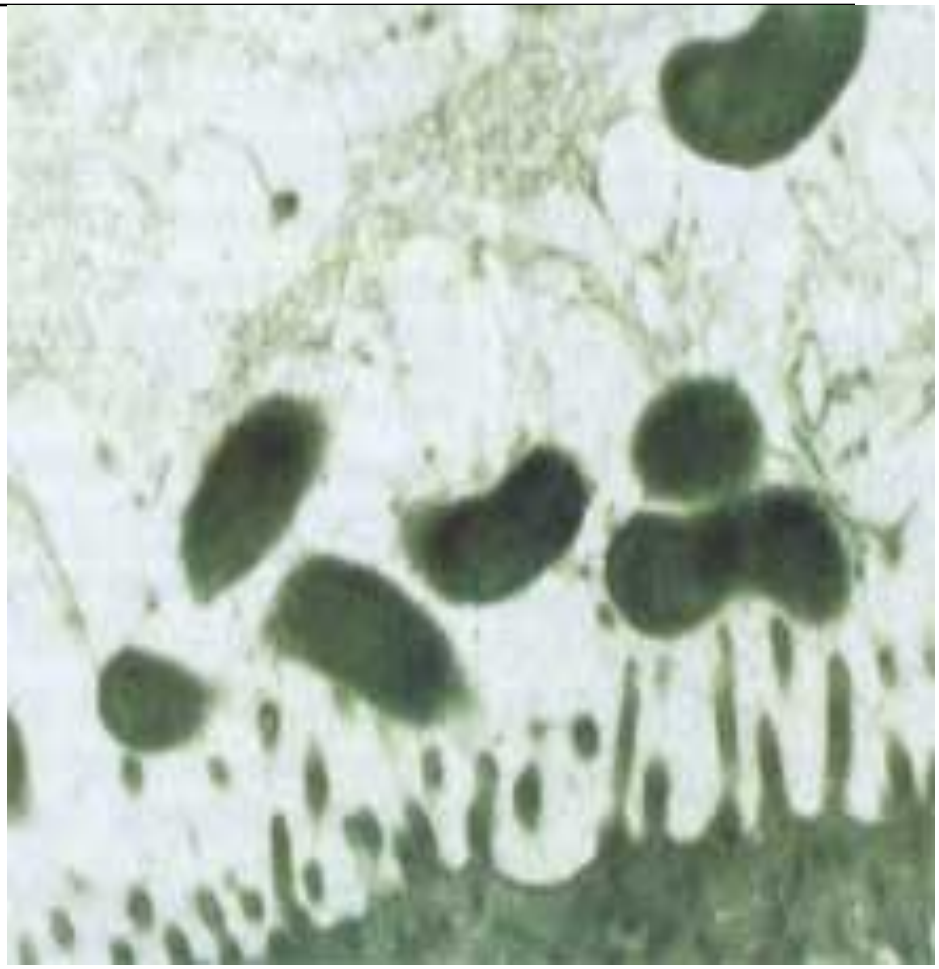
Морфология *Helicobacter pylori*



Электронная микроскопия

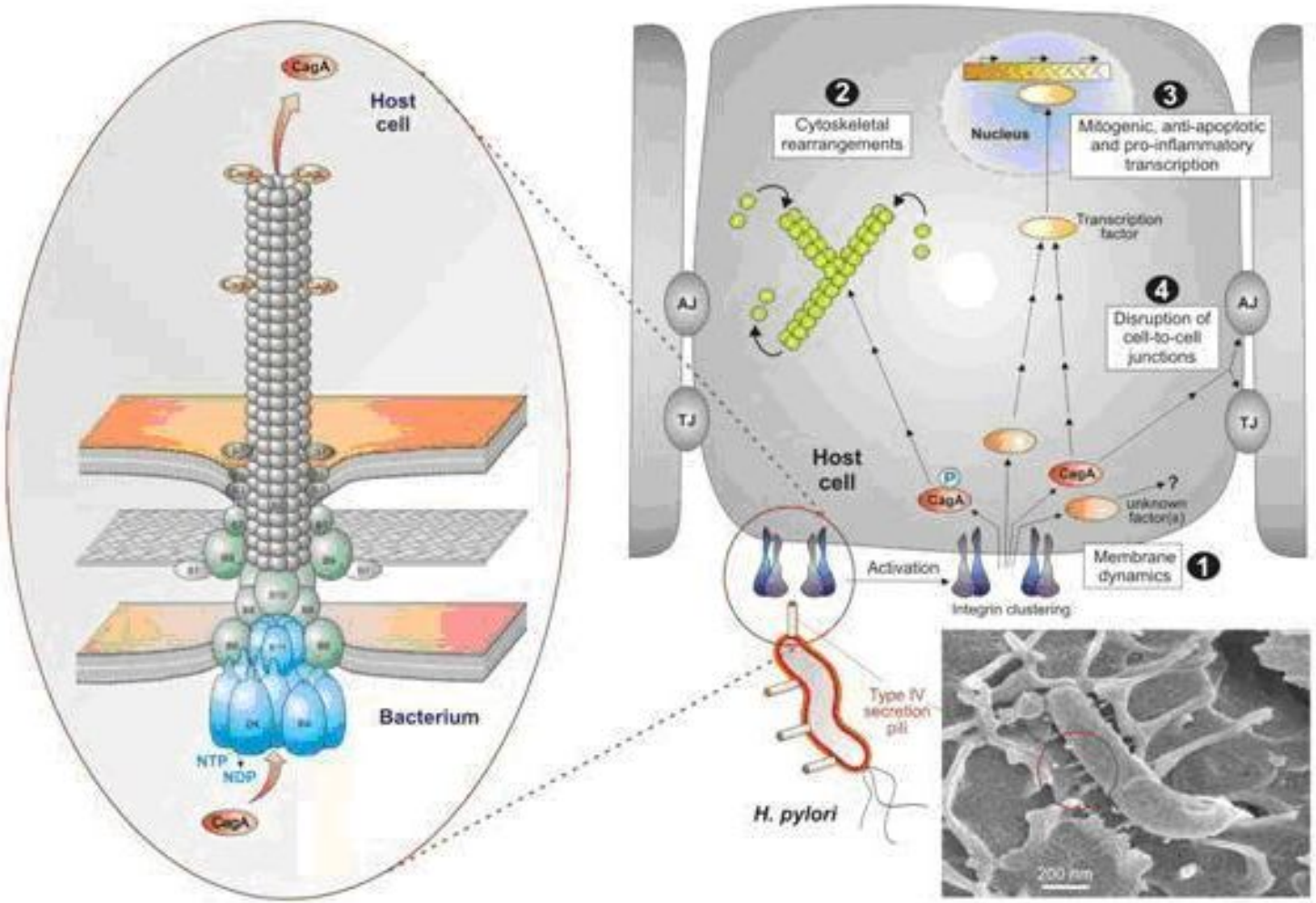
Колонизация *Helicobacter pylori* на слизистой желудка





Культуральные свойства

- Микроаэрофилы (менее 5% O_2)
- pH 4-7
- Каталаза –
- Оксидаза +
- Не окисляет и не ферментирует сахара
- Окисляет органические кислоты

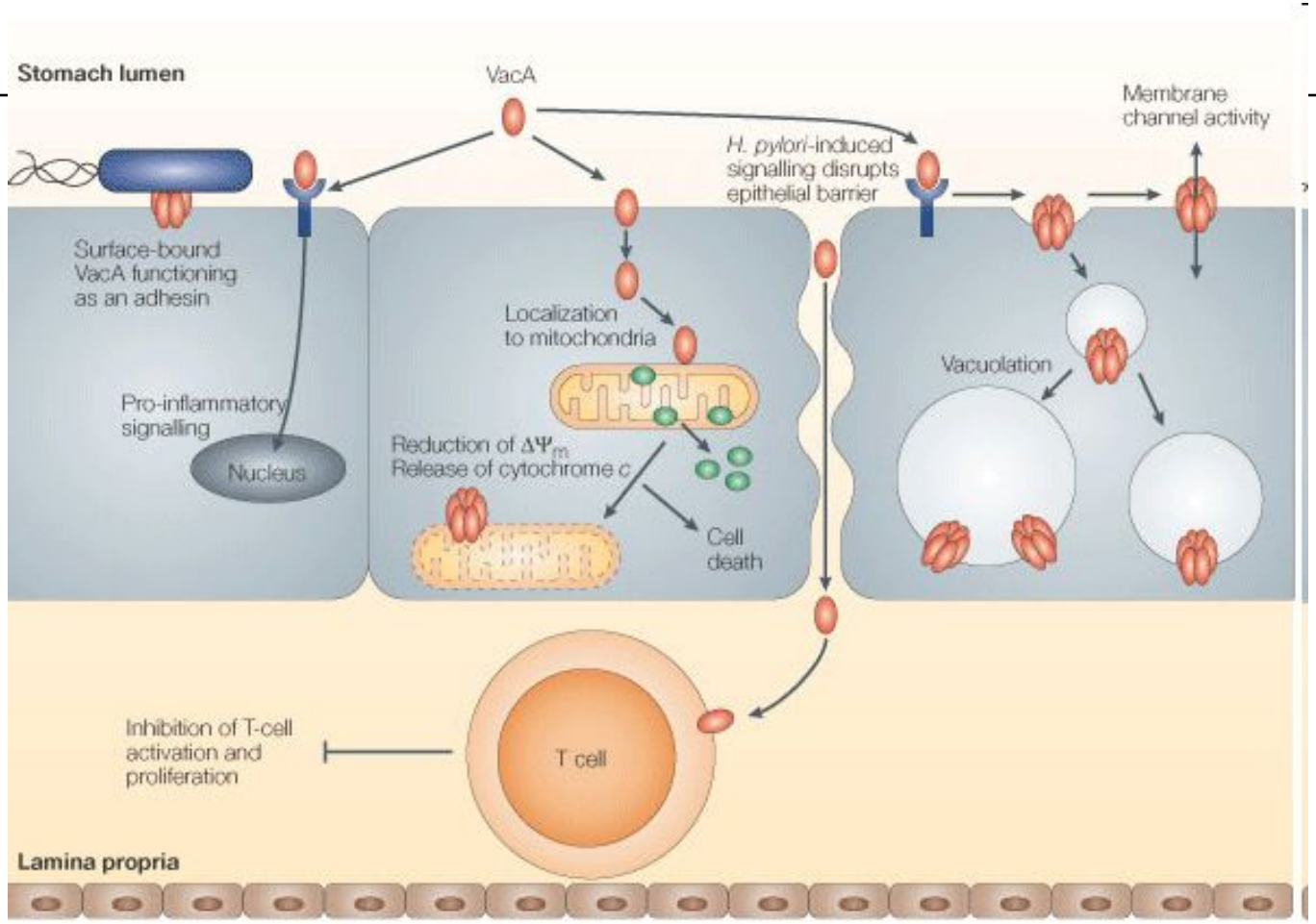


Model for the assembled type IV secretion machinery and its role in Helicbacter pylori-induced cell signalling

(image courtesy of Prof. Steffen Backert, SBBS)

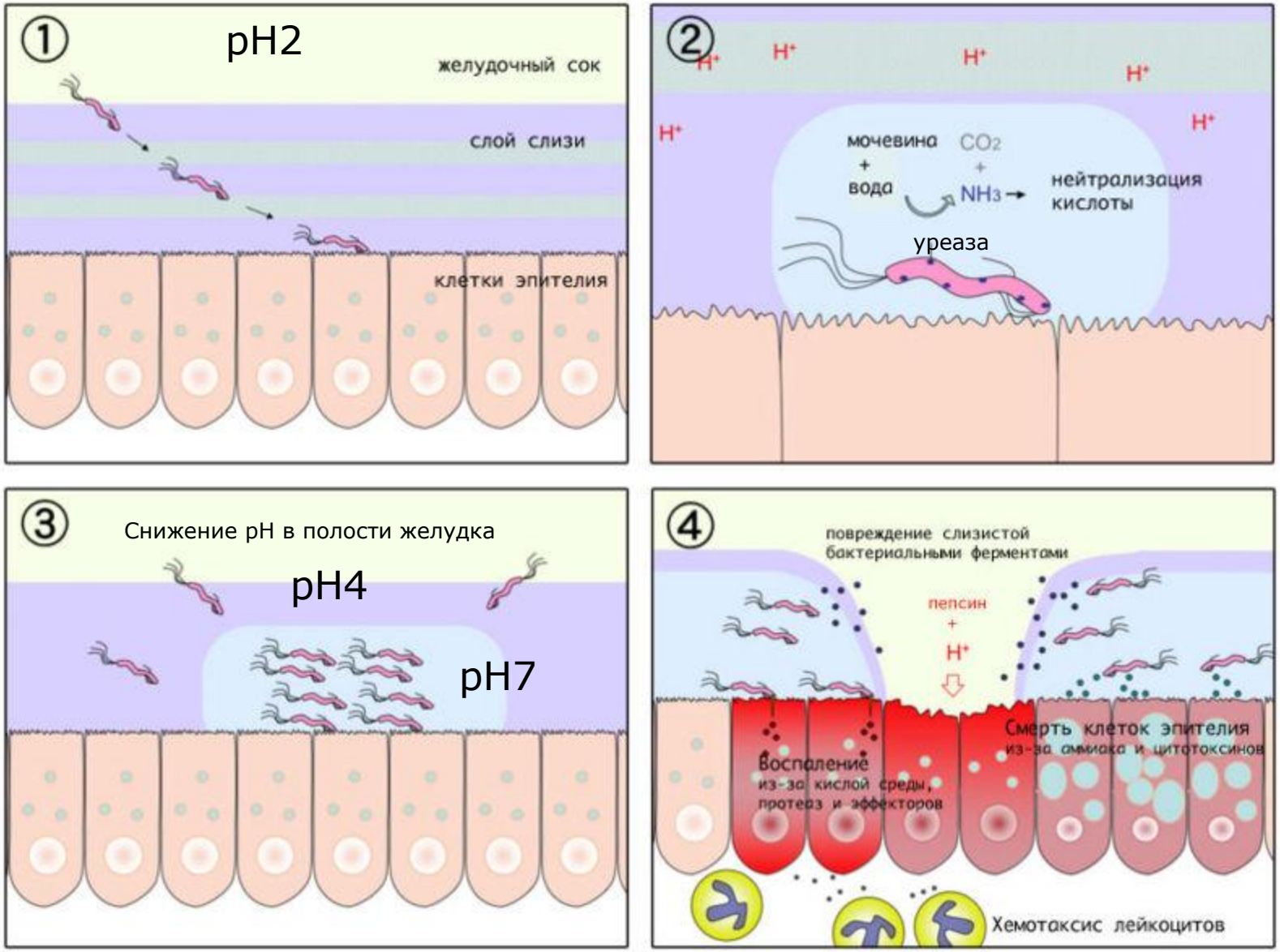
Факторы патогенности *Helicobacter pylori*

Механизм действия экзотоксина VacA

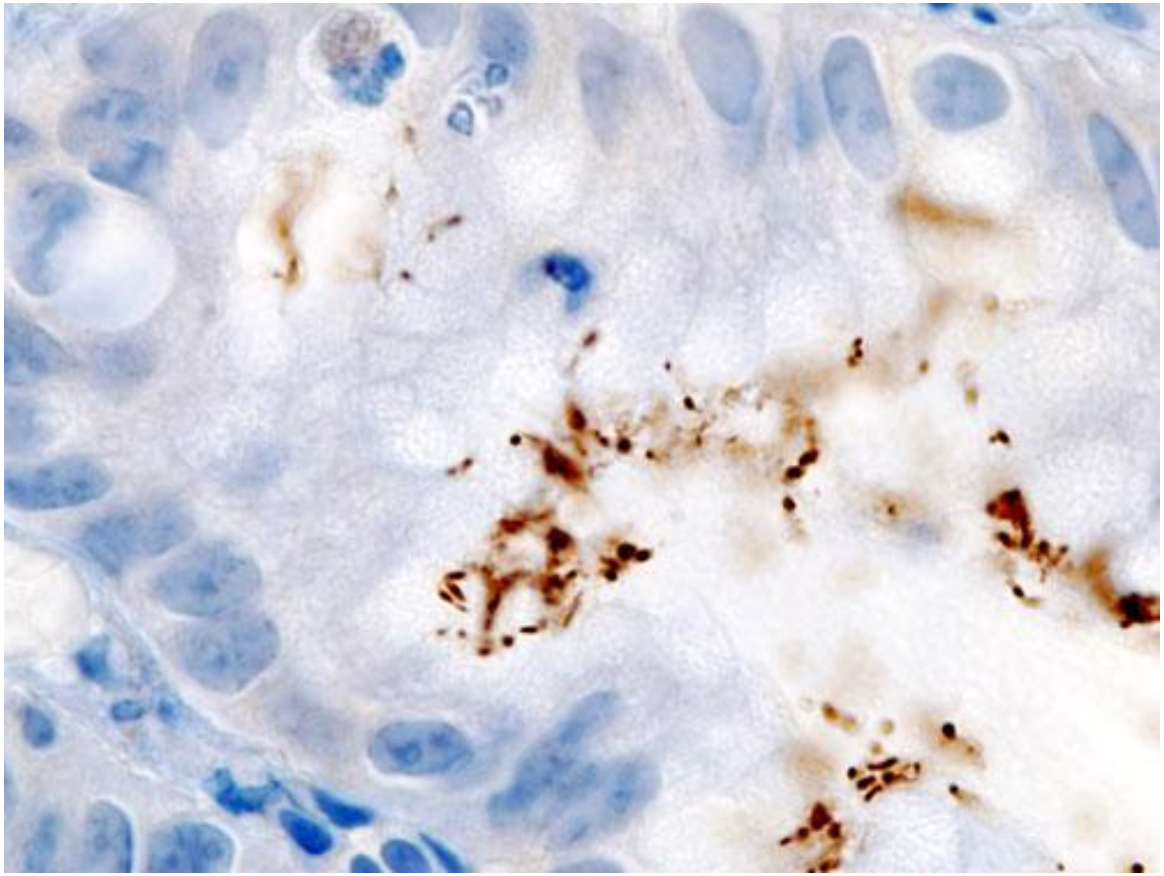


Effects of VacA on gastric epithelial cells include alterations in mitochondrial membrane permeability and apoptosis, stimulation of pro-inflammatory signalling, increased permeability of the plasma membrane and alterations in endocytic compartments. Multiple H. pylori factors, including CagA, disrupt the gastric epithelial barrier and might thereby facilitate passage of VacA through the epithelial layer148, 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. m indicates mitochondrial transmembrane potential.

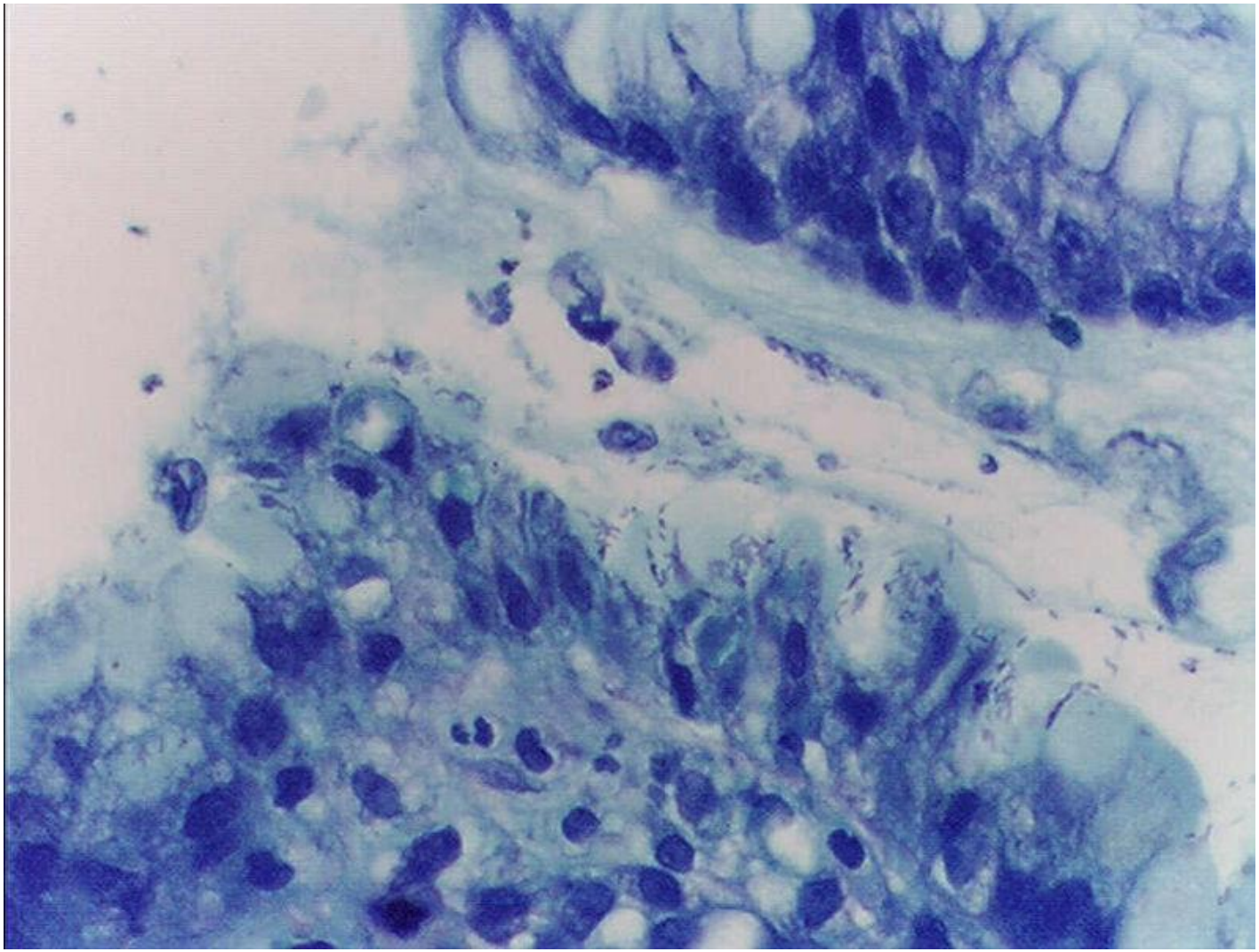
Патогенез *Helicobacter pylori*



Иммуногистохимическая окраска *H. pylori* в биоптате слизистой желудка

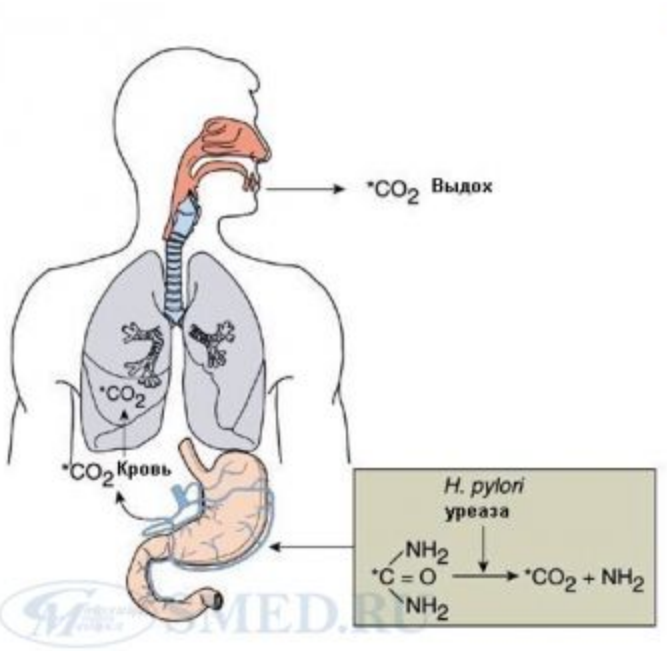


H. pylori в слизистой желудка. Окраска по Романовскому-Гимзе.

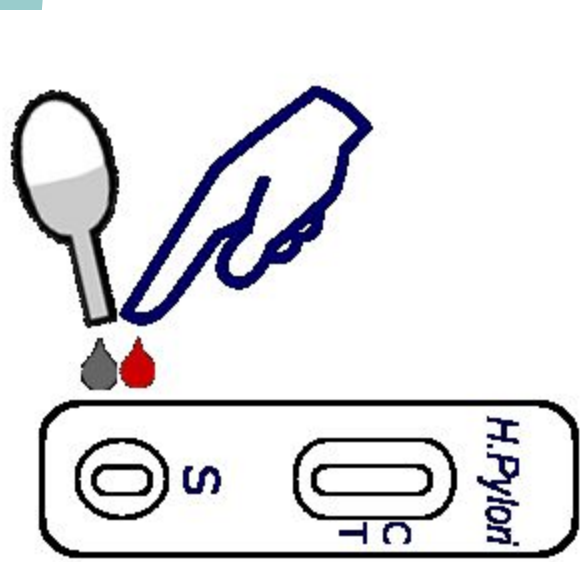


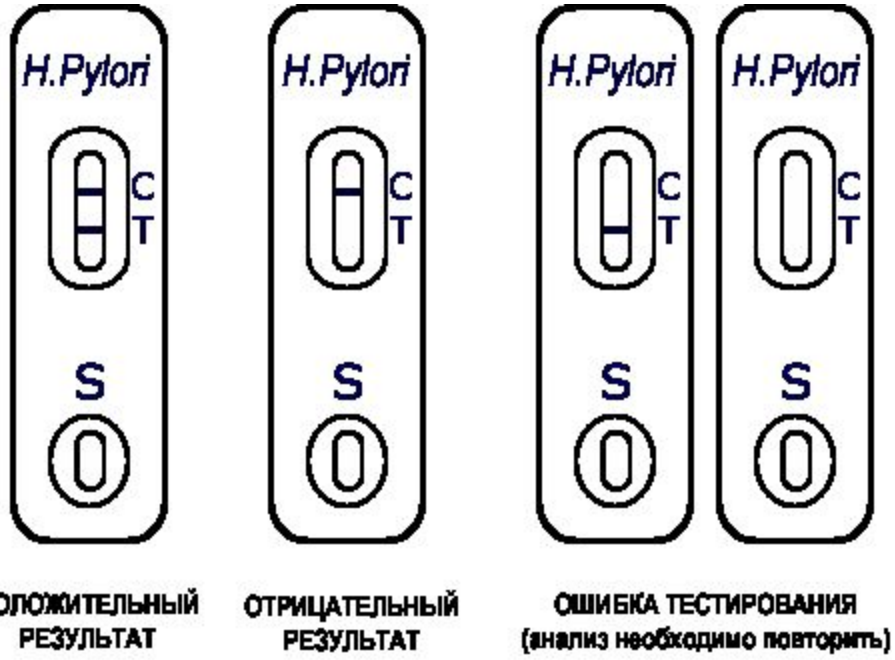
Лабораторная диагностика

- 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 изотипов (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

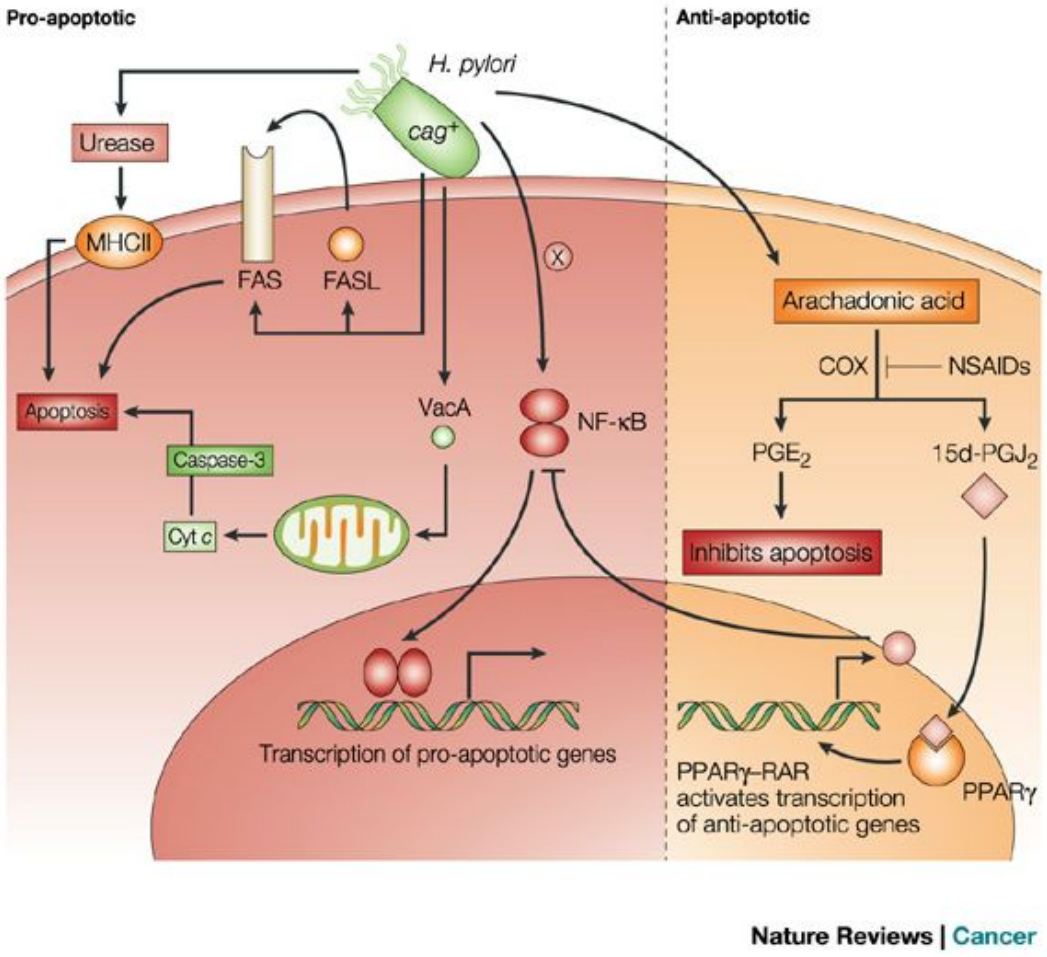
Лечение хеликобактериозов

- **Антибиотики:** амоксициллин, кларитромицин, азитромицин, метронидазол, тинидазол, тетрациклин, фуразолидон.

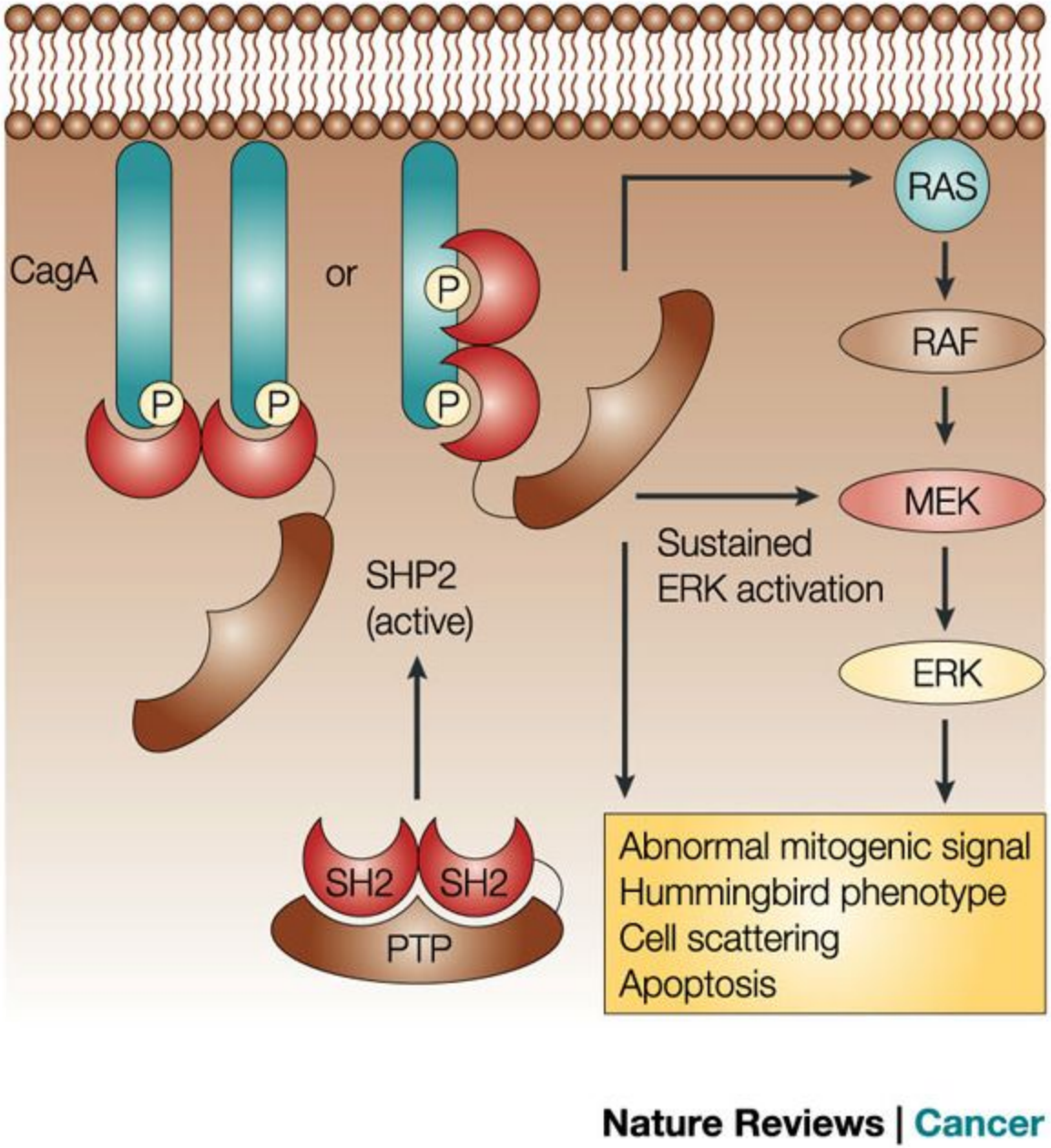
- **Препараты висмута** – лечение язвы и гастрита

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*

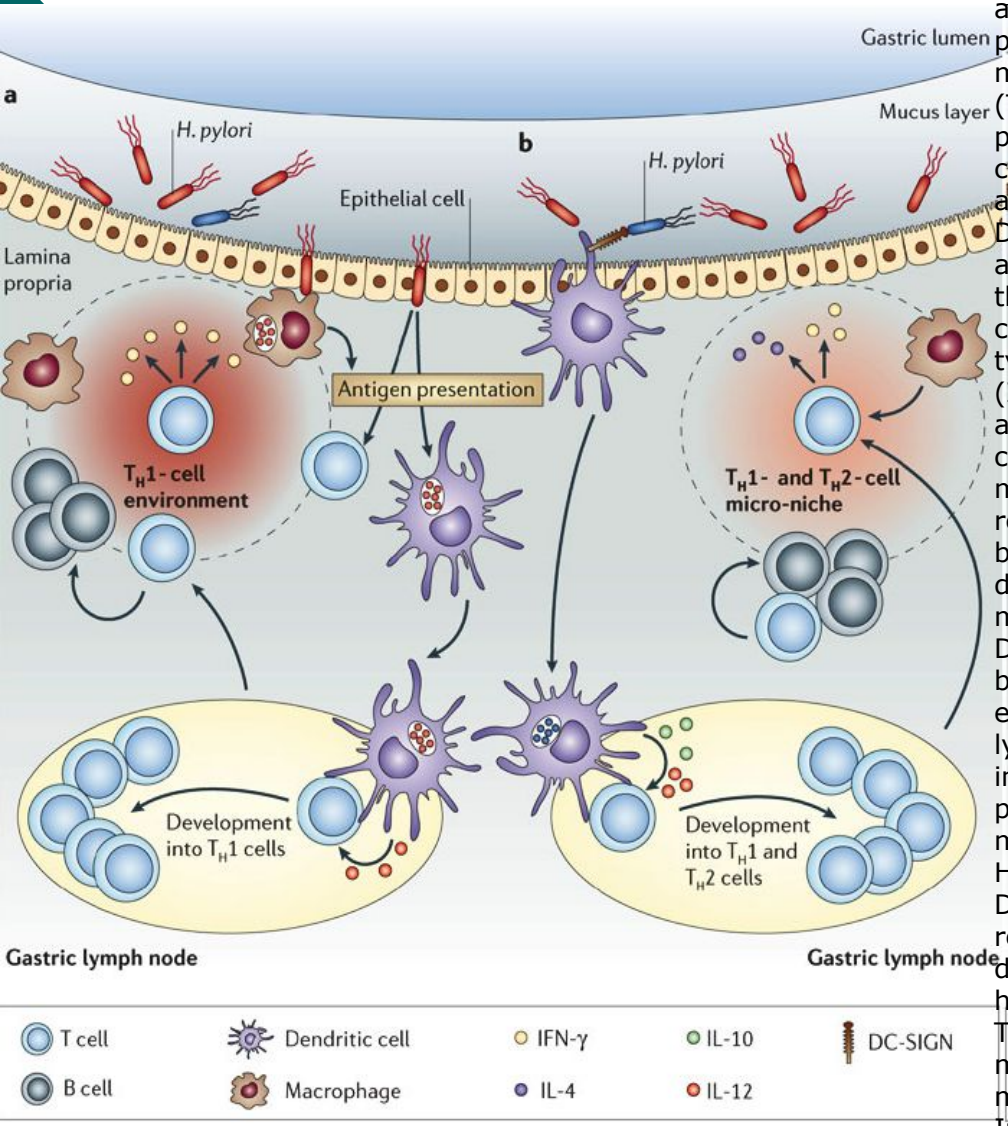


H. pylori can regulate gastric epithelial apoptosis through several mechanisms. Following adherence, signalling by the cag secretion system (but not CagA per se) leads to activation of an unknown factor(s) X that leads to activation of nuclear factor-B (NF-B). NF-B translocates to the nucleus to activate transcription of pro-apoptotic genes. H. pylori can also induce apoptosis by stimulating expression of FAS and its ligand (FASL). The H. pylori protein urease can induce apoptosis by binding to class II major histocompatability complex (MHC) molecules. 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- (PPAR), 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-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.



Nature Reviews | Cancer

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 tryosine 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 cells84, 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 mechanisms29, 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.