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## Shijie Huaren Xiaohua Zazhi

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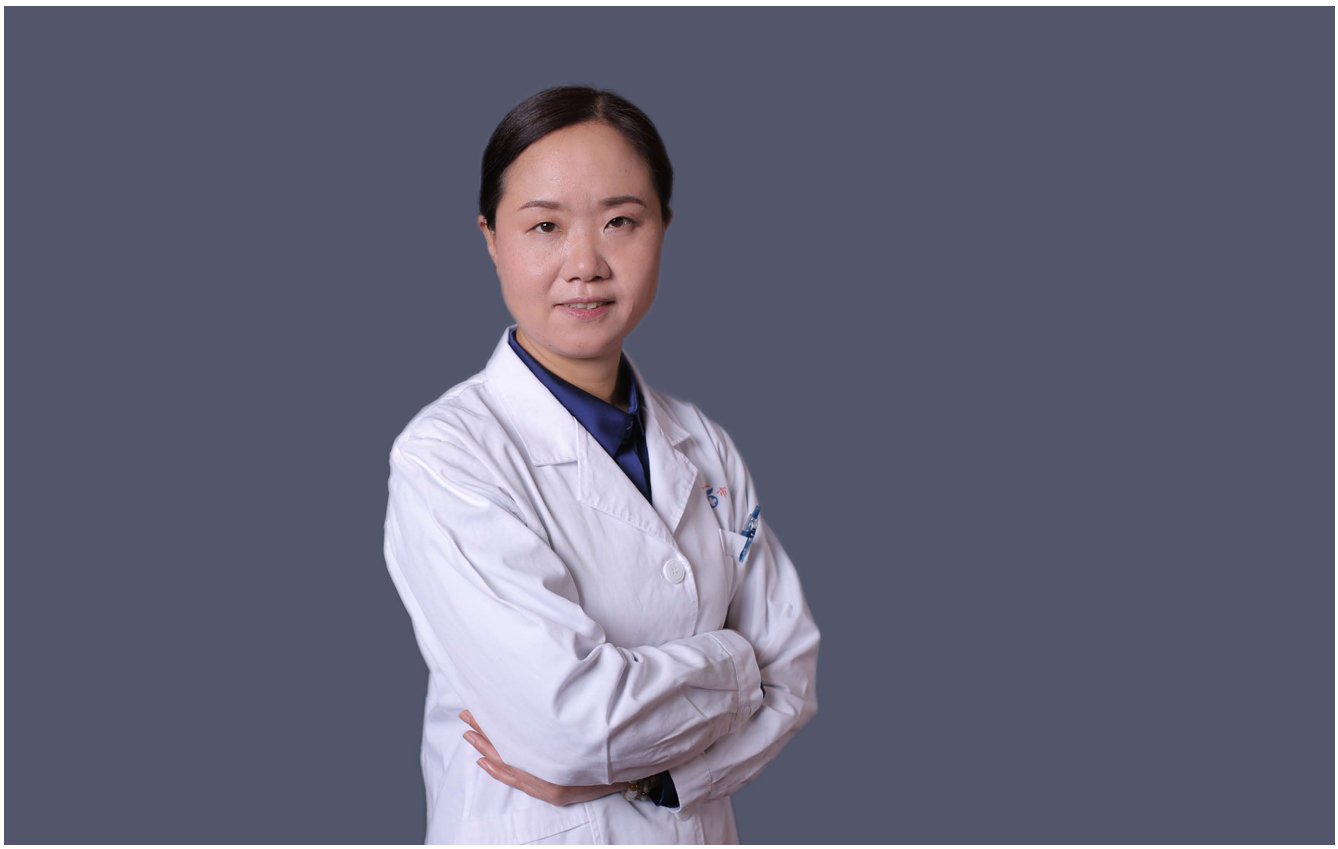

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目　次

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## 述评



## 基础研究



## 临床研究



## 文献综述



## 临床实践

## 消　　息



## 封面故事

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Contents

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## EDITORIAL



## BASIC RESEARCH



## CLINICAL RESEARCH



## REVIEW



## CLINICAL PRACTICE

**Contents**

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文献综述 REVIEW

# 幽门螺杆菌感染引起的免疫应答与免疫逃逸机制研究进展

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## Immune response and immune escape mechanism in *Helicobacter pylori* infection

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## Abstract

*Helicobacter pylori* (*H. pylori*) is a Gram-negative bacterium which is parasitic on the surface of the gastric mucosa, and it is a causative agent in the development of chronic gastritis, gastric and duodenal peptic ulcer, gastric adenocarcinoma, and lymphoid tissue lymphoma associated with the gastric mucosa. After *H. pylori* infection, the bacterium is first recognized by the pattern recognition receptors of immune cells, which in turn causes the innate immune and adaptive immune responses, but these responses are usually insufficient to eliminate bacterial infections. *H. pylori* can evade the identification and clearance by the immune system by modifying and attenuating the immunogenicity of its pathogen-associated molecular patterns, regulating the immune responses of innate immune cells and T cells, and leading to persistent infection. A thorough understanding of the immune response and immune escape mechanism in *H. pylori* infection is of great significance for eliminating *H. pylori* infection and controlling the occurrence of *H. pylori* infection-related diseases.



Key Words: *Helicobacter pylori*; Immune response; Immune escape

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## 摘要

幽门螺杆菌(*Helicobacter pylori, H. pylori*)是一种专性寄生于胃黏膜表面的革兰氏阴性菌, 与慢性胃炎、

胃和十二指肠消化性溃疡、胃腺癌, 以及胃黏膜相关的淋巴样组织淋巴瘤的发生密切相关. *H. pylori*感染机体后, 首先被体内免疫细胞的模式识别受体家族识别, 进而引起机体的固有免疫和适应性免疫应答, 但这些应答通常不足以清除细菌感染, *H. pylori*可以通过改装并减弱其病原体广泛共存的相关分子模式的免疫原性, 调控固有免疫细胞和T细胞的免疫应答来逃避免疫系统的识别和清除, 导致持续感染. 深入了解*H. pylori*感染引起的免疫应答与免疫逃逸机制, 对于消除*H. pylori*感染, 控制*H. pylori*感染相关性疾病的发生具有极其重要的意义.



**关键词: 幽门螺杆菌; 免疫应答; 免疫逃逸**

**核心提要**: 幽门螺杆菌(*Helicobacter pylori, H. pylori*)在全世界范围内特别是发展中国家感染率高, 危害严重, 被WHO列为第一类致癌因子. 深入了解其感染引起的免疫应答与免疫逃逸机制, 为打破*H. pylori*在体内长期定植现状, 根除其感染, 减少感染相关的慢性胃炎、消化性溃疡, 以及胃腺癌等疾病发生具有重要意义.

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## 0 引言

幽门螺杆菌(*Helicobacter pylori, H. pylori*)是一种专性寄生于胃黏膜表面的革兰氏阴性菌, 其感染与慢性胃炎、胃和十二指肠消化性溃疡、胃腺癌, 以及胃黏膜相关的淋巴样组织淋巴瘤的发生密切相关[1]. 在全世界范围内有50%以上的人口感染*H. pylori*, 但通常80%以上的感染者无自觉症状, 仅15%-20%的感染者发展为消化性溃疡, 约1%的感染者发展为胃腺癌[2]. *H. pylori*感染的不同结局可能取决于多种因素, 如细菌毒力因子及其亚型、患者的遗传易感性、受体基因多态性、特定的细胞因子反应和环境因素影响等[3]. *H. pylori*感染通常是在儿童时期获得的, 如果不加以根除治疗, 宿主可以终生感染该菌[4].

*H. pylori*感染可以激发机体产生固有免疫和适应性免疫应答. 进化上保守的固有免疫系统能够为机体提供第一道防线, 抵抗微生物的入侵; 而适应性免疫系统在感染的后期阶段出现, 是高度特异和持久的, 包括细胞免疫和体液免疫. 与此同时, *H. pylori*可以通过多种途径逃避宿主的免疫应答, 使得机体产生的针对*H. pylori*的固有免疫和适应性免疫不足以清除本菌感染. 本文就*H. pylori*自然感染时引起的免疫应答和免疫逃逸机制进行了综述.

## 1 *H. pylori*感染引起的免疫应答

人胃黏膜活检标本检测显示, 持续感染*H. pylori*的人与未感染者相比会发生不同类型的白细胞浸润[5], 其中包括淋巴细胞(T和B细胞)、单核细胞、肥大细胞、中性粒细胞、巨噬细胞、嗜酸性粒细胞和树突状细胞(dendritic cells, DCs)等[6,7]. $CD4^+$T细胞、B细胞和DCs通常在淋巴滤泡中, 参与免疫应答和抗原呈递. 在*H. pylori*感染者的外周血和胃黏膜中可以检测到*H. pylori*特异性$CD4^+$T细胞, 而在未感染的个体中则检测不到. 与未感染者相比, 在感染*H. pylori*的受试者胃中, 细胞因子如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、干扰素-γ(interferon, IFN-γ)、白细胞介素-1(Interleukin-1, IL-1)、IL-6、IL-7、IL-8、IL-10、IL-17和IL-23、IL-18等的表达水平高; 在*H. pylori*感染的患者胃黏膜中通常检测不到IL-4[3]. *H. pylori*自然感染时, 机体的免疫应答由多种细胞和细胞因子参与, 以下从免疫识别、固有免疫应答和适应性免疫应答三个方面分析其可能的免疫应答机制.

1.1 免疫识别 固有免疫识别微生物是由细胞表面的病原体模式识别受体家族(pattern recognition receptors, PRRs)分子介导的, 可识别病原体广泛共存的相关分子模式(pathogen-associated molecular patterns, PAMPs). *H. pylori*的PAMPs包括肽聚糖(peptidoglycan, PG), 脂多糖(lipopolysaccharide, LPS), 鞭毛蛋白和非甲基化CpG DNA等. 分布于宿主胃上皮细胞(gastric epithelial cells, GECs)、抗原提呈细胞(antigen presenting cells, APCs)和中性粒细胞上的PRRs识别*H. pylori*的PAMPs, 启动机体对*H. pylori*的免疫应答[8](表1). 可以识别*H. pylori* PAMPs的PRRs有四大类: 细胞膜和内体膜(endosome membrane)上的Toll样受体(Toll-like receptors, TLRs)和C型凝集素受体(C-type lectin receptors, CLRs), 细胞质内的NOD样受体(NOD-like receptors, NLRs)和RIG样受体(RIG-like receptors, RLRs). 一般来说, TLRs, CLRS或RLRs的识别可激活核内炎性转录因子, 而大多数NLRs参与组成多蛋白复合物——“炎性小体”, 促进IL-1β和IL-18由前体成为成熟的具有生物活性的细胞因子[9].

*H. pylori* Ⅳ型分泌系统(type-Ⅳ secretion system, T4SS)是突出于细菌表面的针状结构, 它可以刺入宿主细胞, 将细胞毒性相关基因A蛋白(cytotoxin-associated gene A product, CagA)、PG代谢产物和DNA等递送到宿主细胞内, 启动对*H. pylori*的免疫应答. *H. pylori*感染

表 1 宿主模式识别受体家族与相应识别的*H. pylori*广泛共存的相关分子模式及其产生的免疫应答反应

| 宿主PRRs | *H. pylori* PAMPs | 免疫应答反应 |
|---|---|---|
| TLRs | LPS, HSP60, NAP, DNA, RNA, 鞭毛[1] | 激活NF-κB、AP-1和IRFs, 诱导炎性细胞因子(IL-8、IL-6、IL-1β、TNF-γ)、抗菌肽和Ⅰ型IFN等产生 |
| CLRs | LPS的Lewis抗原 | 抑制Th1, 促进抗炎症细胞因子IL-10的分泌, 抑制宿主免疫应答清除*H. pylori*, 有利于*H. pylori*慢性长期定植 |
| NLRs | PG代谢产物, CagA, VacA | 激活NF-κB、AP-1和CASP1, 释放IL-8, IL-1β和IL-18 |
| RLRs | RNA | 诱导Ⅰ型IFN |

[1]TLR识别鞭毛活性低, 与*H. pylori*免疫逃逸相关.

后, 首先通过T4SS递送LPS的生物前体1, 7-二磷酸-庚糖(heptose-1, 7-bisphosphate, HBP)进入宿主细胞质中, 激活肿瘤坏死因子相关因子(tumor necrosis factor receptor-associated factor, TRAF)和叉头相关结构域相互作用蛋白(interacting protein with forkhead-associated domain, TIFA)依赖性细胞监视通路, 随后陆续启动PG-NOD1和CagA相关的应答[10]. T4SS依赖的HBP-TIFA通路是诱导人上皮细胞分泌促炎症因子IL-8的关键[11], 巨噬细胞可以不依赖TLR信号通路识别cagPAI$^+$*H. pylori*的T4SS, 进而启动固有免疫应答[12].

1.1.1 TLRs和免疫识别: TLR家族的成员都是Ⅰ型跨膜蛋白, 含有富含亮氨酸重复序列的胞外结构域参与PAMP识别, 一个跨膜区, 胞内部分含有一个Toll-IL-1受体(TIR)结构域参与激活下游的信号传导通路. 人类有10个TLR基因[13], TLRs表达在细胞表面或细胞内的囊泡膜上. TLR1、TLR2、TLR4、TLR5和TLR6在细胞表面结合各自的配体识别微生物膜成分如脂质、脂蛋白和蛋白质, TLR3、TLR7、TLR8, TLR9在细胞内的囊泡如内涵体、溶酶体或内质网膜上, 主要涉及微生物核酸的识别[14]. 髓样细胞分化蛋白88(myeloid differentiation primary response protein 88, MyD88)是一个关键的TLR适配体蛋白, 负责发送信号诱导炎性细胞因子.

胃上皮细胞、单核/巨噬细胞、DCs、中性粒细胞和B细胞的TLR2可以识别*H. pylori*的LPS、热休克蛋白60(heat shock proteins 60, HSP60)和中性粒细胞激活蛋白(neutrophil-activating protein, NAP), 激活核因子-κB(nuclear factor-κB, NF-κB)产生细胞因子, 例如IL-8、IL-6、IL-1β和TNF-γ等[15,16]; TLR2参与的免疫应答可能与*H. pylori*感染的结局相关[17]. TLR4可能的配体为*H. pylori*的LPS和HP015, TLR9识别*H. pylori*的DNA[14,18]. *H. pylori*的鞭毛可激活TLR5, 但活性较低, 原因是*H. pylori*鞭毛的D0区能够逃避TLR5的识别[19], 这被认为是*H. pylori*能够逃避宿主的免疫应答而长期定植的机制之一.

TLRs识别PAMP触发细胞信号转导通路, 导致: (1)激活转录因子NF-κB、活化蛋白-1(activating protein-1, AP-1)和干扰素调节因子(interferon regulatory factors, IRFs); (2)表达炎性细胞因子、抗菌肽、Ⅰ型IFN; (3)后续招募中性粒细胞, 激活巨噬细胞和树突状细胞, 诱导IFN刺激基因表达[14].

1.1.2 其他PRRs和免疫识别: NLRs主要分为两类: NOD1和NOD2识别肽聚糖代谢产物, 激活转录因子NF-κB诱导固有免疫和适应性免疫应答, 而其他大多数NLRs促进多蛋白复合物(炎症小体)形成, 激活半胱氨酸蛋白酶caspase-1(CASP1)[20]. *H. pylori*的PG、CagA可以通过T4SS或细菌分泌外膜囊泡递送入上皮细胞内, 被细胞内NOD1识别, 导致MAPK(mitogen-activated protein kinase)磷酸化, 激活NF-κB和AP-1, 释放IL-8[15]. NLRC3, NLRP12和NLRX1通过调节激活NF-κB和MAVS(mitochondrial antiviral signalling adaptor)信号通路减轻炎症反应[21,22]. 此外, 在*H. pylori*感染者的DC中, TLR2和NOD2可协同调节IL-1β[23].

*H. pylori*的RNA除了可以被TLR8识别外, 还可以被RIG-I识别, 诱导MyD88非依赖的Ⅰ型干扰素[24].

CLRs包括DC-SIGN(DC-specific ICAM3-grabbing non-integrin)和Mincle(Macrophage inducible C-type lectin, 巨噬细胞诱导的C型凝集素), DC-SIGN与其配体(*H. pylori* LPS的Lewis抗原)结合, 抑制原始T细胞分化为T辅助细胞1(T helper 1, Th1)细胞, 调控细胞因子表达, 从而抑制宿主免疫应答清除*H. pylori*[25]; Mincle同样与LPS的Lewis抗原相互作用, 促进抗炎症细胞因子IL-10的分泌, 为*H. pylori*的慢性长期定植提供了帮助[26].

1.2 固有免疫应答 胃上皮细胞识别*H. pylori*抗原后分泌趋化因子, 例如IL-8、CXC趋化因子配体(CXC chemokine ligand 1, CXCL1)、CXCL2, CXCL3和CC趋化因子配体20(CC chemokine ligand 20, CCL20), 随后招募中性粒细胞、嗜酸性粒细胞, 单核细胞, DCs和巨噬细胞到感染部位[27,28].

巨噬细胞位于固有层内中性粒细胞浸润的部位, 中性粒细胞浸润的胃上皮细胞以及中性粒细胞本身表达高水平的中性粒细胞的趋化因子Gro-α(growth-related oncogene-α)和IL-8[8]. *H. pylori*启动的中性粒细胞相关固有免疫应答是由TLRs介导的, 可以观察到早期IL-8, IL-1β和TNF-α快速上调, 随后IL-10产物增加[29]. *H. pylori*的NapA在胃黏膜上通过TLR2诱导中性粒细胞和单核细胞分泌IL-12和IL-23, 进而引起抗原特异性Th1应答[30]. *H. pylori*细胞外囊泡(extracellular vesicles, EVs)包含的CagA和空泡毒素A(vacuolating toxin A, VacA), 可诱导巨噬细胞产生TNF-α、IL-6和IL-1β, 诱导胃上皮细胞产生IL-8. 此外, EVs可诱导小鼠体内IFN-γ、IL-17和EV特异性免疫球蛋白Gs(immunoglobulin Gs, IgGs)的表达[31].

DCs细胞的主要功能是获取、加工、提呈抗原, 激活适应性免疫应答[32], 人DCs和*H. pylori*共培养可释放细胞因子IL-6、IL-10和IL-12p70, 将*H. pylori*激发过的DCs与$CD4^+$T细胞共培养产生细胞因子IFN-γ、IL-17A并表达Foxp3, 验证了Th1、Th17和调节性T细胞(regulatory T cells, Treg)在体外的混合应答反应[33]. *H. pylori*的γ-谷氨酰转肽酶(γ-glutamyltranspeptidase, GGT)诱导DC分泌促炎性细胞因子IL-6, 但这一细胞因子的表达水平较其他细菌(如大肠杆菌)低, 也较其他的细胞因子如IL-10低, 导致T细胞免疫应答Th17/Treg比例降低, 有利于*H. pylori*长期定植. IL-6可诱导Th17分化, 抑制Treg分化[34]. *H. pylori*感染诱导DCs分泌抗炎症因子IL-10, 激活信号转导和转录激活子3(signal transducer and activator of transcription 3, STAT3), 调节DCs成熟, 降低IL-1β分泌; 而IL-1β可增强效应性T细胞, 包括Th17、Th1和Th2的增殖和分化, 诱导DCs分泌细胞因子如IL-12, 通过阻止$Foxp3^+$Treg的抑制功能从而打破外周耐受性[35].

固有淋巴细胞(innate lymphoid cells, ILCs)是新发现的淋巴细胞亚群, 其中ILC2是重要的固有免疫组成部分, *H. pylori*感染时ILC2增加, 产生IL-4进而促进Th2型适应性免疫反应[36].

炎性小体在*H. pylori*固有免疫应答中也起着重要作用, NLRs家族中的NLRP1(NLR pyrin domain containing 1)、NLRP3、NLRC4和ASC(apoptosis-associated speck-like protein containinga Caspase recruitment and activation domain)配适器是其主要组成部分. 炎性小体是一个多蛋白复合物, 介导CASP1(caspase-1)激活, 促进细胞因子IL-1β和IL-18的分泌[37]. *H. pylori*的VacA和CagPAI等能够诱导NLRP3炎性小体产生IL-1β[38,39].

### 1.3 适应性免疫应答

1.3.1 T细胞介导的免疫应答: *H. pylori*感染后, 位于派伊尔集合淋巴结(Peyer's patches, PPs)中的DC识别抗原, 进而激活PPs中的原始T细胞[40]. 被激活的T细胞通过归巢受体, 例如α4β7整合素, 迁移到胃部的感染位置, 发挥保护胃黏膜的作用[41](表2).

原始的$CD4^+$辅助T细胞(T helper cells, Th)可以根据局部细胞因子环境诱导分化为Th1, Th2, Th17和Treg. Th1和Th2是较早发现的Th细胞亚群, 其特征是分泌不同的细胞因子: Th1产生IL-2和IFN-γ, 促进细胞介导的免疫反应; Th2分泌IL-4, IL-5, IL-6和IL-10, 诱导B细胞的活化和分化. 一般情况下, 大多数细胞内的细菌诱导产生Th1的应答, 而细胞外病原体刺激Th2型应答. IL-17诱导的Th17为新发现的Th亚群, 这些细胞的特征是产生IL-17A、IL-17F、IL-21和IL-22, 并参与宿主针对各种感染的防御机制, 尤其是胞外细菌感染, 而且与自身免疫性疾病的发病机制有关. Treg能够抑制效应T细胞增殖及相关细胞因子的产生, 因此他们在维持外周免疫耐受中发挥重要作用, 通过调节免疫与炎症之间的平衡以缓和对病原体的免疫反应, 避免严重的多器官的自身免疫性疾病. *H. pylori*感染后引起的慢性胃炎, 以细胞炎症浸润为特征, 表现为固有和适应性免疫应答. 固有免疫应答主要引起急性炎症, 适应性免疫应答中, $CD4^+$T细胞是建立慢性炎症的主要因素[3,42].

Th1参与*H. pylori*的免疫保护, 且与胃部炎症相关. Th1通过分泌IFN-γ参与对多种病原菌的免疫应答, IFN-γ与胃部炎症有密切关系, 因为中和IFN-γ可显著减少胃部炎症[43]. 早期的研究认为, Th1和Th2共同参与*H. pylori*的获得性免疫, 但Th1应答更具优势. 原始T细胞分化为Th1细胞时产生IFN-γ, IFN-γ的增加为Th1优势应答提供微环境, 同时抑制Th2应答[44]. 随着对*H. pylori*相关T细胞免疫应答研究的深入, 目前认为Th1和Th17共同参与*H. pylori*感染的免疫保护, 降低细菌定植密度, 促进炎症反应. 当IL-17或IL-23缺失导致Th17免疫应答缺失后, Th1或IL-12可以对*H. pylori*感染起免疫保护补偿作用, 导致胃炎症增加、细菌定植减少[45]. *H. pylori*抗原, 例如LPS通过APC和细胞因子诱导Th1在胃黏膜增值, 导致IFN-γ、IL-12和IL-18的分泌[46]. DCs属于APC的一种, 它被*H. pylori*激活后通过释放IL-12, 激活/起始Th1应答, 但这种应答比其他阴性菌(例如不动杆菌)弱, 这是由于宿主和*H. pylori*通过多种细胞因子抑制DC分泌IL-12, 从而抑制强烈的Th1应答[15]. *H. pylori*-NAP可促进DCs成熟, 进而诱导Th1极化和迁移, Th1免疫应答特点是高IL-12, 低IL-10[47]. 另有研究表明, IFN-γ是导致胃炎的主要原因, 而Th1不是, 因此

表 2 *H. pylori*感染诱导T细胞免疫反应类型及其可能的作用

| T细胞亚群 | 细胞因子 | 可能的作用 |
|---|---|---|
| Th1 | IFN-γ, IL-2和IL-12 | 促进胃炎, 免疫保护 |
| Th2 | IL-4, IL-5, IL-10 | 细菌负荷减少 |
| Th17 | IL-17, IL-21, IL-22 | 促进胃炎, 免疫保护 |
| Treg | IL-10, TGF-β | 限制炎症反应, 免疫耐受, 促进*H. pylori*持续感染 |
| Th22 | IL-22 | 抑制Th1细胞 |
| $CD8^+$T细胞 | IFN-γ | 促进胃炎 |

引起胃炎的IFN-γ也可能是由其他免疫细胞分泌产生, 自然杀伤细胞(natural killer cell, NK)和$CD8^+$T细胞可能是产生IFN-γ的补充来源. 另外, IL-17, TNF-α也与胃炎发生有关[48].

Th2, 早期的研究认为, Th2在*H. pylori*感染中起保护作用. Mohammadi等[49]研究发现, 将*H. pylori*感染小鼠的Th2转移到未感染小鼠中, 然后用*H. pylori*感染小鼠, 可以使*H. pylori*负荷急剧减少, 而IL-4缺乏的小鼠细菌数量增加. 随后的研究用重组*H. pylori* UreB亚单位对小鼠进行黏膜免疫试验, 来诱导Th2免疫应答消除病原体感染. 然而, 小鼠出现了严重的胃炎, 与Th1介导的炎症反应一致, 这一结果弱化了Th2在预防*H. pylori*相关疾病中的作用[50]. 疫苗诱导IL-4缺乏小鼠的免疫保护提示, 尽管Th2可以在清除细菌感染机制中发挥一定作用, 但对免疫的保护并不是必须的[51].

Th17, 近年来, 很多研究支持Th17在人*H. pylori*感染中的作用, Th17应答的抑制可能与*H. pylori*的持续定植相关. IL-17是Th17细胞产生的专属细胞因子, 是宿主防御细菌和真菌病原体的炎症介质, 特别是在黏膜表面[52]. 在IFN-γ或T-bet(T-box expressed in T cells)缺乏小鼠中可以观察到胃炎的产生, 虽然比C57BL/6小鼠弱, 但Th1的缺失验证了IL-17在促炎症作用中的作用[48]. *H. pylori*感染后巨噬细胞释放的细胞因子B细胞活化因子(B-cell activating factor, BAFF), 可以通过直接或间接的方式诱导Th17应答[53]. *H. pylori*感染小鼠的胃组织中IL-17和IFN-γ显著增加, 提示*H. pylori*诱导Th17/Th1混合应答, 且Th17应答先于Th1应答, 并对Th1应答有调控作用[54]. IL-23属于IL12家族, 可以促进Th17增殖, *H. pylori*感染后GECs和DCs均可以检测到IL-23的增加[55]. IL-23不仅促进IL-17分泌, 同时也促进IFN-γ分泌[56]. 另外, IL-21也可以促进Th17/Th1应答, IL-21缺乏可引起*H. pylori*负荷增加, 炎症减少, 细胞浸润和细胞因子TNF-α, IL-1b, IL-17A和IFN-γ减少[57]. 尽管在慢性胃炎中可以观察到IL-17, 但其水平并不足以清除感染, 可能与*H. pylori*能够对宿主的免疫应答产生调控有关. 有研究表明, *H. pylori*的CagA可下调GECs上的B7-H2配体, 进而抑制Th17的应答, 增强*H. pylori*在小鼠胃中的定植[58]. 人胃活检标本显示, *H. pylori*感染的胃黏膜高表达吲哚胺2,3-双氧化酶(indoleamine 2, 3-dioxygenase, IDO)可下调IL-17[59]. Kao等[60]研究认为, *H. pylori*改变DC极化导致Th17/Treg应答平衡向Treg倾斜, Th17应答减弱导致宿主无法清除*H. pylori*; 当Treg耗尽时, Th17应答增强, *H. pylori*浓度降低, 从而验证了Th17在细菌*H. pylori*清除中的作用. *H. pylori*还可以通过诱导DC产生IL-18, 导致T细胞分化倾向于Treg而不是Th17[61].

Treg, 尽管*H. pylori*感染能够引起多种促炎症T细胞应答, 但仍然无法彻底清除细菌, 导致*H. pylori*终生定植. 目前的研究认为, Treg是导致*H. pylori*定植的主要原因之一. Treg可限制效应T细胞的增殖和功能, 在*H. pylori*感染患者的胃黏膜和体循环中, 均能检测到Treg水平升高[62]. 这表明*H. pylori*定植导致Treg增殖并招募到感染部位限制炎症反应, 成为细菌持续感染的一种可能的机制. Treg缺乏或耗竭, 小鼠感染*H. pylori*后发生的胃炎比正常小鼠严重, *H. pylori*定植减少[8]. Treg细胞是免疫系统中维持免疫耐受的重要调控细胞, 通过抑制*H. pylori*诱导的Th1和Th17介导的免疫应答, 减轻感染引起的免疫病理损伤, 同时有助于细菌在胃黏膜中的持续定植, 从而可能在慢性胃炎中起主要作用[63]. Treg表达FoxP3转录因子, 通过产生IL-10和转化生长因子(transforming growth factor β, TGF-β)抑制其他T细胞应答. Treg的诱导伴随着TGF-β的存在和APCs表达PDL-1, GECs可以表达MHC-Ⅱ(class Ⅱ major histocompatibility complex)使其具有APCs的功能, GECs在*H. pylori*刺激下产生TGF-β, 进而抑制$CD4^+$T细胞增殖, 促进Treg分化[64].

Th22是另一个新发现的T细胞亚群, 也与*H. pylori*引起的胃炎相关. 研究表明, Th22细胞富集在*H. pylori*感染患者和小鼠的胃黏膜. DC遇到$CagA^+$ *H. pylori*后分泌IL-23, 诱导$CD4^+$T细胞分泌IL-22, 这导致CXCR2C髓源性单核细胞通过IL-22R1信号通路和后续胃上皮细胞分泌CXCL2招募抑制性细胞(Myeloid-derived suppressor cell, MDSC)到胃黏膜, MDSC在IL-22刺激下可以分泌两种促炎蛋白S100A8和S100A9, 并抑制Th1细胞[65].

$CD8^+$T细胞, 目前大部分研究认为, 针对*H. pylori*的T细胞免疫主要由$CD4^+$T细胞(Th和Treg)介导, 关于$CD8^+$T细胞在*H. pylori*感染中作用的相关研究报道较少. Barbara等[66]报道的猪感染*H. pylori*模型证实, 虽然传统上认为*H. pylori*属于细胞外感染细菌, 但在上皮细胞和免疫细胞中也发现了*H. pylori*的存在, 而$CD8^+$T细胞参与部分存在于黏膜固有层和上皮细胞中*H. pylori*的免疫应答, 诱导IFN-γ产生, 促进胃部炎症. 另有研究表明, *H. pylori*抗原激发的B细胞能够通过MHC-I引发$CD8^+$T细胞应答[67].

儿童和成人感染*H. pylori*时T细胞免疫应答的差异(表3), 研究儿童和成人感染*H. pylori*时细菌毒力因子、细胞因子和免疫应答的差异显示: 儿童感染的*H. pylori*相关毒力因子(CagA/VacA)与成人类似, 细胞因子TGF-α1、IL-10较成人升高, 与成人相比T细胞相关免疫应答表现为高Treg和Th2应答与低Th1和Th17应答, 这些结果导致最终的感染结局为儿童感染者发生胃炎、中性粒细胞浸润和消化道溃疡均较成人轻[3,42,68], 这或许提示Th1和Th17主要介导炎症反应, 而Treg和Th2主要介导免疫耐受或保护.

1.3.2 体液免疫应答: 几乎所有的*H. pylori*感染者都会产生体液免疫应答[69], 在*H. pylori*感染者的血清和胃液中可以检测到针对不同的*H. pylori*抗原的IgG和sIgA抗体, 例如*H. pylori*的膜蛋白、鞭毛、Ure、LPS和幽门螺杆菌黏附素A(adhesin A of *H. pylori*, HpaA)等的抗体. 在*H. pylori*慢性感染者也可以检测到针对*H. pylori*抗原的局部黏膜免疫反应的抗体, 与未感染者相比, *H. pylori*感染者的总IgA和IgM抗体分泌细胞高40-50倍, 而IgG分泌细胞相同[70,71]. 虽然大多数或几乎所有的*H. pylori*感染者都会产生抗体反应, 但发展为胃癌的患者与发生胃炎或十二指肠溃疡的患者相比, 它们的抗体反应是有所不同的. 通过检查患者血清抗体水平发现, 胃炎或十二指肠溃疡的患者比发展为胃癌的患者有更强烈的IgG反应, 而胃癌患者的IgA反应比胃炎和十二指肠溃疡患者更为强烈[72]. 在日本的一项研究表明, 对*H. pylori*的弱抗体反应与受感染者患胃癌的高风险有关[73].

*H. pylori*感染的患者血清抗体滴度升高, 可用于诊断感染[74]. *H. pylori*是一种通过黏膜感染的病原体, 最初认为*H. pylori*感染可以触发潜在的保护性黏膜IgA反应. 然而, 早期通过B细胞或IgA抗体缺乏小鼠研究证明, 疫苗诱导B细胞或抗体缺陷小鼠的保护性免疫与野生型相同[75]. 部分研究者认为, 在*H. pylori*相关的适应性免疫应答中, $CD4^+$T细胞, 尤其是Th1, Th17及其细胞因子对控制*H. pylori*感染比B细胞和抗体更为重要.

## 2 *H. pylori*感染的免疫逃逸机制

尽管*H. pylori*自然感染后能够启动机体产生多种免疫应答, 但通常情况下, 这些免疫反应不足以从体内彻底清除细菌. *H. pylori*可以通过多种途径, 逃避免疫系统对它的识别和清除, 导致其在体内能够长期定植并引起慢性炎症.

2.1 *H. pylori*改装并减弱其PAMPs的免疫原性 *H. pylori*通过改装其表面分子LPS和鞭毛的结构, 并减弱其PAMPs的免疫原性, 来逃避PRRs的识别. LPS是革兰氏阴性菌外膜上的糖脂类物质, 包括脂质A和O-抗原. *H. pylori*表达多种O-抗原, 包括Lewis抗原, 它与人类的血型抗原类似, 利用这种形式的分子模拟, 逃避TLRs的识别[76]. 脂质A位于LPS的内部核心区域, 称为内毒素, 是TLR4-MD2免疫复合物的配体. 幽门螺杆菌LPS内毒素活性较其他细菌, 如大肠杆菌弱1000倍, 这一免疫逃逸机制主要是由*H. pylori* LPS的低酰基化和低磷酸化引起的[77].

*H. pylori*具有5-6根鞭毛, 由鞭毛蛋白组成, 使*H. pylori*能够穿过胃黏膜表面的黏液层在胃黏膜上皮细胞表面定植. TLR5与*H. pylori*的鞭毛亲和力低, 使其识别*H. pylori*鞭毛, 进而导致激活NF-κB及其下游的信号通路作用弱, 这被认为是*H. pylori*逃避宿主识别的方式之一[19].

2.2 *H. pylori*调控固有免疫细胞的功能 *H. pylori*感染可招募巨噬细胞、中性粒细胞和淋巴细胞到感染部位, 但*H. pylori*可以有效地逃避这些吞噬细胞摄取. *H. pylori*通过多种途径诱导巨噬细胞凋亡, 例如通过ERK(extracellular regulated protein kinases)路径[78]、Fas路径[79]或ERK MAPK(mitogen-activated protein kinases)依赖路径[80]诱导巨噬细胞凋亡. 此外, *H. pylori*还可诱导巨噬细胞表达精氨酸酶Ⅱ(Arginase-Ⅱ, Arg2), 限制M1巨噬细胞活化, 加强巨噬细胞凋亡, 抑制Th1和Th17免疫应答[81].

*H. pylori*可以下调人中性粒细胞表达趋化因子受体CXCR1和CXCR2, 影响中性粒细胞迁移[82]. *H. pylori* VacA蛋白也会引起单核细胞凋亡, 这一过程的可能机制涉及VacA氨基末端的476个残基的片段(P52), 这一片段可激活NF-κB通路, 诱导促炎性细胞因子的产生, 例如TNF-α、IL-1β, 同时诱导NO(nitric oxide)、ROS(reactive oxygen species), 随后引起单核细胞凋亡[83]. 另外, *H. pylori*还能通过hsa-miR-223-3p和IL-10抑制NLRP3的表达、炎性小体的激活和成熟IL-1β的分泌, 这也是*H. pylori*逃避免疫应答的一种方式[84].

2.3 *H. pylori*通过毒力因子调控T细胞免疫应答 DCs是

表 3 儿童和成人感染*H. pylori*免疫应答的差异

| | 儿童 | 成人 |
|---|---|---|
| Th1 | ↑ | ↑↑ |
| Th17 | ↑ | ↑↑ |
| Treg | ↑↑ | ↑ |
| Th2 | ↑↑ | ↑ |
| 胃炎 | ↑ | ↑↑ |
| 中性粒细胞浸润 | ↑ | ↑↑ |
| 消化道溃疡 | ↑ | ↑↑ |
| 细菌毒力因子(CagA/VacA) | – | – |

启动T细胞免疫应答的重要APCs, *H. pylori*的毒性因子CagA、VacA和外膜炎症蛋白(outer inflammatory protein A, Oip)可抑制DCs的成熟和功能, 进而调控T细胞免疫应答. VacA可引起DCs的表面共刺激分子表达减少, 如CD40、CD80、CD86、MHC-Ⅱ, 使DCs分泌IL-1β、IL-12p70、TNF-α减少[85]. CagA也可调节DCs, 抑制$CD4^+$T细胞分化为Th1型细胞; CagA蛋白进入细胞后被磷酸化导致SHP-2激活, 进而抑制TBK-1酶(TANK-binding kinase 1)的活化, IRF-3(Interferon regulatory Factor 3)的磷酸化及核转位, 使DCs产生干扰素减少[86]. *H. pylori* Oip通过抑制DCs成熟, 减少IL-10分泌, 进而影响T细胞免疫应答[87].

IL-2是促进淋巴细胞活化和增殖的细胞因子, VacA可通过干扰IL-2信号通路, 进而抑制T细胞增殖和活化[88]. 此外, VacA还可能通过减少$CD4^+$T细胞的线粒体膜电势, 抑制$CD4^+$T细胞增殖[89]. GGT是*H. pylori*的分泌蛋白, 可通过破坏Ras信号通路诱导G1期细胞周期阻滞, 抑制T细胞增殖[90]. *H. pylori*精氨酸酶可水解L-精氨酸为尿素和鸟氨酸, L-精氨酸是T细胞活化和功能所必须的, 精氨酸酶引起的L-精氨酸的消耗可导致T细胞的增殖减少[91]. *H. pylori*可通过T4SS、CagA、PG以及p38 MAPK信号通路, 使GEC表达B7-H1上调, 导致胃黏膜细菌定植量增加, 诱导胃内Treg产生, 抑制Th1/Th17免疫应答, 同时血清IL-10水平上升; 而$B7\text{-}H1^{-/-}$小鼠感染*H. pylori*后, Treg表达水平和*H. pylori*定植量均有所降低, 这一研究结果提示Treg在*H. pylori*免疫逃逸和持续感染中起重要作用[92]. 最新的研究表明, *H. pylori*可以通过产生超氧化物歧化酶(Superoxide dismutase, SOD), 抑制NF-κB依赖路径促炎症因子的产生, 例如MIP-2(macrophage inflammatory protein 2), TNF-α, IL-6和IL-13等, 避免胃部产生过度炎症反应, 以利于其长期定植[93]. 也有研究表明, *H. pylori*还可以通过其产生的外膜囊泡(Outer membrane vesicle, OMV)诱导单核细胞表达COX-2(cyclo-oxygenase-2), 抑制人T细胞应答[94].

## 3 结论

*H. pylori*感染是导致人类发生慢性胃炎、消化性溃疡、胃腺癌和胃黏膜相关的淋巴样组织淋巴瘤的重要原因. 人一旦感染*H. pylori*, 如不进行有效的根除治疗, 将会终身携带该菌. *H. pylori*感染后, 机体能够启动固有免疫应答和适应性免疫应答, 固有免疫细胞、T细胞和抗体等都参与了机体对感染微生物的免疫反应, 但是这些免疫反应虽然具有一定的保护作用, 仍不足以实现机体对感染细菌的完全清除. *H. pylori*通过改装并减弱其PAMPs的免疫原性, 调控固有免疫细胞和T细胞的免疫应答, 来逃避免疫系统的识别和清除, 导致持续感染. 今后, 进一步深入了解与阐明在*H. pylori*感染过程中, 哪些免疫应答因素对清除细菌更为有利、以及如何增强机体产生的这类免疫保护反应、如何避免或减弱*H. pylori*引起的免疫逃避反应等将会为打破*H. pylori*在体内长期定植的现状, 最终有效根除*H. pylori*的感染, 减少*H. pylori*感染相关性疾病的发生, 尤其是胃腺癌的发生提供极大的帮助; 并为研发治疗或预防*H. pylori*感染的疫苗提供理论依据.

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