

# HMGB1/TLR信号通路在*H. pylori*感染中作用的研究进展

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## ■背景资料

早期研究认为高迁移率族蛋白B1(high mobility group box 1 protein, HMGB1)作为一种警报素在“危险信号”出现时可释放至胞外参与多种炎症与免疫反应。而其胞外受体-Toll样受体(Toll-like receptor, TLR)与幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染致病关系密切。因此HMGB1/TLR信号通路在*H. pylori*感染中可能发挥重要作用。

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## Role of HMGB1/TLR signaling pathway in *Helicobacter pylori* infection

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## Abstract

High mobility group box 1 protein (HMGB1), as a mediator of late inflammation, provides a wide therapeutic window. Extracellular HMGB1 as an endogenous injury-related molecule promotes the development of inflammation and damage by binding to its receptors. Studies have discovered that lipopolysaccharide and vacuolating cytotoxin A (VacA) of *Helicobacter pylori* (*H. pylori*) are strong stimulating factors of HMGB1 expression, and its extracellular receptors Toll-like receptors (TLRs) are closely associated with *H. pylori* infection and pathogenicity. Therefore, the HMGB1/TLR signaling pathway may play

an important role in inflammatory response and immune abnormalities caused by *H. pylori* infection. This article will discuss the role of the HMGB1/TLR signaling pathway in *H. pylori* infection.

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**Key Words:** High mobility group box 1 protein; *Helicobacter pylori*; Toll-like receptor; Inflammatory response; Immune abnormality

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## 摘要

高迁移率族蛋白B1(high mobility group box 1 protein, HMGB1)作为晚期炎症介质, 具有较宽泛的治疗窗口期。胞外HMGB1作为内源性损伤相关分子被其受体识别而促进其炎症和损伤的发生、发展。研究发现幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染后其脂多糖成分及细胞空泡毒素(vacuolating cytotoxin, VacA)可强烈刺激HMGB1的表达, 而其胞外受体-Toll样受体(Toll-like receptor, TLR)与*H. pylori*感染及致病关系密切。因此, HMGB1/TLR信号通路在*H. pylori*感染引起的炎症反应与免疫异常中可能发挥重要作用。现主要对其研究进展予以综述。

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**关键词:** 高迁移率族蛋白B1; 幽门螺杆菌; Toll样受体; 炎症反应; 免疫异常

**核心提示:** 近年来研究显示幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)所含的如脂多糖(lipopolysaccharide)成分及VacA蛋白可强烈刺激高迁移率族蛋白B1(high mobility group box 1 protein, HMGB1)表达, 推测HMGB1/Toll样受体(Toll-like receptor, TLR)信号通路在*H. pylori*感染导致的炎症反应与免疫异常中发挥重要作用, 因此干预

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HMGB1/TLR信号通路蛋白表达有望用于防治*H. pylori*感染相关的疾病.

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## 0 引言

幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是人类常见的致病菌之一, 在人群中的感染率高达40%-90%; *H. pylori*感染者不仅可引起上胃肠道疾病[如慢性胃炎、消化性溃疡、胃癌、胃黏膜相关淋巴组织(gastric mucosa-associated lymphoid tissue, MALT)淋巴瘤等]<sup>[1]</sup>, 还可引发许多胃肠道以外的疾病<sup>[2]</sup>. *H. pylori*的高感染率以及严重的致病性使之成为研究热点, 但其发病机制尚未完全阐明, 已明确炎症反应与免疫异常是*H. pylori*感染相关疾病的主要发病机制之一. 因此, 如何控制*H. pylori*感染并防止其导致的胃肠道内外疾病的发生发展成为*H. pylori*感染防治的关键问题.

近年来研究发现, 作为一种晚期炎症介质-高迁移率族蛋白B1(high mobility group box 1 protein, HMGB1), 相对于肿瘤坏死因子(tumor necrosis factor, TNF)、白介素(interleukin, IL)-1 $\alpha$ 、IL-6等经典炎症介质具有较宽泛的治疗窗口期. HMGB1是一种典型的“危险因子”, 正常情况下表达于胞核和胞浆, 仅在“危险信号”出现时释放至胞外发挥作用. 胞外的HMGB1不仅可直接充当炎性细胞因子参与天然免疫效应, 也可作为一种警报素激活抗原提呈细胞(antigen presenting cell, APC), 从而启动、增强特异性免疫应答<sup>[3]</sup>, 参与多种炎症与免疫反应. 本文重点阐述HMGB1及其Toll样受体(Toll-like receptor, TLR)信号通路在*H. pylori*感染引起的炎症反应与免疫异常中的作用.

## 1 *H. pylori*感染致病的重要机制-炎症反应与免疫异常

*H. pylori*是感染人类最常见的细菌之一, 全世界超过50%的人有*H. pylori*感染, 其中西方国家感染率为25%-50%, 发展中国家高达90%<sup>[4]</sup>. 自从1982年澳大利亚学者Warren和Marshall从慢性胃炎患者胃窦黏膜分离出*H. pylori*以来, *H. pylori*已经被公认为导致慢性胃炎、消化性溃疡等发生的致病菌, WHO在1994年将*H. pylori*列为I类

致癌因子<sup>[5]</sup>. *H. pylori*感染若不予根除, 将伴随人体一生. 其中, 90%的*H. pylori*感染者可无明显症状, 其余10%感染者将表现为慢性胃炎、消化性溃疡, 严重者可发展为胃癌、胃MALT淋巴瘤等消化系统恶性疾病<sup>[6]</sup>. 此外, *H. pylori*感染还参与特发性血小板减少性紫癜、缺铁性贫血及慢性荨麻疹等消化系以外疾病的发生<sup>[7-9]</sup>. *H. pylori*具有高感染率及严重的致病性, 使之成为近年来微生物学和临床医学领域最被关注的研究热点之一, 但其确切致病机制迄今尚未完全阐明. 因此, 深入阐明*H. pylori*感染相关疾病的发生机制, 探索干预*H. pylori*感染的新策略, 具有重要的理论和实践指导意义.

*H. pylori*感染所致的炎症反应与免疫异常是导致胃黏膜屏障损伤的重要机制之一. 人体感染*H. pylori*后, 能诱导胃黏膜上皮细胞应答分泌多种炎性细胞因子, 如IL-1、IL-6、IL-8和TNF- $\alpha$ 等, 从而诱发和促进炎症反应<sup>[10]</sup>; *H. pylori*感染还可激发机体产生强烈的细胞免疫应答, 表现为: 胃黏膜Th1细胞应答占优势, 通过分泌IL-2、 $\gamma$ -干扰素(interferon- $\gamma$ , IFN- $\gamma$ )、TNF等而导致持续的胃黏膜炎症反应, 机体无法清除*H. pylori*感染; 反之, Th2细胞可减缓黏膜炎症反应, 并抑制*H. pylori*定植于胃黏膜<sup>[11,12]</sup>; Th1细胞应答强度与疾病严重程度呈正相关<sup>[13]</sup>. 因此, Th1/Th2细胞偏移在*H. pylori*感染致病中起重要作用, 但导致其偏离的机制尚不清楚.

TLR家族是一类重要的模式识别受体, 包括TLR1-TLR13, 其表达于多种免疫细胞表面, 通过识别相应的病原体组分即病原相关分子模式(pathogen associated molecular pattern, PAMP)而启动胞内信号转导, 并参与炎症反应和适应性免疫应答. 已发现, PAMP-TLR信号通路与*H. pylori*感染致病关系密切<sup>[14]</sup>, 其机制为: *H. pylori*或其菌体成分[如脂多糖(lipopolysaccharide, LPS)、热休克蛋白60(heat shock proteins 60, HSP60)]与免疫细胞表面TLR结合 $\rightarrow$ 髓样分化因子88(myeloid differentiation factor 88, MyD88)依赖性信号途径 $\rightarrow$ 激活下游信号分子[核因子- $\kappa$ B(nuclear factor- $\kappa$ B, NF- $\kappa$ B)、丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPKs)、转录激活蛋白(activator protein 1, AP-1)等] $\rightarrow$ 促进炎症分子分泌 $\rightarrow$ 诱发胃黏膜炎症反应<sup>[15]</sup>. 虽然各种TLR共享下游信号通路, 但是不同的配体却能导致同一种TLR产生不同的免疫反应<sup>[16,17]</sup>. TLR信号通路除了参与*H. pylori*

■研究前沿  
TLR信号通路在*H. pylori*感染所致的炎症反应与免疫异常中发挥重要作用, 但目前确切机制尚不清楚, 这是当前乃至今后的研究热点.

### ■相关报道

大量研究证实胞外HMGB1可介导非特异性炎症反应,参与组织损伤、清除异物、组织修复等;启动、增强适应性免疫应答,广泛参与炎症反应、移植排斥反应、自身免疫病、肿瘤等多种免疫病理过程的发生和发展。

介导的炎症反应以外,还与Th1/Th2细胞偏移有关。不同病原体PAMP与固有免疫细胞表面相应TLR结合,介导不同炎性细胞因子合成与分泌,并诱导Th0细胞分化为不同功能亚群[Th1、Th2或调节性T细胞(regulatory T cells, Treg)等]<sup>[18]</sup>,但其确切机制尚不清楚。

## 2 HMGB1参与*H. pylori*感染相关疾病的发生

HMGB1属高迁移率蛋白(high mobility group protein, HMG)家族成员,因在聚丙烯酰胺凝胶电泳中具有高迁移能力而得名。正常情况下, HMGB1广泛存在于各类组织细胞胞核内,发挥调节基因转录、稳固胞核结构等功能<sup>[19]</sup>。在组织细胞坏死或某些免疫细胞遭受刺激的情况下, HMGB1作为一类重要的损伤相关的分子模式(damage associated molecular pattern, DAMP),可被动或主动地释放至胞外<sup>[20]</sup>。胞外HMGB1的主要受体是晚期糖基化终末产物受体(receptor for advanced glycation end products, RAGE)、TLR2和TLR4<sup>[21-23]</sup>,其中TLR4是HMGB1介导细胞因子释放所必需<sup>[24-26]</sup>。胞外HMGB1与相应受体结合,可发挥多种生物学效应:(1)介导非特异性炎症反应<sup>[27,28]</sup>,参与组织损伤、清除异物、组织修复等;(2)激活树突状细胞(dendritic cell, DC),促进CD4<sup>+</sup>T细胞分化、增殖<sup>[29]</sup>,启动、增强适应性免疫应答;(3)广泛参与多种免疫病理过程的发生和发展<sup>[30]</sup>,如急慢性炎症(脓毒症、肺炎、肝炎等)<sup>[31-33]</sup>、自身免疫病(如系统性红斑狼疮、类风湿性关节炎等)<sup>[34-36]</sup>、肿瘤<sup>[37]</sup>、移植排斥反应<sup>[38]</sup>等。

HMGB1介导的炎症反应与*H. pylori*感染相关疾病密切相关。*H. pylori*所含的LPS成分及细胞空泡毒素(vacuolating cytotoxin, VacA)蛋白均可强烈刺激免疫细胞分泌HMGB1<sup>[39,40]</sup>。释放至胞外的HMGB1与*H. pylori*毒素[VacA、细胞毒素相关蛋白A(cytotoxin-associated gene A protein, Cag A)]一样,均能通过MAPK磷酸化和核因子NF- $\kappa$ B途径促进多种炎性因子表达,从而介导或加重炎症反应<sup>[41]</sup>。*H. pylori*毒素VacA可刺激胃上皮细胞株AGS细胞高表达HMGB1,*H. pylori*毒素、HMGB1与IL-8可协同参与炎症反应<sup>[42]</sup>。临床资料也证明HMGB1与*H. pylori*感染相关,例如:慢性活动性胃炎患者血清HMGB1及其他警报素水平升高<sup>[43]</sup>;在*H. pylori*所致胃炎发病中,*H. pylori*可诱导HMGB1表达和释放,可能是参与胃肠黏膜免疫损伤的重要效应分子<sup>[44]</sup>。

另外, HMGB1介导的免疫调节作用与Th1/Th2细胞偏移有关。有研究发现,不同剂量HMGB1可通过抗原提呈细胞及协同刺激分子途径参与Th1/Th2、Tc1/Tc2亚群的调节<sup>[45]</sup>。因此,推测HMGB1在*H. pylori*感染引起的炎症反应与免疫异常中具有重要作用,但其作用机制尚待阐明。

## 3 丙酮酸乙酯(ethyl pyruvate, EP)抑制HMGB1释放的抗*H. pylori*感染策略

HMGB1参与多种疾病发生,以其为靶点探索相关的干预策略受到高度关注。已报道, HMGB1抗体、HMGB1 A box(HMGB1拮抗剂)、EP等可通过不同途径干预HMGB1表达和功能,均有可能成为临床干预HMGB1相关疾病的新策略<sup>[46-48]</sup>。其中, EP作用并非如HMGB1抗体或A box那样具有特异性,但其作为一种食品添加剂被美国食品和药品管理局划分为无毒性物质,因此具有重要的临床治疗开发研究的价值。

EP是丙酮酸的酯化物,研究发现丙酮酸在出血性休克和心肌、肝、肾的缺血再灌注模型中均有保护作用<sup>[49]</sup>,但其在水溶液中的不稳定性,限制了其在临床上的使用。为了开发出一种丙酮酸的稳定制剂,研究发现EP具有其相同的生物学作用,二者均能减轻大鼠肠黏膜损伤,并且等量EP溶液的保护作用更显著<sup>[50]</sup>。EP药效学作用的机制为:改善氧化还原反应所致细胞损伤;减少促炎因子分泌;增强抗肿瘤免疫;在不同条件下可抑制或促进细胞凋亡等。近年来发现, EP还是一种有效的HMGB1释放抑制剂。相关文献报道为<sup>[51-53]</sup>:抑制损伤早期炎症因子(IL-1 $\alpha$ 、IL-6、IL-8及TNF- $\alpha$ )产生,并降低感染后期致炎因子HMGB1释放;下调出血性休克鼠肝脏和肠黏膜NF- $\kappa$ B活性,抑制HMGB1等促炎因子释放,降低动物死亡率<sup>[54]</sup>;明显抑制LPS刺激的巨噬细胞主动分泌HMGB1、TNF- $\alpha$ 等,改善大鼠存活率<sup>[55]</sup>。因此, EP以其使用安全、作用稳定且具有较宽泛的治疗窗口期等优点,作为HMGB1拮抗剂在临床治疗中具有潜在应用前景,但其抑制HMGB1释放的确切机制尚不明确。

## 4 结论

HMGB1的生物效应的多样性及其分布的广泛性,使其在*H. pylori*感染相关性疾病中发挥重要的作用,但是大多数研究还处于临床实验探索阶段。阐明HMGB1/TLR信号通路在*H. pylori*感染引起的炎症反应和免疫异常中的作用,将为深入阐



明*H. pylori*感染相关疾病的免疫致病机制具有重要意义, 将为临床以HMGB1为靶点用于防治*H. pylori*感染相关疾病提供重要的实验依据。

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## ■创新盘点

本文较系统体现了HMGB1及其胞外受体TLR在*H. pylori*感染引起的炎症反应和Th1/Th2免疫反应异常中的作用, 指出HMGB1/TLR信号通路与*H. pylori*感染所致的疾病相关。

## ■应用要点

HMGB1及其TLR信号通路在*H. pylori*感染中表达上调或功能异常,有望通过EP抑制HMGB1释放调节*H. pylori*感染引起的炎症反应与免疫异常,从而寻求一种以HMGB1为靶点的抗*H. pylori*感染策略。

## ■名词解释

HMGB1: 一种高度保守的核蛋白,广泛分布于哺乳动物细胞。HMGB1先前也称HMG1、amphoterin或SBP-1,因在聚丙烯酰胺凝胶电泳中具有高迁移能力而得名。随着其晚期促炎作用的发现, HMGB1成为近年来医学研究的热点之一。

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#### ■同行评价

本文就HMGB1/TLR信号通路与*H. pylori*感染的关系进行阐述,并分析其在*H. pylori*感染所致的炎症反应与免疫异常中的重要性,具有一定创新性和实用性,目前相关文献不多,可给读者带来新信息。

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