•综述•

幽门螺杆菌外膜囊泡: 从免疫逃逸机制到治疗潜力新视角

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摘要: 幽门螺杆菌 (*Helicobacter pylori*) 全球感染率高达48.5%, 中国约为42.8%, 其胃内定植能力与慢性胃炎、胃癌等疾病密切相关。目前抗*H. pylori*主流抗生素疗法因抗生素耐药性及高复发率, 临床应用受限, 因此亟需开发新型治疗策略。研究表明, *H. pylori*的持续感染依赖其免疫逃逸机制, 而外膜囊泡 (outer membrane vesicles, OMVs) 作为病原体与宿主相互作用的关键媒介, 可通过递送毒力因子、核酸等物质, 介导多重免疫逃逸途径。深入解析OMVs介导的*H. pylori*免疫逃逸机制, 是突破基于OMVs的*H. pylori*疫苗研发瓶颈与开发新型靶向治疗策略的核心前提。本文系统综述*H. pylori* OMVs介导免疫逃逸的最新研究进展, 剖析靶向治疗的挑战与转化困境, 并展望其临床干预前景, 为*H. pylori*防治提供新思路。

关键词: 幽门螺杆菌; 外膜囊泡; 免疫逃逸; 疫苗; 靶向治疗

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Helicobacter pylori outer membrane vesicles: From immune evasion mechanisms to novel therapeutic perspectives

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Abstract: *Helicobacter pylori* (*H. pylori*) infects 48.5% of the global population, with approximately 42.8% in China and is linked to chronic gastritis and gastric cancer. Current mainstream antibiotic therapies against *H. pylori* are limited in clinical application due to antibiotic resistance and high recurrence rates. Consequently, there is an urgent need to develop novel therapeutic strategies. Research indicates that persistent *H. pylori* infection relies on its immune evasion mechanisms. Outer membrane vesicles (OMVs) serve as critical mediators in pathogen-host interactions, facilitating multiple immune escape strategies by delivering virulence factors, nucleic acids, and other substances. Deciphering the mechanisms of OMVs-mediated immune evasion in *H. pylori* is pivotal for overcoming the bottlenecks in OMVs-based *H. pylori* vaccine development and devising novel targeted therapeutic strategies. This review synthesizes recent research advances in OMVs-driven immune evasion, analyzes challenges in translational applications, and proposes future directions to inform innovative anti-*H. pylori* strategies.

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幽门螺杆菌 (*Helicobacter pylori*) 是能在人类胃内酸性环境中定植的革兰阴性菌, 全球感染率约为48.5%, 中国感染率约为42.8%, 其感染与慢性胃炎、消化性溃疡乃至胃癌的发生发展密切相关[1]。目前, 主流抗生素疗法因耐药性蔓延、复发率高及不良反应等问题, 临床疗效日益受限, 亟需开发新型干预策略[2-5]。*H. pylori*的持续感染在很大程度上依赖于其免疫逃逸能力, 而 *H. pylori* 外膜囊泡 (outer membrane vesicles, OMVs) 作为细菌与宿主互作的关键媒介, 在该过程中扮演核心角色。OMVs不仅递送毒力因子与核酸等活性成分, 还通过多种机制协助细菌逃避宿主免疫清除, 从而维持感染状态。

近年来研究发现, OMVs在细菌抗生素耐药性中也发挥重要作用。除介导免疫逃逸外, OMVs可通过载运耐药基因、屏蔽抗生素攻击以及营造免疫抑制微环境等方式, 进一步增强细菌的耐药表现[6], 这为理解 *H. pylori* 治疗的困难提供了新视角。

疫苗研发是防控 *H. pylori* 感染的关键方向, 然而, 由于该菌免疫逃逸机制复杂, 现有疫苗候选物在临床试验中效果尚不理想。OMVs作为细菌表面抗原的天然载体, 具有优良的免疫原性与佐剂潜力[7], 但其成分复杂性也要求研究者在利用之前必须充分解析其作用机制。因此, 系统阐明OMVs在免疫逃逸与耐药性形成中的功能, 不仅有助于揭示 *H. pylori* 持续感染的分子基础, 也为开发靶向OMVs的疫苗及治疗策略奠定理论依据。

本文将对 *H. pylori* OMVs的生物学特性、其在免疫调节与逃逸中的核心作用, 以及耐药性机制展开系统综述, 并进一步探讨OMVs作为疫苗平台或治疗靶点的转化前景, 以期为突破 *H. pylori* 感染防治瓶颈提供新思路。

1 *H. pylori*的致病机制和免疫逃逸策略

H. pylori 的致病性源于毒力因子、宿主免疫反应及免疫逃逸机制间的复杂互作。该菌依赖尿素酶、鞭毛、外膜蛋白和脂多糖 (lipopolysaccharide, LPS) 等因子实现胃黏膜定植[8,9]。其关键毒力因子空泡细胞毒素A (vacuolating cytotoxin A, VacA) 和毒素相关蛋白A (cytotoxin-associated gene A, CagA) 分别通过破坏胃黏膜屏障及干扰宿主细胞信号通路介导组织损伤[10-12]。值得注意的是, 这些致病成分可通过OMVs递送, OMVs的双层膜结构能抵抗胃内低酸与酶解环境, 从而增强 *H. pylori* 的定植与致病能力[13]。

H. pylori 感染会触发宿主固有免疫与适应性免疫应答, 引发胃黏膜持续性炎症[14,15]。在 *H. pylori* 引发的固有免疫反应中, 模式识别受体 (pattern recognition receptors, PRRs) 识别 *H. pylori* 的LPS、鞭毛蛋白等病原体相关分子模式 (pathogen-associated molecular patterns, PAMPs), 触发下游信号级联反应, 招募中性粒细胞浸润及辅助性T细胞1 (T helper cell 1, Th1) 型反应等 (表1)[16-27]; 且中性粒细胞和吞噬细胞等在清除病原的同时也介导适应性免疫的激活[28]。*H. pylori* 引发的适应性免疫的一种以Th1/Th17型反应为主导, 同时伴有显著调节性T细胞反应的混合T细胞应答, 这导致了持续的炎症和组织损伤, 而非细菌清除[29]; 另一种是由B细胞介导的、能够产生高水平循环抗体和黏膜抗体, 却不足以清除感染的体液免疫应答[30]。主要原因是 *H. pylori* 能够利用多种手段逃逸这类免疫攻击[31]。

H. pylori 通过分子伪装、主动免疫抑制、微环境重塑及物理逃避等方式逃避免疫监视 (表2)[32-47]。首先, 分子伪装包括对LPS结构进行修饰以降低Toll样受体4 (Toll-like receptor 4, TLR4) 识别效率, 以及通过定点突变策略削弱对鞭毛蛋白与受体TLR5的结合亲和力, 从而逃避PRRs的识别[32,33]。其次, 主动免疫抑制则表现为VacA经脂筏内吞作用进入宿主细胞诱导线粒体功能障碍, 破坏T细胞、B细胞和树突状细胞 (dendritic cells, DCs) 活性[34,35]; CagA经细胞IV型分泌系统 (type IV secretion system, T4SS) 抑制NOD样受体热蛋白结构域相关蛋白3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3) 炎症小体活化, 并上调程序性死亡配体-1 (programmed cell death ligand 1, PD-L1) 抑制T细胞功能[36-41]; VacA与CagA还可协同调控自然杀伤 (natural killer, NK) 细胞组2成员D (natural killer group 2 member D, NKG2D) 系统, 其中VacA诱导胃上皮细胞表达NKG2D配体主要组织相容性复合体I类链相关基因A/B (MHC class I chain-related protein A and B, MICA/MICB), CagA则通过激活去整合素−金属蛋白酶17 (a disintegrin and metalloproteinase 17, ADAM17) 促使配体脱落, 形成可溶性分子sMICA/sMICB, 进而抑制NK细胞和$CD8^+$ T细胞的细胞毒性, 促进免疫逃逸和癌变[42]。此外, 该菌还通过重塑微环境诱导免疫耐受, 其分泌的尿素酶分解尿素产氨, 破坏胃上皮屏障并抑制吞噬功能[13,43], 同时募集DCs诱导调节性T细胞扩

Table 1 Key pathways and molecular mechanisms of innate immune activation by *H. pylori* infection. PRRs: Pattern recognition receptors; PAMPs: Pathogen-associated molecular patterns; TLR: Toll-like receptor; LPS: Lipopolysaccharide; MyD88: Myeloid differentiation primary response gene 88; NF-κB: Nuclear factor kappa-B; IL: Interleukin; Th: T helper cell; DCs: Dendritic cells; CCL2: C-C Motif chemokine ligand 2; CXCL10: C-X-C motif chemokine ligand 10; JNK: c-Jun-N-terminal kinase; CpG: Cytosine-guanine dinucleotide; IFN: Interferon; NLRP3: NOD-like receptor thermal protein domain associated protein 3; ASC: Apoptosis-associated speck-like protein containing a CARD; NOD: Nucleotide-binding oligomerization domain; RIP2: Receptor interacting protein 2; MAPK: Mitogen-activated protein kinase; DC-SIGN: Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin

PRRs	PAMPs	Downstream signaling pathway	Effector molecules	Involved cell types	Biological function	Ref.
TLR2/4	LPS, lipoproteins, peptidoglycan	MyD88/NF-κB pathway	IL-8, IL-12, IL-23, IL-2, IL-6	Gastric epithelial cells, neutrophils, monocytes, DCs	Activates Th1 immune response	[16-19]
TLR5	Flagellin	MyD88/NF-κB pathway	CCL2, CXCL10	Gastric epithelial cells, neutrophils, monocytes, DCs, T cells	Antiviral response, activates Th1 immune response	[20]
TLR6	/	JNK pathway	IL-8, IL-1β	Gastric epithelial cells, neutrophils	Activates inflammatory pathways, eliminates pathogens	[21]
TLR3/7/8/9	RNA, CpG DNA	NF-κB/IFN pathway	IL-17, IL-8	Gastric epithelial cells, neutrophils, monocytes, macrophages, DCs	Activates inflammatory pathways	[22-24]
NLRP3	/	ASC/caspase-1 inflammasome	IL-1β, IL-18	Gastric epithelial cells, macrophages, neutrophils	Inflammasome activation	[25]
NOD1/ NOD2	Peptidoglycan	RIP2/NF-κB pathway, MAPK pathway	IL-8, IL-17	Gastric epithelial cells, neutrophils, DCs	Activates Th1 immune response, promotes antigen presentation	[26,27]
DC-SIGN	Fucosylated ligands	NF-κB pathway	IL-10	Gastric epithelial cells, DCs, macrophages	Enhances anti-inflammatory response	[25]

Table 2 Core strategies for immune evasion by *H. pylori*. VacA: Vacuolating cytotoxin A; CagA: Cytotoxin-associated gene A; T4SS: Type IV secretion system; PD-L1: Programmed cell death ligand 1; NKG2D: Natural killer group 2 member D; sMIC: Soluble MHC class I chain-related protein A and B; TGF-β: Transforming growth factor-β; OMV: Outer membrane vesicles

Strategy	Key molecules/ pathways	Target cells	Mechanism of action	Net immunological effect	Ref.
Molecular camouflage	LPS modification	DCs, macrophages	Low-acylated/ monophosphorylated lipid A evades TLR4 recognition	Suppression of innate immunity	[32,33]
	Flagellin variation	Epithelial cells, immune cells	Evades TLR5 recognition	Suppression of innate immunity	[33]
Direct immune cell inhibition	VacA	T cells, B cells, DCs	Induces mitochondrial dysfunction, inhibits activation and proliferation	Suppression of adaptive immunity	[34,35]
		Macrophages	Induces apoptosis	Suppression of phagocytic clearance	
Signaling interference & recognition disruption	CagA/T4SS	Epithelial cells, macrophages	Inhibits NLRP3 inflammasome activation	Suppression of pro-inflammatory response	[36-39]
	CagA/PD-L1 axis	T cells	Upregulates PD-L1 to inhibit T-cell function	Suppression of T-cell activity	[40,41]
	CagA/VacA-NKG2D Axis	NK cells, $CD8^+$ T cells	Induces sMICA/sMICB shedding, inhibiting cytotoxicity	Suppression of cellular killing	[42]
Microenvironment remodeling	Urease/ammonia	Phagocytes, epithelial cells	Disrupts epithelial barrier; inhibits phagocytic function	Suppression of clearance; promotion of tissue damage	[43]
	Treg induction	Microenvironment	Promotes secretion of IL-10 and TGF-β	Suppression of Th17 immunity; induction of tolerance	[44]
Physical Evasion	Biofilm formation	-	OMV-mediated aggregation blocks immune access	Immune evasion	[45-47]
	Intracellular residency	-	Provides a physical niche	Immune evasion	

增及白介素 (interleukin, IL)-10、转化生长因子-β (transforming growth factor-β, TGF-β) 分泌, 从而抑制Th17免疫[44]。最后, 生物膜形成和上皮细胞内寄生则为其提供了物理性庇护[9,45-47]。研究表明, *H. pylori* OMVs有利于细菌生物膜的形成, 且*H. pylori*生物膜形成依赖于OMVs介导的细胞间聚集作用[7]。

综上, *H. pylori* 通过上述多种机制成功逃避宿主免疫监视, 实现长期定植, 其作用方式并不仅限于细菌本身。近年来, 研究逐渐揭示, *H. pylori* OMVs作为其分泌的关键亚单位结构, 在递送毒力因子、增强细菌逃逸能力方面具有独特作用[13,48]。因此, 从整体病原体层面转向对其OMVs的研究, 有助于更深入地理解 *H. pylori* 如何在局部和系统层面协调免疫逃避行为。

2 *H. pylori* OMVs生物学特性与免疫调节功能

OMVs作为革兰阴性菌在生长过程中普遍释放的球形纳米结构, 源于细菌外膜的出芽和脱落[7,49]。其在细胞内通讯、微生物毒力和宿主免疫应答的调节中发挥着多种作用[50,51]。尽管 *H. pylori* OMVs在细菌致病和宿主免疫互作中的重要作用日益明确, 其介导免疫逃逸的具体分子机制仍缺乏系统性研究。但现有证据强烈表明, OMVs是 *H. pylori* 实现免疫逃逸和持续感染的核心载体。深入解析其机制, 对阐明 *H. pylori* 慢性感染机制及开发靶向 *H. pylori* OMVs的防治策略具有重要意义。

2.1 OMVs的生物学特性 OMVs外膜由LPS、磷脂及细菌外膜蛋白构成, 腔内包裹周质成分, 包括DNA、RNA、酶、毒素等[52]。*H. pylori* OMVs可携带VacA、CagA等毒力因子通过巨胞饮作用/吞噬作用进入人胃细胞及巨噬细胞、树突状细胞等免疫细胞[13,53-55]。作为细菌分泌系统的延伸, OMVs是 *H. pylori* 与宿主微环境互作的关键介质, 在细菌的定植、生存、致病和免疫调节中扮演着不可或缺的角色。

通常, 来自不同 *H. pylori* 的OMVs直径在20～300 nm之间, 少数直径为400～500 nm[56]。有研究表明OMVs直径随细菌生长期而变化。与从稳定期细菌分离的囊泡相比, 在早期对数期的细菌中分离的囊泡更大, 并可通过分泌IL-8介导更强的促炎反应[57]。此外, 蛋白质组学分析发现, 与亲代细菌相比, OMVs含有一系列不同的蛋白质。并且在 *H. pylori* 的生长过程中的不同阶段, OMVs的蛋白质组分存在很大差异, 如细菌生长后期的OMVs富含参与核心代谢通路、环境适应性代谢及氨基酸转运的蛋白质, 而来自早期对数期的OMVs包含更丰富的毒力因子, 如VacA、CagA、脲酶等[58]。OMVs在大小与组分上呈现的异质性[59,60], 充分揭示了这类膜性结构的动态生物学特征, 同时也彰显了其作为病原体感染介导因子或生物体间信息传递载体的潜在可塑性。

2.2 OMVs介导的细胞间通讯及其宿主细胞靶向能力 OMVs作为关键的纳米级载体, 在 *H. pylori* 与宿主细胞的相互作用中扮演核心角色, 并展现出针对宿主细胞的固有靶向能力。

H. pylori OMVs表面展示的血型抗原结合型(blood group antigen-binding adhesion, BabA)和唾液酸结合型黏附素 (sialic acid-binding adherence, SabA) 能够识别并结合胃上皮细胞表面富含的Lewis血型抗原, 据此介导其高效内化[61]。在此过程中, *H. pylori* OMVs为其内容物, 包括重要的毒力因子如CagA、VacA、脲酶等提供保护性屏障, 抵御胃内严苛的酶解和酸性环境破坏, 并将这些效应分子直接转运至宿主细胞胞浆。最终, 这些效应分子精确调控宿主细胞功能, 诱导细胞凋亡、增殖及迁移, 干扰信号通路, 促进炎症反应或改变基因表达, 进而参与胃炎、溃疡甚至胃癌的发生发展[7,62,63]。

此外, *H. pylori* OMVs能够穿透胃黏膜屏障, 进而将细菌源性效应分子递送至胃上皮深层组织或扩散至更远部位。同时, *H. pylori* OMVs能够穿透黏膜屏障、血脑屏障乃至胎盘屏障, 将细菌源性效应分子递送至宿主体内难以直接抵达的解剖部位引发免疫刺激反应[64,65]。

2.3 *H. pylori* OMVs介导免疫调节与逃逸的机制 *H. pylori* OMVs通过其携带的多种组分, 展现出复杂且看似矛盾的免疫调节功能。大量研究表明, 这些功能的最终目的是协同促进细菌的免疫逃逸, 以实现长期定植。其作用可概括为“双面免疫调节”: 在感染早期, *H. pylori* OMVs通过其携带的LPS、肽聚糖等PAMPs激活巨噬细胞与DCs, 诱导IL-8、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α) 等促炎因子释放, 并以其外膜蛋白作为抗原激活Th1/Th17分化, 从而驱动炎症、破坏胃黏膜屏障以利于定植[66]。这种早期促炎反应有助于破坏胃黏膜屏障, 为细菌定植创造条件。而在慢性感染期, OMVs则表现出强烈的免疫抑制与耐受诱导倾向。如 *H. pylori* OMVs能直接抑制T细胞活性, 削弱宿主免疫防御能力[64]; 其机制与某些肠道共生菌OMVs诱导调节性T/B细胞分化、分泌IL-10、TGF-β等抗炎因子以促进免疫耐受的策略类似[67,68]。

上述“双面免疫调节”的底层机制, 实质上是OMVs执行免疫逃逸的多种分子途径 (表3)[48,69-74]。在逃逸天然免疫识别层面, *H. pylori* OMVs所携带LPS因其脂质A结构域为低酰化及单磷酸化形式, 能显著削弱其免疫原性, 从而使其能够逃逸宿主TLR4介导的免疫识别[48]。在直接调控免疫细胞功能层面, *H. pylori* OMVs可通过携带VacA经线粒体途径诱导巨噬细胞凋亡, 并直接抑制B细胞与T细胞的活化和增殖, 从而阻碍抗原呈递[69]。值得注意的是, OMVs还能通过递送VacA激活胃上皮细胞的核因子κB (nuclear factor kappa-B, NF-κB) 通路诱导IL-8分泌, 甚至可以

不依赖VacA直接刺激上皮细胞产生持续性炎症, 有利于其胞内存活与传播[70]。此外, 近年研究揭示了OMVs介导免疫逃逸的前沿机制。其一, 在OMVs与宿主外泌体的相互作用网络中, *H. pylori* OMVs通过携带热休克蛋白 (heat shock protein, HSP) 60/70等毒力因子, 激活宿主TLR通路, 并与宿主外泌体双向传递热休克蛋白, 放大NF-κB信号并持续分泌IL-8, 最终驱动慢性炎症向癌变转化[71]。其二, 小非编码RNA (small non-coding RNA, sncRNAs) 调控假说为OMVs介导的免疫逃逸提供了新视角。现有证据表明: *H. pylori* OMVs中富集的特定sncRNAs (sR-2509025/sR-989262) 可能在不同感染阶段发挥适应性调控作用。体外实验证实, 这些sncRNAs可直接进入胃上皮细胞并靶向宿主, 抑制IL-8等促炎因子的分泌, 因此被认为是一种在感染早期或局部微环境中利于细菌初始定植的免疫逃逸机制[72]; 然而, 动物研究则显示, 相同的sncRNAs可显著提升血清IgG/IgA及局部sIgA水平, 进而增强宿主黏膜与体液免疫[73]。这种看似矛盾的双重调控暗示sncRNAs可能在感染早期介导局部免疫抑制以利于定植, 而在慢性期则参与调节体液免疫应答, 其精确的阶段特异性分子互作机制仍有待进一步解析[74]。

3 OMVs与抗生素耐药性

*H. pylori*抗生素耐药性的日益严峻, 是全球范围内其根除治疗失败的主要原因。近年来, OMVs作为一种在细菌通讯和致病中发挥关键作用的纳米载体, 其在抗生素耐药性中的潜在角色逐渐受到关注。尽管针对*H. pylori* OMVs的直接研究尚在起步阶段, 但基于对其他革兰阴性菌的深入研究, OMVs在推动细菌耐药性中的关键推手角色已愈发明确。其可以直接保护细菌免受抗生素攻击, 并通过多种机制增强细菌耐药性, 包括转移耐药基因、保持关键酶活性和促进外膜重塑[75,76]。此外, OMVs介导的免疫抑制也可能是导致抗生素治疗失败的一个重要间接因素。

首先, OMVs能够直接削弱抗生素的杀菌效果, 为细菌群体提供集体防护。研究发现, 肺炎克雷伯菌在接触多黏菌素等抗生素时, 会大量分泌OMVs以竞争性结合抗生素[77]。类似地, *H. pylori* OMVs也被证实能剂量依赖性地保护细菌免受克拉霉素和左氧氟沙星的杀伤[51], 展现了这种物理屏蔽作用的普遍性。其次, OMVs是水平基因转移的强大载体, 能包裹并保护质粒DNA或完整的耐药基因单元, 从而在不同菌种间加速耐药基因的扩散[78]。OMVs也可作为活性耐药酶的“运输船”。鲍曼不动杆菌的碳青霉烯酶可通过OMVs递送, 以水解抗生素[79,80]。最后, 除了抗生素的直接抗菌作用, 宿主的免疫系统在协同清除病原体过程中也至关重要。*H. pylori* OMVs强大的免疫调节与逃逸功能, 能够削弱宿主先天免疫与适应性免疫应答, 这种由OMVs营造的免疫抑制微环境, 可能显著降低抗生素的根除效率, 间接导致治疗耐受。综上所述, OMVs是*H. pylori*多重耐药性的关键推手。深入理解其作用机制, 为克服耐药性提供了新靶点。另一方面, OMVs所具备的强免疫原性的“双刃剑”特性, 也使其成为开发新型疫苗的理想平台。

4 *H. pylori* OMVs疫苗的开发潜力与机制优势

目前, OMVs已成功应用于B群脑膜炎奈瑟球疫苗的研发。基于OMVs的多组分疫苗4CMenB (商品名: Bexsero®) 已获得欧洲药品管理局与美国食品药品管理局的批准上市。该疫苗对多种血清型的B群脑膜炎球菌均具有广泛的保护效力, 非脑膜炎球菌疫苗包括百日咳、志贺菌、新型冠状病毒的OMVs疫苗已进入临床试验阶段[81,82]。在*H. pylori*感染的防治中, OMVs作为治疗干预靶点与疫苗载体的联合策略也展现出显著潜力[83-85]。OMVs能有效诱导全面且强烈的免疫应答, 包括体液免疫、Th1/Th17细胞免疫和黏膜免疫[84,86]。*H. pylori*疫苗常用的佐剂霍乱毒素、大肠杆菌不耐热毒素、铝佐剂和壳聚糖等因免疫刺激弱、毒性高、无法有效诱导特异性保护性免疫等问题而存在局

Table 3 Mechanisms of immune evasion mediated by *H. pylori* OMVs. HSP: Heat shock protein

Level of action	Key component	Target cell	Specific mechanism	Overall effect	Ref.
Evasion of innate immune recognition	Modified LPS	DCs, macrophages	Low-immunogenicity LPS evades TLR4 recognition	Suppression	[48]
Immunomodulation of immune cells	VacA	T cells, B cells	Inhibits lymphocyte activation and proliferation	Suppression	[69]
		Macrophages	Induces mitochondrial-dependent apoptosis	Suppression	[69]
Driving chronic inflammation & carcinogenesis	CagA, VacA, HSP60/70	Gastric epithelial cells	Activates NF-κB pathway, induces persistent IL-8 secretion	Promotion inflammation	[70]
		Host exosomes/ epithelial cells	Forms a feedback loop with host exosomes, amplifying NF-κB signaling	Promotion (inflammation→ carcinogenesis)	[71]
sncRNA-mediated immunomodulation	sR-2509025, sR-989262	Gastric epithelial cells	Inhibits secretion of pro-inflammatory cytokines	Suppression (early colonization)	[72-74]

限性[87,88]。*H. pylori* OMVs的强免疫原性使其优于传统佐剂, 和*H. pylori*一致, OMVs主要通过激活固有免疫并启动适应性免疫来激发保护性细胞免疫反应[89,90](图1), 尤其在于其能够高效驱动DCs介导的抗原交叉呈递, 这一过程是激活细胞毒性$CD8^+$ T细胞, 对抗细胞内病原体的关键[91]。另有研究表明, OMVs的作用远不止于激活, OMVs能为DCs提供显著的生存优势, 延长其抗原处理与呈递的窗口期, 从而为持续激活T细胞应答创造了有利的微环境[92]。

5 工程化改造OMVs: 逆转免疫逃逸与增强疫苗效力的协同策略

近年来, 研究者致力于对*H. pylori* OMVs进行工程化改造, 以增强其佐剂活性或赋予其递送特定免疫调节分子的功能。

最新一项研究将IL-17A或干扰素-γ (interferon-γ, IFN-γ)的真核表达质粒装载至OMVs, 构建重组疫苗。研究结果表明, 相比于野生型OMVs甚至霍乱毒素佐剂, 这种重组OMVs佐剂能在小鼠中诱导更强烈的体液免疫、黏膜免疫以及平衡Th1/Th2/Th17混合型免疫应答, 并最终实现了更显著的*H. pylori*清除效果[93]。

除主动递送免疫刺激分子之外, 靶向OMVs中固有免疫抑制成分也成为重要策略。研究表明, *H. pylori* OMVs中所含的sncRNAs (sR-2509025和sR-989262)可抑制宿主的Th1/Th17型免疫应答。敲除sR-989262或sR-2509025的OMVs经免疫小鼠口服后, 在小鼠中表现出良好的安全性, 并可显著提升血清IgG及黏膜sIgA水平, 同时有效激发Th1/Th17免疫反应, 这表明野生型OMVs中的sncRNAs可能抑制宿主的Th1/Th17保护性免疫, 其敲除成功逆转了免疫抑制, 提升了保护效力。

不仅如此, 对OMVs中LPS的抗原性改造也显示出良好前景。*H. pylori*可借由修饰脂质A磷酸基团逃逸TLR4的免疫识别, 从而逃逸宿主先天免疫应答。基于这一机制, 研究者尝试对LPS进行定向改造, 将其转化为免疫刺激性的单磷酸脂质A, 以用于疫苗佐剂。然而, 该策略需谨慎平衡免疫刺激强度: 活性过强易引发炎症反应, 而过弱则可能导致疫苗保护效力不足。值得注意的是, 一项研究通过敲除LPS修饰基因lpxF、lpxE增强其脂质A抗原性, 更进一步, 该研究将上述基因敲除株为基础, 构建了一种新型重组OMVs疫苗, 该疫苗能同时递送修饰后的脂质和尿素酶β亚基(urease subunit beta, UreB)、VacA和CagA抗原等多种保护性抗原, 从而实现对多血清型*H. pylori*的广谱免疫保护[73]。实验结果表明, 该OMVs重组疫苗可诱导特异性体液免疫应答及以Th17为主导的Th1/Th2/Th17混合免疫应答, 使小鼠免受*H. pylori*感染[73]。综上, 基于OMVs的疫苗策略通过协同干预克服免疫逃逸。这些工程化改造显著提升了OMVs疫苗的免疫原性、广谱性和保护效力, 为开发高效疫苗提供了新方向。

6 展望

OMVs作为宿主−病原体相互作用的关键参与者, 通过复杂的机制在免疫激活与抑制间取得平衡, 已成

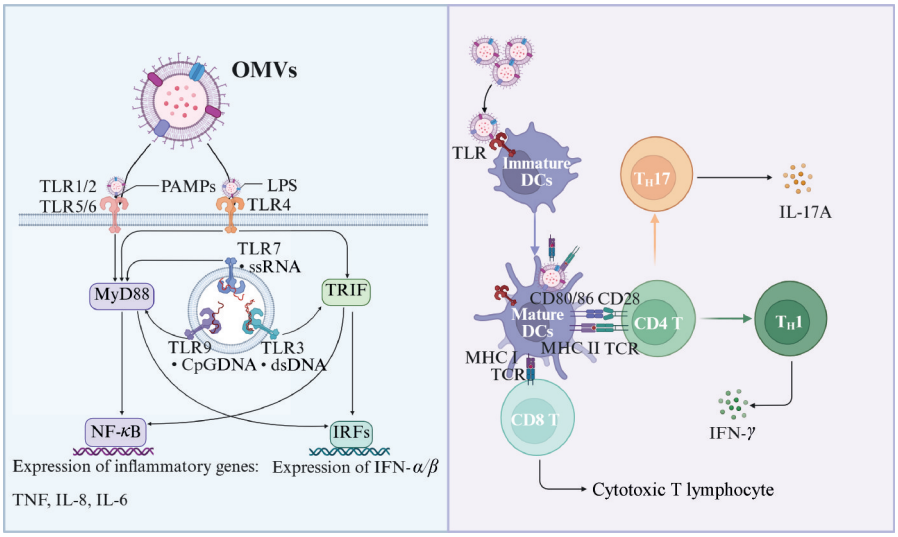


Figure 1 Immune responses induced by *H. pylori* OMVs. Left: Innate immune recognition and activation. Surface TLRs recognize various PAMPs carried by OMVs, such as LPS, flagellin, and nucleic acids. This triggers downstream signaling *via* the adaptors MyD88 or TRIF, activating transcription factors NF-κB and IRFs, which drive the expression of pro-inflammatory factors/co-stimulatory molecules and type I interferons, respectively. Right: Adaptive immune initiation. Activated antigen-presenting cells present antigens *via* MHC class II to $CD4^+$ T cells, promoting their differentiation into Th17. Concurrently, MHC class I cross-presentation activates $CD8^+$ T cells, driving their differentiation into cytotoxic T lymphocytes that directly clear infected target cells

为细菌跨界通讯的核心工具。尤其值得关注的是, 致病菌已进化出利用OMVs作为多功能武器以逃避宿主免疫防御的策略。深入解析OMVs在免疫调节、免疫逃逸与抗生素耐药性的作用机制, 不仅对揭示感染性疾病发病机制具有重要意义, 更将为开发新型抗感染策略及设计OMVs-based疫苗提供关键理论基础。

尽管前景广阔, 将*H. pylori* OMVs研究成果转化为临床应用仍面临严峻挑战。未来研究在继续解析其分子组成与体内动态作用的同时, 必须聚焦于其作为疫苗平台的临床转化瓶颈。与其他革兰阴性菌OMVs疫苗 (如已成功上市的脑膜炎奈瑟球菌OMVs疫苗) 相比, *H. pylori*因菌株抗原异质性高、微需氧培养条件苛刻且其OMVs天然携带更多免疫抑制成分等特殊性, 其疫苗研发面临着更为严峻的挑战。这些固有特性对实现疫苗的广谱保护性、规模化生产及安全性控制提出了更高要求。首先, OMVs的工程化改造须平衡安全性与免疫原性, 确保在“减毒”或增强免疫反应的同时不引发不良反应。其次, 须攻克其产业化生产的标准化难题, 解决*H. pylori*苛刻培养条件导致的产量、纯度和批次一致性等问题。未来的研究应致力于将OMVs从“免疫逃逸载体”重编程为“免疫激活平台”, 探索其作为治疗性疫苗或预防性疫苗的可行性。通过理性设计优化其组分, 并与佐剂策略联用, 有望克服固有的免疫抑制倾向, 真正释放其作为新型疫苗的巨大潜力。

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