

细菌糖质影响感染的研究进展

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摘要: 细菌糖蛋白、糖脂、多糖等多种成分统称为糖质, 其可作为重要的致病因子参与感染过程。细菌蛋白糖基化修饰主要包括 N-糖基化、O-糖基化、S-糖基化以及精氨酸化修饰。糖脂和多糖也是重要的糖质, 主要包括脂多糖、脂阿拉伯甘露聚糖、鼠李糖脂、肽聚糖、磷壁酸和荚膜多糖等。细菌糖质可促进宿主-病原体相互作用, 影响细菌毒力、耐药性以及生物膜形成等, 进而促进细菌感染。此外, 细菌糖质还可通过调控宿主免疫发挥双重作用: 一方面帮助细菌实现免疫逃逸, 引起机体感染; 另一方面激活宿主免疫, 帮助清除细菌、抑制感染。本文综述了细菌糖质的种类、结构特征, 以及其在黏附、定殖等感染过程中的作用, 还阐述了细菌糖质调控免疫影响感染的作用; 总结归纳了细菌糖质对感染的影响, 从糖质的角度为细菌感染致病机制研究提供了新视角, 也为以糖质为潜在靶点的新型药物研发提供了新思路。

关键词: 细菌; 糖质; 感染; 糖蛋白; 糖脂; 多糖; 免疫应答

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Research progress in the influences of bacterial glycans on infection

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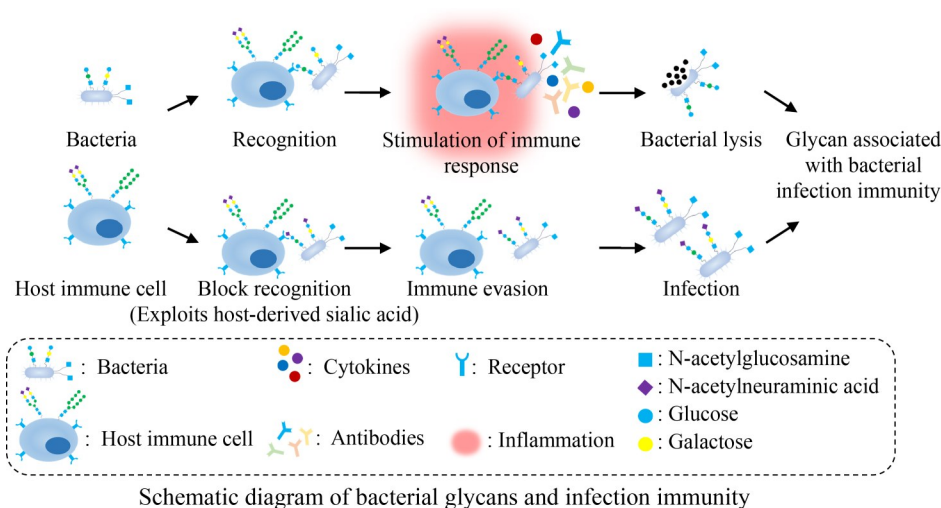
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Abstract: Bacterial glycoproteins, glycolipids, and polysaccharides are collectively known as glycans, which can serve as pivotal pathogenic factors leading to infection. Bacterial protein glycosylation mainly includes N-glycosylation, O-glycosylation, S-glycosylation, and arginine glycosylation. Glycolipids and polysaccharides are also important glycoconjugates, mainly including lipopolysaccharides, lipoarabinomannan, rhamnolipids, peptidoglycan, teichoic acids, and capsular polysaccharides. Bacterial glycoconjugates can promote host-pathogen interactions, influencing bacterial virulence, drug resistance, and biofilm formation, thereby facilitating bacterial infection. In addition, bacterial glycoconjugates can exert dual effects by modulating the host immune system: on one hand, aiding bacteria in achieving immune evasion and causing host infection; on the other, activating host immunity to help eliminate bacteria and suppress infection. This article provides an overview of bacterial glycans regarding the types, structural characteristics, roles in bacterial adhesion and colonization, and regulation of host immune responses and summarizes the effects of bacterial glycans on infection, aiming to offer a distinct perspective from glycoimmunology and an alternative strategy for clinical prevention and treatment of bacterial infectious diseases.

Keywords: bacteria; glycans; infection; glycoproteins; glycolipids; polysaccharides; immune response

Graphical abstract:



细菌是自然界中数量最多、种类最丰富、分布最广泛的微生物。细菌既可以作为正常菌群维持肠道稳态、抵抗病原微生物入侵,也可作为病原体导致多种疾病发生^[1]。细菌感染性疾病已成为全球第二大死因,2019年全球约有1 370万人死于细菌感染^[2]。

细菌感染与其糖质存在一定联系,其糖质主要包括糖蛋白、糖脂、多糖等^[3]。糖质不仅参与构成细菌结构,还可对细菌的黏附^[4]、侵入^[5]、毒力^[6]、耐药性^[7]以及生物膜(biofilm)形成^[8]产生影响,进而提高细菌对外界环境的适应能力,增强其感染宿主细胞的能力。此外,流感嗜血杆菌(*Haemophilus influenzae*)糖蛋白(HMW1)可利用其表面聚糖分子相互识别,从而黏附在宿主细胞表面^[9]。结核分枝杆菌(*Mycobacterium tuberculosis*)的脂阿拉伯甘露聚糖(lipoarabinomannan, LAM)能诱导机体免疫应答并调控免疫反应,进而出现免疫逃逸现象导致细菌性感染^[10]。本文通过总结归纳细菌糖质的类型、细菌糖质与感染的关系、细菌糖质与宿主免疫系统的相互作用等研究现状,以期深入了解细菌糖质在感染过程中的作用,为细菌感染机制的研究提供新思路。

1 细菌糖质的类型

1.1 细菌糖蛋白

细菌蛋白糖基化是常见的蛋白翻译后修饰方式之一,根据糖基化过程中是否需要寡糖转移酶(oligosaccharyltransferase, OST)可分为 OST 依赖性和 OST 非依赖性^[11]。OST 依赖性是指寡糖先与脂质载体形成脂连寡糖,随后通过 OST 将寡糖整体转移至靶蛋白;OST 非依赖性是指通过糖基转移酶依次将单糖转移至靶蛋白,这 2 种形式均可形成糖蛋白^[11]。根据寡糖连接位点的不同可分为 N-糖基化、O-糖基化、S-糖基化以及精氨酸糖基化,形成不同类型的糖蛋白^[11-12]。

1.1.1 细菌的 N-糖蛋白

N-糖基化是指寡糖识别多肽链中由天冬酰胺(Asn)-X [除脯氨酸(Pro)以外的任何氨基酸]-丝氨酸(Ser)/苏氨酸(Thr)组成的 3 个氨基酸序列,并连接到天冬酰胺的氮原子上形成 N-糖蛋白^[13]。

OST 依赖性 N-糖基化以空肠弯曲杆菌(*Campylobacter jejuni*)的研究最多。2002 年从空肠弯曲杆菌中鉴定出 PEB3 和 Cgp A 这 2 种 N-糖蛋白^[14]。空肠弯曲杆菌的蛋白 N-糖基化过程以尿苷二磷酸-N-乙酰半乳糖胺(uridinediphosphate-N-acetylgalactosamine, UDP-GalNAc)为起始,通过糖基转移酶 PglD、PglE、PglF 催化生成尿苷二磷酸-N,N'-二乙酰基胞壁酸(UDP-N,N'-diacetyl bacillosamine, UDP-diNAcBac),再由糖基转移酶 PglC 转移至脂质载体十一烯基焦磷酸(undecaprenyl pyrophosphate, Und-PP),然后通过 4 种糖基转移酶(PglA、PglJ、PglH、PglI)依次添加不同的单糖形成七糖链(diNAcBac-GalNAc-GalNAc-Glc-GalNAc-GalNAc-GalNAc),并借助翻转酶 PglK 将其转移至周质中,由寡糖 PglB 将七糖链释放到周质中或完整转移至靶蛋白的天冬酰胺残基上,上述参与 N-糖基化过程的酶由 Pgl 基因簇编码^[15]。

OST 非依赖性 N-糖基化过程常见于细菌黏附素蛋白和自动转运蛋白^[16]。流感嗜血杆菌借助糖基转移酶对黏附素蛋白 HMW1 进行 N-糖基化修饰,从而增强其对呼吸道上皮细胞的黏附能力^[9]。Gross 等^[17]水解 HMW1 片段后,发现该片段存在 31 个糖基化修饰位点,其中 30 个修饰位点位于天冬酰胺,其修饰位点的糖链成分包含葡萄糖、半乳糖和甘露糖。此外,Rempe 等^[18]报道金氏金氏菌(*Kingella kingae*)具有一种新型糖基转移酶,该酶与流感嗜血杆菌糖基转移酶具有同源性,可对三聚体自动转运蛋白 Knh 进行 N-糖基化修饰,从而增强细菌的自聚集能力和黏附性。

1.1.2 细菌的 O-糖蛋白

O-糖基化是指寡糖与多肽链中的丝氨酸

(Ser)/苏氨酸(Thr)中的氧原子连接,形成 O-糖蛋白^[11]。1995 年, Castric 等^[19]首次发现铜绿假单胞菌(*Pseudomonas aeruginosa*)糖基转移酶 PilO 可将三糖(α -5N β OHC47NFmPse-Xyl-FucNAc)转移至 IV 型菌毛蛋白 C 端的第 148 位丝氨酸,形成菌毛 O-糖蛋白^[20]。此外,奈瑟氏球菌属(*Neisseria*)的 OST 依赖性 O-糖基化研究较多,其糖基化过程以尿苷二磷酸-N-乙酰半乳糖胺(uridinediphosphate-N-acetylgalactosamine, UDP-GalNAc)为起始,通过糖基转移酶 PglB1/B2、PglC、PglD 形成 Und-PP-diNAcBac 或者 Und-PP-2,4-二乙酰氨基-2,4,6-三脱氧己糖(2,4-diacetamido-2,4,6-trideoxyhexose, GATDH),再通过糖基转移酶 PglA 和 PglE 催化形成 Und-PP-diNAcBac-Gal-Gal 或 Und-PP-GATDH-Gal-Gal,借助翻转酶 PglF 将其转运至周质中,最后利用寡糖转移酶 PglL 将糖链转移至受体蛋白^[21]。

OST 非依赖性糖基化常见于鞭毛蛋白和自转运黏附蛋白^[16]。研究表明类鼻疽伯克霍尔德氏菌(*Burkholderia pseudomallei*)鞭毛蛋白 FliC 仅有一个糖基化位点,而空肠弯曲杆菌鞭毛蛋白 FlaA 存在 19 个糖基化位点,这种修饰对鞭毛的正常组装是必需的,进而影响其对宿主的黏附和侵袭^[22-23]。此外,艰难拟梭菌(*Clostridioides difficile*)和单核增生李斯特氏菌(*Listeria monocytogenes*)等的鞭毛蛋白也存在类似糖基化^[24-25]。大肠埃希氏菌(*Escherichia coli*)庚糖基转移酶在细胞质对自转运黏附蛋白 AIDA-I 进行 O-糖基化,该糖基化缺失可明显降低其与肠道上皮细胞的黏附^[26]。

1.1.3 细菌的 S-糖蛋白

S-糖基化是指寡糖与多肽链中的半胱氨酸(Cys)的硫原子形成共价键^[11]。原核生物中蛋白质翻译后修饰以 N/O-糖基化较为常见,而 S-糖基化仅见于少数细菌的糖化素(细菌素)。例如,枯草芽孢杆菌(*Bacillus subtilis*)细菌素枯草菌肽(sublancin)^[27]、苍白好氧芽孢杆菌(*Aeribacillus pallidus*)细菌素帕博西尼(pallidocin)^[28]及苏云金

芽孢杆菌(*Bacillus thuringiensis*)细菌素 thurandacin A^[29],这些细菌素中的半胱氨酸可与葡萄糖形成 S-葡萄糖苷键。此外,Main 等^[30]报道植物乳植杆菌(*Lactiplantibacillus plantarum*)菌株能够产生一种新型的细菌素,名为 ASM-1,其分子结构中包含 O-连接和 S-连接的 N-乙酰葡萄糖胺。然而,关于 S-糖蛋白与感染免疫等生物学功能的研究仍较少。


























1.1.4 细菌的精氨酸糖基化蛋白

细菌蛋白的糖基化修饰除了上述 N-糖基化修饰、O-糖基化修饰、S-糖基化修饰外还有一种较为少见的精氨酸糖基化,即多肽链上的精氨酸连接 N-乙酰葡萄糖胺或鼠李糖^[31]。目前研究发现,肠致病性大肠埃希菌/肠出血性大肠埃希菌/腐蚀柠檬酸杆菌(*Citrobacter rodentium*)的毒力因子 NleB 家族、沙门氏菌(*Salmonella*)的毒力因子 SseK 家族、铜绿假单胞菌和脑膜炎奈瑟氏球菌属的毒力因子 EarP 家族具有糖基转移酶的活性,可催化精氨酸的 N-乙酰葡萄糖胺化或鼠李糖化^[31]。毒力因子 NleB 和 SseK 进入宿主细胞内可将 N-乙酰葡萄糖胺靶向转移至宿主的肿瘤坏死因子受体 1、丝氨酸/苏氨酸蛋白激酶 1、Fas 的相关蛋白等精氨酸残基上促进细菌感染和传播^[31]。铜绿假单胞菌 EarP 可催化其蛋白翻译延伸因子(elongation factor P, EF-P)第 32 位精氨酸的鼠李糖化,对其环境适应能力和毒力维持具有重要作用^[32]。

1.2 细菌糖脂

细菌糖脂是一类由糖类和脂质组成的复合物,位于细胞壁和细胞膜,主要包括脂多糖(lipopolysaccharide, LPS)、脂阿拉伯甘露聚糖(LAM)和鼠李糖脂等^[10,33-34]。脂多糖是革兰阴性细菌外膜的重要组成部分,它可阻止大多数疏水抗生素进入细菌,保障细菌在恶劣环境下的生存^[35]。脂多糖的 O-抗原多糖链的长短对沙门氏菌的生存有一定影响,长链 O-抗原多糖链可遮蔽脂质 A,减少补体成分(如 C3b)在细菌表面的沉积有效抑制补体膜攻击复合物(membrane

(续表 1)

Classification of glycans	Source of glycans	Name of glycans	Type of glycans	Major functions
	<i>Clostridioides difficile</i> ^[3,24]	Flagellin (FliC)	-S/T- ^{β-1}  -PO ₃ -D-Me	Adhesion, motility, flagellar protein stability
	<i>Listeria monocytogenes</i> ^[11,25]	Flagellin (FliC)	-S/T- ^β 	Adhesion, motility, immune regulation
	<i>Escherichia coli</i> ^[11,26]	Autotransporter (AIDA-I)	-S/T-  -  -  - 	Adhesion, invasion, Autoaggregation, biofilm formation
S-glycoprotein	<i>Bacillus subtilis</i> ^[27]	Glycocin (sublancin)	-C- ^β 	Inhibit the activity of methicillin-resistant <i>Staphylococcus aureus</i>
	<i>Aeribacillus pallidus</i> ^[28,30]	Glycocin (pallidocin)	-C- ^β 	Inhibit the activity of some Gram-positive bacteria
	<i>Bacillus thuringiensis</i> ^[29-30]	Glycocin (thurandacin A)	-C- ^β 	Inhibit the activity of <i>Bacillus thuringiensis</i>
	<i>Lactiplantibacillus plantarum</i> ^[30]	Glycocin (ASM-1)	-S/T- ^β  -C- ^β 	Inhibit the activity of some closely related <i>Lactobacillus</i> species and <i>Enterococcus faecalis</i>
Glycolipids	<i>Salmonella enterica</i> ^[43]	O-antigen polysaccharide	<p>Abe ^{α-1,3}-^{α-1,2}-^{α-1,2}-^{α-1,3}-^{α-1,4}-Und-PP</p> <p>Abe ^{α-1,3}-^{α-1,2}-^{α-1,2}-Und-PP</p> <p>Tyv ^{α-1,3}-^{α-1,4}-^{α-1,3}-Und-PP</p> <p>Par ^{α-1,3}-^{α-1,4}-^{α-1,3}-Und-PP</p>	Adhesion, invasion, outer membrane stability, signal recognition, immune evasion

(待续)

(续表1)

Classification of glycans	Source of glycans	Name of glycans	Type of glycans	Major functions
	<i>Mycobacterium tuberculosis</i> ^[10]	Lipoarabinomannan		Survival, virulence, immune regulation
	<i>Pseudomonas aeruginosa</i> ^[34]	Rhamnolipid		Inhibit the activity of <i>Klebsiella pneumoniae</i> and <i>Listeria monocytogenes</i> , surfactant
Polysaccharides	<i>Bacillus subtilis</i> ^[44]	Peptidoglycan		Survival, osmotic pressure stability, immune regulation
	<i>Escherichia coli</i> ^[44]			
	<i>Staphylococcus aureus</i> ^[39,45]	Wall teichoic acid		Toxicity, drug resistance, proliferation, immune regulation
	<i>Escherichia coli</i> ^[3]	Capsular polysaccharide K5		Toxicity, drug resistance, immune evasion
	<i>Acinetobacter baumannii</i> ^[3]	Capsular polysaccharide K83		Toxicity, drug resistance, immune evasion

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2 细菌糖质与感染

目前多项研究表明细菌糖质与感染过程密切相关,其在细菌的黏附、侵入、毒力、耐药和生物膜等方面发挥重要作用^[4-8]。细菌糖质参与细菌黏附过程如图 1A 所示。

2.1 细菌糖质与黏附

细菌糖质参与感染过程,而黏附是感染宿主过程的第一步^[4]。研究表明细菌糖质可帮助细菌黏附于宿主细胞表面进而引发宿主感染;糖质缺失会影响其黏附和定殖能力^[4]。Zamora 等^[46]研究发现敲除空肠弯曲杆菌糖基转移酶基因 *pglE* 可降低鞭毛 N-糖蛋白表达水平,进而影响其对肠道上皮细胞的黏附和定殖。Gault 等^[47]发现奈瑟氏球菌属中的 2 类菌毛蛋白均存在 O-糖基化修饰位点,其中 I 类菌毛蛋白有 1 个位点,II 类菌毛蛋白有 5 个位点。Poole 等^[48]进一步研究发现淋病奈瑟氏球菌属的菌毛蛋白上的 α/β -Gal 均能与人类宫颈上皮细胞的 III 型补体受

体的 I 型结构域结合,促进该菌黏附至宿主细胞。Le Guennec 等^[49]发现脑膜炎奈瑟氏球菌属通过 IV 菌毛能特异性识别宿主细胞表面 CD147/Basigin 受体中的 N-糖链;然而,CD147/Basigin 受体发生岩藻糖修饰可显著降低细菌的黏附。此外,酿脓链球菌(*Streptococcus pyogenes*)表面荚膜多糖能与呼吸道上皮细胞 CD44 分子特异结合介导细菌的迁移和黏附^[50]。一般而言,荚膜多糖的存在可增强细菌的黏附能力。Whiteway 等^[51]发现,与野生型相比鲍氏不动杆菌 $\Delta itrA$ 和 Δwza 突变体荚膜多糖合成减少,即荚膜多糖表达水平较低的突变株却表现出更强的黏附力,这表明荚膜多糖合成量可能与细菌黏附力密切相关。

2.2 细菌糖质与侵入

聚糖-凝集素相互作用在病原体穿透或侵入上皮屏障方面发挥着关键作用。研究表明细菌糖质与侵入过程密切相关^[4]。O-糖基化的鞭毛蛋白和菌毛蛋白作为细菌常见的糖质可影响其定

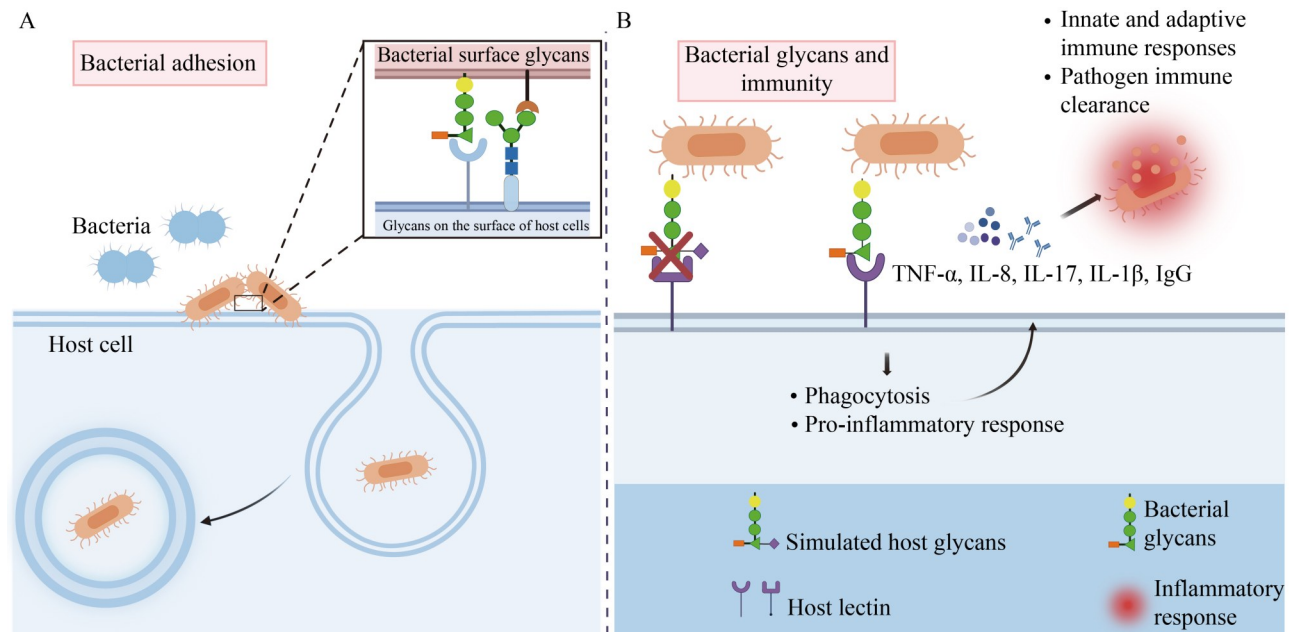


图1 细菌糖质与感染免疫示意图。A: 细菌黏附示意图; B: 细菌糖质与免疫示意图。

Figure 1 Schematic diagram of bacterial carbohydrates and immunity to infection. A: Schematic diagram of bacterial adhesion; B: Schematic diagram of bacterial glycosynthesis and immunity.

殖和侵入能力^[19]。例如,空肠弯曲杆菌的鞭毛蛋白被九碳唾液酸样糖修饰,使其能够穿透肠黏液到达上皮细胞底部,定殖于上皮细胞并引起炎症反应^[52]。Sacher 等^[53]研究发现噬菌体蛋白 FlaGrab 可特异性结合空肠弯曲杆菌鞭毛蛋白的九碳唾液酸样糖,导致其运动能力降低,无法到达肠上皮细胞的底部。Mahdavi 等^[54]研究发现敲除空肠弯曲杆菌鞭毛蛋白基因 *flaA* 可导致鞭毛糖蛋白 FlaA 合成受阻,进而降低突变体与人组织血型抗原(BgAgs)的结合能力,表明糖质缺失可能影响细菌的定殖和侵袭。此外,空肠弯曲杆菌表面的 N-糖蛋白可保护菌体免受环境中蛋白酶的水解,增强其环境适应力^[55]。Smedley 等^[56]发现,与铜绿假单胞菌野生型相比 $\Delta PiiO$ 菌株形成缺少 O-糖基化的菌毛蛋白,这导致其在小鼠肺组织中的存活能力下降。此外,肺炎链球菌荚膜多糖可促进其传播和定殖,其合成相关基因 *spd1672* 缺失会导致无法形成完整的荚膜多糖,使细菌失去感染宿主细胞的能力^[57]。

2.3 细菌糖质与毒力

细菌糖质与许多病原体感染宿主过程中产生的毒力高度相关,可直接或间接影响细菌感染^[3]。Iwashkiw 等^[58]发现鲍氏不动杆菌膜蛋白 O-糖基化缺失会导致该菌在小鼠腹膜炎模型中毒力较弱。铜绿假单胞菌基因 *rhIA* 参与毒力因子鼠李糖脂的合成及胶束形成过程,从而使巨噬细胞质膜迅速裂解^[34,59]。Van Gennip 等^[59]发现基因 *rhIA* 功能缺失会导致鼠李糖脂合成受阻且无法形成胶束,进而使铜绿假单胞菌无法分泌有效的毒力因子抵抗多形核白细胞杀伤,减少感染部位菌体含量,这或许可作为药物研发的依据。Yethon 等^[60]研究发现参与沙门氏菌 LPS 合成的基因 *waaP* 突变会导致其在宿主体内的生存和复制能力降低同时毒力减弱。此外,本课题组前期实验发现 N-糖苷酶(peptide:N-glycanase F, PNGase F)能去除细菌 N-糖链,协同 LPS 促进小鼠细胞因子风暴,加

重脑膜脓毒伊丽莎白金菌 (*Elizabethkingia meningoseptica*)感染的炎症反应^[61]。上述研究提示,细菌毒力因子的糖基化修饰对其致病性有一定影响,去除宿主细胞糖链也可促进细菌感染。

2.4 细菌糖质与耐药

研究表明糖质可影响细菌对抗菌药物的敏感性,使其耐药性发生变化。细菌耐药机制主要包括药物外排泵、外膜通透性、药物灭活酶等^[62-64]。Abouelhadid 等^[62]报道空肠弯曲杆菌周质的融合蛋白(CmeA)、内膜外排蛋白(CmeB)和外膜蛋白(CmeC)均存在 N-糖基化修饰以维持蛋白稳定性,且三者共同组成药物外排泵蛋白复合体,糖基化缺失可调控外排泵的活性,使其对抗生素的敏感性增加。革兰阴性菌富含 LPS 的外膜结构对维持细胞活力至关重要,破坏外膜结构会增加其对抗生素的敏感性。在外膜组装过程中 LPS 依赖于内膜上的脂多糖转运蛋白(LptB2FGC)水解 ATP,将 LPS 从内膜运输到外膜^[65]。Pahil 等^[65]开发了新型抗菌大环肽(zosurabalpin),其可抑制 LptB2FGC 复合物进而阻断 LPS 从内膜到外膜的运输,从而有效抑制鲍氏不动杆菌活性。此外,García-Quintanilla 等^[63]研究发现鲍氏不动杆菌 LPS 缺失可能会削弱其毒力,同时影响外膜通透性,使抗生素更容易进入胞内,也可能增加其对抗生素的敏感性。在低剂量的 β -内酰胺类抗生素作用下铜绿假单胞菌体内肽聚糖循环改变,导致 β -内酰胺酶 AmpC 表达量增加,从而使其耐药性增强^[64]。

2.5 细菌糖质与生物膜

研究表明细菌糖质在生物膜形成过程中发挥独特作用。生物膜可影响细菌毒力及耐药性,帮助细菌实现免疫逃逸,进而导致宿主感染^[66-68]。生物膜也称为生物被膜,是指附着在有生命或无生命物体表面、被细菌胞外大分子包裹的有组织的细菌群落,其主要成分包括蛋白质、甘露糖、岩藻糖等^[69]。Billings 等^[66]发现

铜绿假单胞菌生物膜基质中的胞外多糖 Psl 是早期生物群落抵抗外界药物侵害的第一道防线, 去除 Psl 可增强抗生素治疗早期感染的疗效。此外, Psl 还能阻止补体的激活, 阻碍中性粒细胞吞噬作用, 使菌体逃避机体的免疫攻击^[67]。Rainey 等^[68]报道, 变异链球菌生物膜基质中存在 2 个关键组分: 葡聚糖和环境 DNA (environmental DNA, eDNA), 糖基化转移酶缺失可导致葡聚糖含量下降, 进而影响其在大鼠龋齿模型中的毒力。除此之外, 金黄色葡萄球菌多糖细胞间黏附素、霍乱弧菌多糖、变形链球菌的葡聚糖和果聚糖等胞外多糖均可参与生物膜三维空间结构的形成^[70]。

综上所述, 细菌糖质可通过影响菌体的运动能力、毒力调控外膜通透性和生物膜等影响细菌的感染过程及耐药性。因此, 基于调控细菌的鞭毛蛋白、细胞膜蛋白、毒力因子等糖质信号可能对细菌感染或耐药性的防控具有重要意义。

3 细菌糖质对宿主免疫系统的作用

细菌糖质是细菌表面的重要组成部分, 不仅参与细菌的感染过程, 还与宿主免疫系统相互作用。一方面, 细菌糖质协助细菌采用“隐秘”的方式躲避免疫系统的攻击, 帮助细菌在宿主体内存活繁殖; 另一方面, 细菌糖质参与宿主免疫应答, 即宿主的模式识别受体识别病原体相关模式分子, 促使免疫细胞分泌细胞因子和趋化因子, 并募集吞噬细胞进入感染部位, 进而激发适应性免疫应答^[71]。细菌糖质与免疫的关系如图 1B 所示。

3.1 细菌糖质参与免疫逃逸促进感染

细菌糖质可通过模拟宿主细胞的聚糖结构、抑制补体的激活、抵抗吞噬细胞的吞噬、影响免疫细胞的识别和分化等机制来逃避免疫系统的攻击, 促进感染。

Hanuszkiewicz 等^[72]研究发现类鼻疽伯克霍尔德氏菌(*Burkholderia pseudomallei*)存在一种逃逸现象, 即该菌鞭毛蛋白糖基化会影响其与宿主细胞 TLR5 受体的相互识别, 进而显著降低宿主上皮细胞的炎症反应, 从而躲避免疫系统攻击。流感嗜血杆菌依靠自身产生的唾液酸转移酶(Lic3A/Lic3B)可在 LPS 末端添加 α -2,3/ α -2,8-唾液酸, 与无唾液酸修饰的流感嗜血杆菌相比唾液酸修饰使其抵抗补体杀菌能力提高约 30%^[73]。另一方面, 布鲁氏菌中的脂质 A 含有更长的脂肪酸链(C₂₈), 而典型的 LPS 脂肪酸链为(C₁₂₋₁₆), 这种结构改变显著减少了对 TLR4 的激活, 从而帮助其实现免疫逃逸促进感染^[74]。此外, 幽门螺杆菌(*Helicobacter pylori*)通过修饰 O-抗原多糖上的海藻糖残基进而生成 Lewis 抗原 I 型和 II 型, 其中 II 型抗原与人细胞表面的 Lewis 血型抗原高度相似, 这种模拟宿主细胞表面抗原的结构使其躲避宿主 TLR4 免疫识别^[75]。值得注意的是, 作为脂多糖的重要组成部分 O-抗原多糖在免疫逃逸中扮演关键角色。例如, 沙门氏菌 O-抗原多糖的高度变异性使宿主难以产生广谱抗体, 同时 O-抗原多糖的长短和侧链结构可遮蔽抗体结合的关键位点, 由此躲避免疫系统攻击促进其持续感染^[36]。Yethon 等^[60]研究发现沙门氏菌 *waaP* 突变株的 O-抗原多糖链合成缺陷对血清补体杀菌作用的敏感性显著增加, 导致其毒力减弱。Yuan 等^[76]则发现结核分枝杆菌的甘露糖阿拉伯甘露聚糖(mannose-capped-lipoarabinomannan, ManLAM)通过激活 TLR2/MyD88/PI3K/AKT/Ap-1 和核因子 κ B (nuclear factor kappa-B, NF- κ B)信号通路诱导 B 细胞产生细胞因子白细胞介素(interleukin, IL)-10, 进一步抑制 CD4⁺ Th1 介导的免疫应答, 进而躲避免疫系统的清除导致宿主慢性感染。脑膜炎奈瑟氏球菌属的菌毛蛋白发生 O-糖基化后还进一步被磷酸胆碱修饰, 影响其与呼吸道上皮细胞的血小板激活因子受体的相互识别^[77]。除菌毛修饰外, 大部分侵袭性脑膜炎奈瑟氏球菌属

表面均存在荚膜多糖抗原, 它可通过影响 IgG Fc 段与 C1q 的结合减少 C4b 的沉积, 从而抑制补体经典途径的激活, 帮助该菌躲避补体的杀伤作用^[78]。不仅如此, 脑膜炎奈瑟氏球菌属的荚膜多糖还可隐蔽其表面的抗原表位, 一方面使 IgG 无法与抗原表位结合, 另一方面也使 Fc 段与中性粒细胞表面 Fc γ 受体结合受阻, 因此抑制中性粒细胞的吞噬作用^[79]。Yang 等^[80]进一步研究发现高度 O-乙酰化的多唾液酸荚膜多糖与唾液酸结合免疫球蛋白样凝集素(siglec)的结合能力下降约 300%–400%, 同时还可阻止内吞小泡与溶酶体融合避免溶菌酶降解。最后, Newton 等^[81]研究发现肠致病性大肠埃希菌的 Nle E/Nle B 阻断了转录因子 NF- κ B 的 p65 亚基向细胞核的移位, 降低肠上皮细胞中 IL-8 的表达, 借此调控炎症反应。

3.2 细菌糖质激活宿主免疫应答

免疫应答是宿主免疫系统识别抗原性物质, 通过效应机制调控其清除或耐受的动态生物学过程, 涵盖固有免疫与适应性免疫两大协同体系。细菌糖质作为关键抗原可通过模式识别受体激活固有免疫, 也可经抗原提呈触发适应性免疫, 部分糖质还可诱导免疫耐受从而双向调控感染进程^[82]。

研究表明在固有免疫应答中空肠弯曲杆菌借助 N-糖蛋白感染宿主细胞后依赖 α -激酶 1 (alpha kinase 1, ALPK1) 激活 NF- κ B 通路产生 CXCL1、CXCL10、CCL2 等炎症趋化因子, 通过募集免疫细胞到达感染部位、释放炎症因子和抗菌蛋白、吞噬病原体等机制抵抗感染^[4]。此外, 朗格汉斯细胞表面受体 Langerin (CD207) 特异性识别金黄色葡萄球菌细胞壁中的 β -1,4-N-乙酰氨基葡萄糖, 激活免疫应答, 进而促进炎症因子 IL-8、IL-17 和肿瘤坏死因子(tumor necrosis factor, TNF)- α 释放导致皮肤炎症^[83-84]。在细菌脂多糖(LPS)介导的炎症反应方面, LPS 与 TLR4 互作后巨噬细胞发生代谢重编程, 驱动 ATP 的产生从氧化磷酸化转为糖酵解, 从而减

少对 F1FO-ATP 合酶活性的依赖, 进而提高质子动力, 导致产生线粒体衍生的活性氧促进 IL-1 β 的释放^[85]。Voss 等^[86]进一步证明, LPS 与小鼠巨噬细胞表面 CD300b 的结合能增强其与 TLR4-MyD88-TRIF 复合体的相互作用, 进一步促进下游 DAP12-Syk-PI3K 的激活, 并最终抑制 IL-10 的产生, 加剧炎症反应。不仅如此, 在 LPS 引起的系统性炎症过程中宿主细胞可释放外囊泡捕获血液循环中的 LPS, 并将其递送至宿主细胞内, 胞质内的半胱氨酸蛋白酶 (caspase-4/5/11) 感知 LPS, 从而触发非经典炎症小体的激活, 最终导致细胞裂解死亡(焦亡)以及 IL-1 β 和 IL-18 的成熟释放^[87]。同时, Shi 等^[88]进一步研究发现, LPS 活化的 caspase-4 可切割 Pro-IL-18 第 36 位天冬氨酸并且该切割完全依赖 Pro-IL-18 中 33–36 位的四肽序列 LESD, 揭示了非经典的炎性小体介导的 LPS-caspase-4/5-IL-18 作用机制。此外, Zhou 等^[89]研究发现 LPS 合成过程中的重要中间代谢产物二磷酸腺苷庚糖能与宿主细胞内的新型激酶分子 α -激酶 1 (ALPK1) 特异性识别, 进而激活 NF- κ B 通路, 产生 MCP-1、IL-1 β 、MIP-1 α 等细胞因子和趋化因子, 募集中性粒细胞到达小鼠肺部炎症感染部位参与免疫清除。在结核分枝杆菌感染中, 其甘露糖阿拉伯甘露聚糖(ManLAM)与 C 型凝集素受体(dectin-2)识别可促进 DC 细胞分泌细胞因子, 提高 DC 细胞抗原提呈能力, 激活初始 T 和 B 淋巴细胞, 进而启动适应性免疫应答^[90]。此外, LAM 糖脂结构一方面能被 CD1 分子识别并呈递给 CD1 限制性 CD8⁺ T 细胞, 从而激活免疫细胞分泌干扰素(interferon, IFN)- γ 等炎症因子介导炎症反应; 另一方面通过释放颗粒酶 B 和穿孔素等方式杀伤清除该菌^[91-92]。Weidenmaier 等^[93]发现金黄色葡萄球菌细胞壁中 N-乙酰葡糖胺可通过 MHCII 分子的提呈激活 CD4⁺ T 细胞增殖, 诱导小鼠皮肤感染模型形成皮肤脓肿。最后, Lei 等^[94]研究发现肠道微环境的岩藻糖基化水平能够影响产生 IgA 的 B 细胞增殖, 因此对维持

肠道免疫稳态和调控肠道炎症反应具有重要作用。

上述研究提示，细菌糖质对宿主免疫的影响是双向的。一方面，细菌通过模拟宿主表面的糖质、对表面糖质进行修饰以改变其抗原性等策略干扰宿主免疫激活；另一方面，宿主利用细菌的糖质与宿主细胞特异性识别后激活宿主免疫应答，促进炎症因子和趋化因子的释放，募集免疫细胞到达细菌感染部位发挥抗菌和免疫清除作用。

4 总结与展望

细菌的糖蛋白、糖脂及多糖等糖质是重要分子，不仅参与细菌结构组成，而且在黏附、定殖、侵入等细菌感染过程中发挥着重要作用。细菌糖质也可通过多种机制，如模拟宿主聚糖结构、抑制补体激活、抑制免疫细胞分化等躲避机体免疫系统的攻击，从而影响机体的免疫应答促进感染。研究表明特异性抑制空肠弯曲杆菌九碳唾液酸样糖的生物合成可导致其运动能力和致病性显著降低^[95]。因此，细菌糖质可能会成为新型抗菌药物研发的潜在新靶点，未来可用于研发调控细菌糖质的药物、筛选中药单体，从而发挥抗感染作用。

细菌糖质与感染的研究将会是微生物感染新的研究热点，相信还会有更多研究探索病毒糖质与感染、真菌糖质与感染的关系。糖质结构解析是阐明微生物糖质对感染影响的重要一环，因糖质结构具有复杂性和多样性的特点增加了研究难度。目前，糖质结构的常用分析方法包括聚糖微阵列芯片技术、次级离子技术、质谱、核磁共振和凝集素微矩阵等^[96-97]，然而糖结构分析的准确性和分析通量也是当前的瓶颈。糖蛋白的糖链结构解析通常可采用糖生物学研究广泛使用的工具酶 N-糖苷酶(PNGase F)以及本课题组发现的新型 N-糖苷酶(PNGase F-II)先将糖蛋白的糖链水解后，再结合质谱技术分析糖链的结构^[98-99]。此外，本课题组发现其他

糖苷酶如岩藻糖苷酶(cFase I)^[100]、木糖苷酶(gpcXase I)^[101]、 α -甘露糖苷酶(MA3)^[102]、 α -半乳糖苷酶(EmGalase)^[103]等可能作为糖质结构解析的工具为细菌糖质与感染的研究奠定基础。

糖质作为组成细菌结构的重要成分，一方面影响细菌生存，另一方面在细菌感染过程中发挥重要作用，为抗菌治疗药物的研发提供了独特视角。通过多学科交叉破解细菌糖质的“结构密码”与“功能密码”，例如将人工智能技术与糖组学技术结合应用于分析细菌糖质相关大数据、研究糖质在细菌与宿主相互作用中的功能有望开辟细菌感染、病毒感染及真菌感染研究的新纪元。

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作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

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