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Review 综述

靶向金黄色葡萄球菌 α-溶血素的防治策略

孙婷婷[1,2]，王新宇[1,2]，刘洋[1,2]，李應英[1,2]，王宇星[1,2]，徐飞[1,2*]

1 中国农业科学院饲料研究所，国家饲料中药物基准实验室，北京
2 农业农村部动物源细菌耐药性监测重点实验室，北京

孙婷婷, 王新宇, 刘洋, 李應英, 王宇星, 徐飞. 靶向金黄色葡萄球菌 α-溶血素的防治策略[J]. 微生物学报, 2026, 66(10): 4661-4678.
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摘　要：兼具高致病性和高抗药性的超级细菌是公共卫生领域的重要挑战，金黄色葡萄球菌(*Staphylococcus aureus*) α-溶血素(α-hemolysin, Hla)是介导其感染的关键毒力因子，也是防控的重要靶点。本文首先回顾了 Hla 晶体与七聚体孔道结构的特征；继而系统阐明了 *hla* 基因座以及 Agr 系统、Sar 蛋白家族、葡萄球菌辅助调节因子双组分系统(*Staphylococcal* accessory element regulator, SaeRS)和其他辅助调控因子对其表达的多重精细控制；从细胞及宿主受体 2 个方面揭示 Hla 的致病机理；最后重点总结了近年来靶向 Hla 的疫苗、单克隆抗体、天然化合物和纳米颗粒防治策略的研究进展，为金黄色葡萄球菌耐药感染精准预防提供新思路与候选方案。

关键词：金黄色葡萄球菌；α-溶血素(Hla)；致病机理；防治

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*Corresponding author. E-mail: xufei@caas.cn
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Prevention and treatment strategies targeting α-hemolysin (Hla) of *Staphylococcus aureus*

SUN Tingting[1,2], WANG Xinyu[1,2], LIU Yang[1,2], LI Yingying[1,2], WANG Yuxing[1,2], XU Fei[1,2*]

1 National Feed Drug Reference Laboratories, Institute of Feed Research of Chinese Academy of Agricultural Sciences, Beijing, China

2 Key Laboratory of Animal Antimicrobial Resistance Surveillance, Ministry of Agriculture and Rural Affairs, Beijing, China

Abstract: The emergence of superbugs with both high pathogenicity and high antimicrobial resistance poses a major challenge to public health. In *Staphylococcus aureus*, α-hemolysin (Hla) is a key virulence factor mediating infection and thus represents a crucial target for prevention and control. This review first summarized the structural characteristics of Hla in its monomeric crystalline form and heptameric pore assembly. It then systematically delineated the multi-layered and fine-tuned regulation of Hla expression, involving the *hla* gene locus, the Agr quorum-sensing system, the Sar protein family, the *Staphylococcal* accessory element regulator (SaeRS) two-component system, and other auxiliary regulators. The pathogenic mechanisms of Hla were further elaborated from the perspectives of both cellular effects and host receptors. Finally, this review summarized recent advances in prevention and treatment strategies targeting Hla, including vaccines, monoclonal antibodies, natural compounds, and nanoparticles, offering new insights and candidate approaches for the precise prevention of drug-resistant *S. aureus* infections.

Keywords: *Staphylococcus aureus*; α-hemolysin (Hla); mechanism of pathogenesis; prevention and treatment

金黄色葡萄球菌(*Staphylococcus aureus*)，简称金葡菌，是重要的人畜共感染革兰氏阳性致病菌。它可引起人类多种局部感染(如肺炎、伪膜性肠炎、心内膜炎)及全身性感染(如败血症、脓毒症)[1]。每年在全球范围内导致难以计数的皮肤感染和数十万至数百万例侵袭性感染[2]。该菌也是全球菌血症的主要病原之一，发病率居高不下[3-4]。在畜牧领域，金黄色葡萄球菌同样是关键病原，可引发奶牛临床型与亚临床型乳腺炎，导致产奶量下降、治疗成本增加和感染个体提前淘汰，对畜牧业造成重大经济损失[5-9]，并伴随一系列动物福利问题[10-11]，从而构成显著的公共卫生负担[12]。我国抗生素耐药性形势严峻，金黄色葡萄球菌是导致抗微生物药物耐药性(antimicrobial resistance, AMR)相关死亡的主要病原体之一，其中耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*, MRSA)表现突出[13]。

金黄色葡萄球菌是重要的人畜共患机会性致病菌。该菌可在健康成人的鼻腔中呈现无症状定植状态，但在免疫功能低下或者屏障破坏时可引发从局部感染到全身脓毒症等多种疾病。不同菌株的毒力因子谱存在显著差异，其致病潜能差异较大。致病性金黄色葡萄球菌可依赖于其分泌的多种毒力因子，包括溶血素、杀白细胞素、肠毒素、凝固酶和耐热核酸酶等，

✉ actamicro@im.ac.cn, ☏ 010-64807516

其中溶血素尤为关键[14]。α-溶血素(α-hemolysin, Hla)在人与动物疾病中的作用已被认识近百年。其发现可追溯至1928年的一次疫苗污染事件[15]，后经纯化与结构解析，逐步确立了其作为关键成孔毒素(pore forming toxins, PFTs)的地位[16-18]。金黄色葡萄球菌可产生α、β、γ、δ、ε等多种溶血素，其中Hla是对数生长后期分泌的主要外毒素之一[19]，但并非所有菌株均产生该毒素，其表达受生长阶段、环境信号及多层级调控网络的精密控制，呈现显著的菌株间和时间差异性。此外，Hla可作为一种水溶性单体分泌，在宿主细胞膜上自我组装形成跨膜β桶状七聚体通道[20]，可导致多种细胞的裂解死亡[21]。动物模型研究进一步证实，Hla能破坏大鼠肺组织的气血屏障，且缺失*hla*基因的菌株在小鼠感染模型中毒力显著减弱[22-23]。鉴于其在致病过程中的核心作用，Hla已成为研发新型抗感染药物的重要靶点。

本文系统概述Hla的分子生物学特性与致病机理，并重点综述近年来靶向该毒素的疫苗、单克隆抗体、天然化合物及纳米颗粒等防控策略的研究进展，以期为应对金黄色葡萄球菌感染提供新的思路与方案。

1 Hla的分子生物学特性

1.1 Hla的结构

首个高分辨率三维结构的α-溶血素发表于1996年，Song等[24]通过X射线晶体学成功对Hla的七聚体跨膜孔道复合物(即毒素在细胞膜上组装后的活性形式)进行结晶，获得了高质量晶体，收集衍射数据，经计算和建模，最终确定原子水平的三维结构，其孔道的结构解析至1.9 Å分辨率(图1)。该结构证实了Hla低聚物的七聚体亚基化学计量比，提示水溶性蛋白质中富含甘氨酸且溶剂暴露的区域，可通过自组装形成具有特定结构的跨膜孔道；同时，该结构也为深入理解β桶型成孔毒素(β-barrel pore-forming toxin)的膜相互作用机制及转运活性原理提供了依据[24-25]。

1.2 Hla的基因与调控

1.2.1 Hla的基因

1984年，Gray等[26]首次完成了*hla*基因及其编码蛋白的全序列测定。该基因座以单拷贝形式定位于金黄色葡萄球菌染色体上，在所测序的菌株中序列高度保守，其编码的蛋白质一级结构展现出近乎完全的氨基酸序列一致性；*hla*基因座编码产生由293个氨基酸组成的成熟

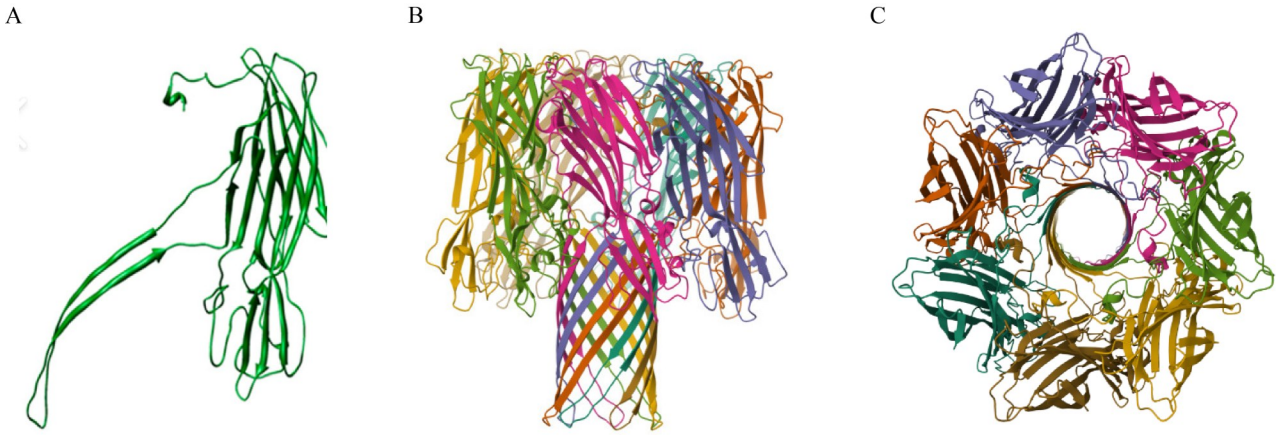


图1 金黄色葡萄球菌α-溶血素(Hla)结构(https://doi.org/10.2210/pdb7AHL/pdb)

Figure 1 Structure of *Staphylococcus aureus* α-hemolysin (Hla) (https://doi.org/10.2210/pdb7AHL/pdb). A: Monomer; B: Heptamer side view; C: Heptamer top view.

细胞外蛋白，约 33 kDa[27]。成熟的毒素几乎完全由 β 链组成，几乎无 α 螺旋结构[28]。尽管其基因序列与蛋白结构高度保守，但 Hla 的表达在转录水平上受到一个复杂而精密的调控网络的动态控制，主要包括群体感应系统、Sar 蛋白家族以及其他辅助因子等，以此发挥其致病性。

1.2.2 辅助基因调控系统

辅助基因调控系统(accessory gene regulator, Agr)是金黄色葡萄球菌关键的全局调控系统之一，其借助群体感应机制对 Hla 及其他毒力因子的表达进行调控。随着细菌群体密度的增加，胞外自诱导肽(autoinducing peptide, AIP)的积累浓度逐渐升高，当 AIP 浓度达到临界阈值时会启动双组分信号转导系统 AgrC-AgrA 的激活过程：首先 AIP 与细胞膜上的 AgrC 蛋白结合，触发 AgrC 发生自身磷酸化，随后磷酸基团被转移至 AgrA 蛋白；磷酸化后的 AgrA 蛋白会结合到 Agr 基因座上的 P2 和 P3 2 个启动子区域，其中 P2 启动子调控 Agr 系统自身的表达(维持系统活性)，P3 启动子则控制非编码 RNA (non-coding RNA, ncRNA)——*RNAIII*的表达；值得注意的是，*RNAIII*也是 Agr 系统的重要组成部分，它可通过直接结合 Hla 的 mRNA 分子起到稳定 mRNA 结构、促进其翻译过程的作用[29-30] (图 2)。

1.2.3 Sar 蛋白家族

葡萄球菌辅助调节(*Staphylococcal* accessory regulator, Sar)蛋白家族是与 Agr 系统协同作用的关键转录调控家族，不同成员的作用机制具有显著差异。根据序列与结构特征，该家族可分为 3 个亚类：单结构域蛋白(SarA、SarR、SarT、SarV、SarX 及 Rot)、双结构域蛋白(SarS、SarU、SarY)以及与 MarR 家族高度同源的单结

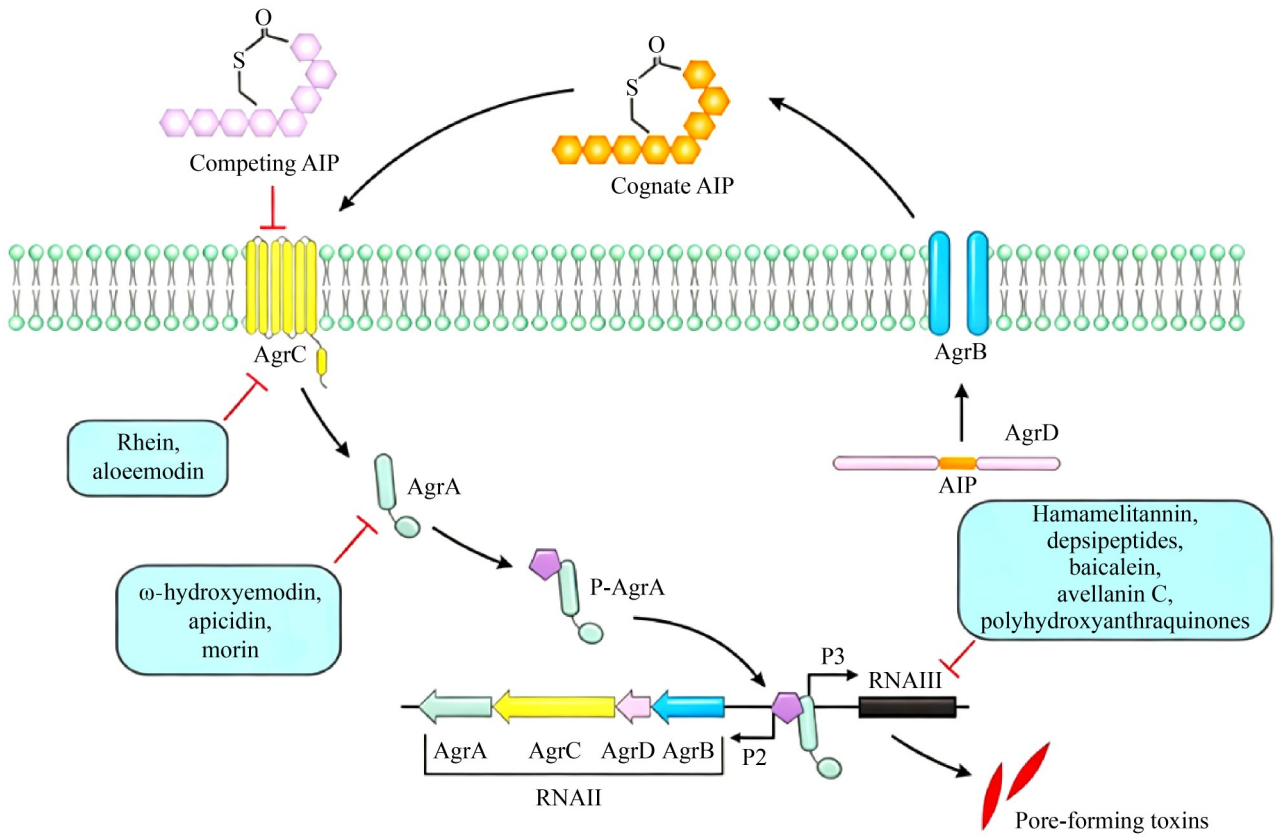


图2 金黄色葡萄球菌Agr群体感应系统[30]

Figure 2 Agr quorum-sensing system of *Staphylococcus aureus*[30].

构域蛋白(SarZ、MgrA/Rat及其同源物)[31]。

SarA是一种分子量约14.7 kDa的DNA结合蛋白[32]。它是Hla表达的关键正向调控因子，通过直接结合于*hla*启动子并激活其转录；还能间接结合至Agr系统的P2 (调控*agrABCD*)和P3 (调控*RNAIII*)启动子区域，增强Agr系统活性；Agr系统激活后产生的*RNAIII*能够稳定*hla* mRNA并促进其翻译，从而进一步放大Hla的表达[33-34]。SarR (约13.6 kDa)是与SarA同源但功能相反的负调控因子，其抑制作用可通过竞争性结合实现；此外还可通过抑制Agr系统，SarR结合至Agr系统的P2与P3启动子，抑制*agrABCD*及*RNAIII*的表达，从而减弱Agr系统对Hla的正向调控[33,35]。SarS (又称SarH1，约29 kDa)可激活*spa*基因并抑制*hla*转录[35]。SarT为单结构域蛋白，通常受SarA与Agr系统抑制，其激活可上调*sarS*，进而抑制*hla*并激活*spa*；位于*sarT*邻近位置的*sarU*编码一双结构域蛋白，其表达受SarT抑制，而SarT本身又受Agr系统抑制；此外，全局调节因子Rot可通过促进*sarS*转录间接抑制*hla*[36]。SarZ则通过调节SarA与Agr系统活性，最终促进*hla*等毒力因子的表达[37]。

1.2.4 SaeRS双组分系统

葡萄球菌辅助调节因子双组分系统(*Staphylococcal* accessory element regulator, SaeRS)是金黄色葡萄球菌中特有的双组分信号转导系统，可调控Hla等毒力因子的分泌。该系统由组氨酸激酶SaeS (感应蛋白)与反应调节蛋白SaeR构成，其编码基因位于包含*saeP*、*saeQ*、*saeR*和*saeS*的操纵子中；*saeR*与*saeS*的表达由位于*saeQ*编码区内的组成型启动子P3驱动。当细菌感知宿主环境压力信号时，SaeS发生自磷酸化并将磷酸基团转移至SaeR；磷酸化的SaeR可结合于靶基因启动子区，激活包括*hla*在内的多种毒力因子转录。此外，SaeRS与Agr系统之间存在协同调控关系，共同精细调节Hla的表达水平[38]。

1.2.5 其他辅助调节因子

σ因子B (sigma factor B, SigB)在应激条件下可被激活，进而启动应激响应基因的表达[39-40]。SigB可通过与Sar蛋白家族及Agr系统相互作用，调控包括Hla在内的毒力因子表达。研究表明，SigB可下调Hla的表达，帮助细菌在逆境中保存能量；其机制可能包括间接抑制SarA活性，从而在环境压力与毒力表达之间实现平衡[41]。

全局转录调控因子CodY是广泛存在于革兰氏阳性菌中的全局抑制性调控因子，可感应细胞内支链氨基酸与GTP浓度变化，协调代谢与毒力基因的表达[42-43]。在金黄色葡萄球菌中，CodY可通过抑制Agr系统及*RNAIII*间接影响多种毒力因子(如杀白细胞素LukF-PV、透明质酸酶)的表达，也可直接调控Hla及荚膜合成相关基因[42-46]。然而，其具体分子机制仍有待进一步阐明。

2 Hla的致病机理

2.1 Hla的孔道形成与直接细胞毒性

Hla分泌后可在细胞膜上形成破坏性孔道直接损伤靶细胞，同时靶向免疫细胞并激活过度的炎症反应，二者共同推动感染的进展与组织损伤。

金黄色葡萄球菌分泌的Hla结合于宿主细胞表面后形成跨膜孔道，导致胞内物质外泄及细胞裂解[47]。该毒素对多种免疫细胞具有直接细胞毒性，可诱发显著炎症反应，并通过破坏上皮-内皮屏障完整性加剧组织损伤[48]。研究还表明，Hla能够促进革兰氏阴性菌的共感染，加重感染复杂程度[49]。孔道形成所引发的离子失衡与信号紊乱是Hla致病的重要环节。Ca^{2+}内流可激活血小板，导致促凝因子释放，并促使内皮细胞收缩，参与水肿形成[50]；同时，Ca^{2+}内流还能激活内切核酸酶，诱导细胞凋亡[51]。研究显示，Hla处理可显著增加兔及小鼠内皮细胞通透

性，促进金黄色葡萄球菌的组织侵入[25,52]。

Hla 可广泛靶向天然免疫与适应性免疫细胞，引发强烈炎症反应。该毒素能诱导单核细胞、巨噬细胞、T 细胞及吞噬细胞等释放多种细胞因子与血管活性物质，加剧局部炎症[53-54]。特别值得注意的是，Hla 可通过激活 NLRP3 炎症小体促使巨噬细胞与单核细胞分泌白细胞介素-1β (interleukin-1β, IL-1β)，扰乱组织微环境并扩大炎症损伤[55-56]。在 NLRP3 基因敲除小鼠模型中，纯化 Hla 或金黄色葡萄球菌感染所引起的肺部病理损伤、IL-1β 释放及中性粒细胞浸润均显著减轻，证实 Hla 部分依赖 NLRP3 通路诱导细胞程序性坏死及促炎介质释放[56]。此外，Hla 还可通过调控 IL-17A 等细胞因子，影响天然免疫与适应性免疫细胞间的信号传导，进一步调控感染免疫应答[57]。

2.2 Hla 与宿主细胞膜的相互作用及受体介导的致病机制

Hla 与宿主细胞膜的特异性结合是其发挥毒力的首要步骤，其具体机制长期存在争议，主要集中于直接膜脂质相互作用与特异性蛋白受体结合 2 种途径[58]。

Hla 可与细胞膜脂质成分直接结合。研究表明，纯化的 Hla 能在缺乏蛋白受体的人工脂质膜上寡聚成孔，导致囊泡内容物泄漏[59-64]。结构分析提示，毒素七聚体表面的“边缘-茎缝隙”区域直接参与脂质头部基团相互作用[65]。消耗胆固醇或添加外源性磷酸胆碱可显著抑制 Hla 的结合与毒性，且其与鞘磷脂或磷脂酰胆碱的结合效率存在差异，表明结合具有脂质种类与脂相依赖性[64,66]。此外，Hla 可与细胞膜上富含胆固醇和鞘脂的脂筏结构发生相互作用[58,66]。值得注意的是，缺乏 Hla 的金黄色葡萄球菌突变株虽能黏附于肺上皮细胞，但其内化效率显著降低。进一步研究发现，Hla 能与脂筏中的小窝蛋白-1 特异性结合，促进脂筏聚集，从而介导细菌内化[67]。这表明 Hla 的脂质结合能力不仅参与孔道形成，也直接促进细菌侵袭。

另一方面，研究证实去整合素金属蛋白酶 10 (a disintegrin and metalloproteinase 10, ADAM10) 是 Hla 在哺乳动物细胞上的关键功能性蛋白受体[52]。Hla 与 ADAM10 的结合不仅介导毒素在膜上的定位及七聚体孔道形成，还可显著上调 ADAM10 的金属蛋白酶活性[52,68]；活化的 ADAM10 可切割 E-钙黏蛋白等细胞黏附分子，破坏细胞间黏附连接及肌动蛋白细胞骨架，导致上皮/内皮屏障功能严重受损，促进细菌扩散[68-70]。如图 3 所示，目前研究焦点在于厘清 ADAM10 介导的毒性究竟源于其受体功能促进的孔道形成、孔道引发的下游信号，还是其酶活激活导致的直接切割，或三者的协同作用[71]。

3 靶向 Hla 的治疗策略

金黄色葡萄球菌感染可引起从局部脓肿至菌血症、脓毒症等全身性重症感染，临床治疗主要依赖抗生素。然而，抗生素的广泛使用与滥用导致以耐甲氧西林金黄色葡萄球菌(MRSA)为代表的多重耐药菌株的蔓延，传统抗菌治疗面临严峻挑战。因此，开发不直接杀菌、从而不易引发耐药性选择的抗毒力治疗策略已成为应对耐药金葡菌感染的重要方向。在众多毒力因子中，Hla 因其在致病过程中的核心地位而备受关注。鉴于其保守的序列、明确的致病机制以及在感染模型中的关键作用，Hla 被视为极具潜力的抗毒力治疗靶点，为开发新型抗金葡菌药物提供了重要方向。

3.1 疫苗研发

疫苗接种旨在通过诱导机体产生特异性主动免疫应答，以预防金黄色葡萄球菌感染[72]。鉴于其理论上的优越性，针对该菌多种特异性抗原的亚单位疫苗研发已成为重要方向。本文

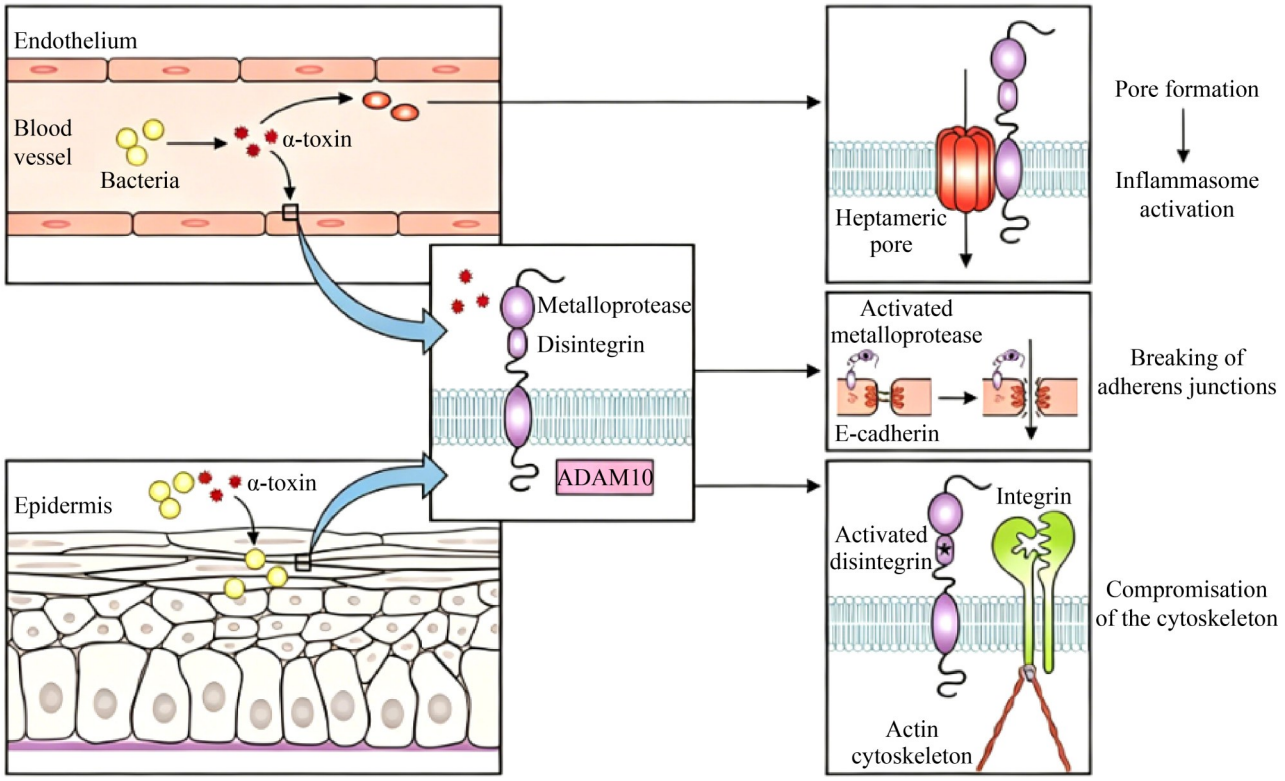


图3 Hla在金黄色葡萄球菌感染中的作用[70]

Figure 3 Role of α-hemolysin in *Staphylococcus aureus* infection[70].

汇总了已进入临床试验阶段的主要金葡菌疫苗候选物[73-79] (表 1)。截至目前，虽有至少 12 种疫苗进行了早期临床评估，但研发进程充满挑战。例如，StaphVax 与 V710 虽曾进入 III 期临床，最终均告失败；近期报道显示，重组五价疫苗(recombinant five-antigen *Staphylococcus aureus* vaccine, rFSAV)与 PENTASTAPH (SA5AG/GSK387858A)可能已进入 III 期研究阶段[80]。总体而言，尽管已投入大量临床前与临床工作，目前尚无任何金葡菌疫苗成功上市。

作为关键毒力因子，Hla 是备受关注的疫苗靶点，但目前尚未有单一靶向 Hla 的疫苗获批。以 Hla 突变体 HlaH35L 为基础的策略显示出潜力：该突变体无毒但保留免疫原性，能在肺炎与皮肤感染模型中提供有效保护[81-82]。含有 Hla_{H35L} 的四价疫苗经单次免疫即可在小鼠模型中减轻肾脏脓肿、腹膜炎及细菌负荷[83]。进一步，包含 Hla_{H35L}-IsdB 融合蛋白的五价疫苗已在多种动物模型(如脓毒症、烧伤、肺炎及骨关节感染)中表现出广谱保护力，据悉已进入 III 期临床试验[84]。此外，新型 Hla 亚单位疫苗 AT62 也被评估可作为多价疫苗的组分之一[85]。尽管前景可观，但以 Hla 为靶点的疫苗研发仍面临诸多挑战，其最终转化成功仍需进一步探索。

3.2 单克隆抗体治疗

单克隆抗体凭借其高特异性与安全性，已成为抗感染治疗的重要策略。针对金黄色葡萄球菌 Hla 的中和性抗体尤其具有吸引力，主要基于以下优势：Hla 蛋白抗原性强，其氨基酸序列在金葡菌中高度保守(98%−100%)；研究表明，针对 Hla 的抗体能有效保护人肺上皮细胞免受金葡菌感染所致的细胞溶解[86-87]。因此，以 Hla 为靶点的单克隆抗体已成为多家医药企业的重点研发方向(表 2)[88-91]。目前，已有多个靶向

表1　针对金黄色葡萄球菌感染的疫苗

Table 1　Vaccines against *Staphylococcus aureus* infection

Vaccine	Antigenic targets	Indications	Phase	Companies	NCT/References
StaphVax	CP5-rEPA+ CP8-rEPA	Patients with advanced chronic kidney disease undergoing hemodialysis, infections following cardiovascular surgery, orthopedic prosthetic implants, and healthy volunteers	III	Nabi	NCT00211913 NCT0007121 NCT00211900 NCT00130260 NCT00211965 NCT00211926 NCT00211991
V710	IsdB	Patients undergoing surgical procedures, renal disease requiring hemodialysis	III	Merck	NCT00518687
NDV-3	Als3	Skin and soft tissue infections (SSTIs)	II	NovaDigm	NCT03455309
SA3Ag	CP5, CP8, ClfA	SSTIs	II	Pfizer	NCT01018641
SA4Ag	CP5, CP8, ClfA, MntC	Nasopharyngeal and cutaneous infections; postoperative spinal infections	II	Pfizer	NCT02492958 NCT0238816 NCT01643941
STEBVax	SEB	Toxic shock syndrome (TSS)	I	NINID	NCT00974935
None	Hla, PVL	SSTIs	II	HJF/Nabi	NCT01011335
Brivalent	RLukS-PV, rAT	Healthy individuals	II	Nabi	[76]
SA75	Whole cell vaccine	Recurrent tonsillitis	I	VRIP	[77]
GSK2392103A+ GSK2392105A+ GSK2392106A+ GSK2392019A	CP5, CP8, Hla, ClfA	Healthy individuals	I	GSK	NCT01160172
Recombinant five-antigen *Staphylococcus aureus* vaccine (rFSAV)	SEB, IsdB, MntC, SpA, Hla	Closed fracture surgery	II	Olymvax	[78]
PENTASTAPH (SA5AG) GSK387858A	CP5, CP8, WTA, PVL, Hla	SSTIs	II	GSK	NCT04420221

CP5/CP8: Capsular polysaccharide; Als3: *Candida albicans* adhesin; ClfA: Clumping factor A; SEB: *Staphylococcal* enterotoxin B; SpA: Surface protein staphylococcal protein A; IsdB: Iron surface determinant B; MntC: Manganese transporter protein C; PVL: Panton-Valentine leukocidin; RLukS-PV/rAT: Two subunits of Panton-Valentine leukocidin and α-hemolysin multivalent vaccine antigen; WTA: Wall teichoic acid; HJF: Henry M. Jackson Foundation for the Advancement of Military Medicine.

表2　靶向金黄色葡萄球菌Hla的单克隆抗体

Table 2　Monoclonal antibodies targeting Hla in *Staphylococcus aureus*

Antibody	Antigenic targets	Phase	Companies
AR-301/Salvecin	Hla	III	Aridis
MEDI4893/AR320	Hla	III	Medimmune
ASN100	Hla and LukGH	II	Arsanis
None	Hla	Primary screening	Trinomab Biotech

Hla 的中和性单抗进入临床后期研究。其中，全人源单抗 MEDI4893 (Suvratoxumab/AR-320)与 AR-301 (Salvecin)均已进入 III 期临床试验，旨在预防或治疗金葡菌引起的肺炎。此外，ASN100 是一种双抗体组合(ASN-1 与 ASN-2)，可同时中和 Hla 及 5 种杀白细胞素(HlgAB、HlgCB、LukED、LukSF[PVL]和 LukGH)，其 II 期研究显示了针对金葡菌毒素的广谱中和潜力[88-91]。

在新型抗体发现方面，噬菌体展示等技术为筛选高亲和力抗 Hla 抗体提供了有效手段。例如，从 Fab 文库中筛选出的 YG1 抗体，以及通过全人源 scFv 文库鉴定并改造获得的 scFv-Fc 融合抗体，均在临床前研究中显示出良好的 Hla 中和活性与感染保护效果[92-93]。这些研究为开发下一代基于抗体的抗毒力治疗剂奠定了重要基础。

3.3 天然化合物小分子抑制剂

天然化合物及其衍生物作为 Hla 抑制剂的重要来源，其价值不仅在于相对低廉的获取成本与良好的成药潜力，更在于其化学结构的多样性为靶向 Hla 的特定功能域(如膜结合区、寡聚化界面)或调控其表达的上游通路(如 Agr、Sae 系统)提供了丰富的分子探针。早期研究如 β-环糊精衍生物提示了通过空间位阻直接物理性阻塞孔道组装的新思路[87,94-95]。

天然化合物是发现 Hla 抑制剂的重要资源。Wu 等[30]曾于 2019 年综述了 24 个具有抗 Hla 活性的天然化合物，其作用机制主要包括抑制 Hla 寡聚化、或通过干扰 Agr 群体感应系统、Sae 双组分系统及 *RNAIII*表达来下调 Hla 的产生。本课题组近年来致力于从天然化合物中筛选金黄色葡萄球菌 Hla 抑制剂。前期研究中筛选出柚皮素与漆黄素，二者可通过靶向 AgrB 蛋白进而抑制 Hla 的分泌。基于此，本文进一步汇总了 2019−2025 年间报道的新型天然化合物抑制剂(表 3)。如表 3 所示，目前已知的抑制剂主要通过以下途径发挥作用：(1)调控上游信号通路，如抑制 Agr 系统、SarA 或 SaeRS；(2)直接作用于 Hla 蛋白，干扰其折叠或寡聚化过程。

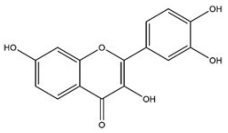
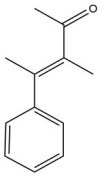
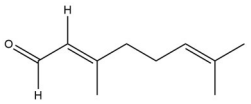
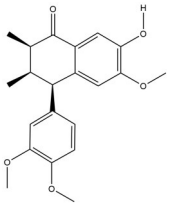
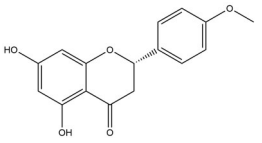
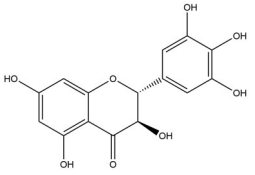
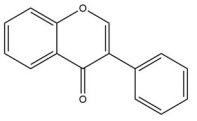
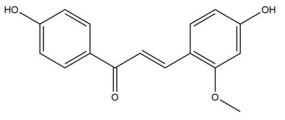
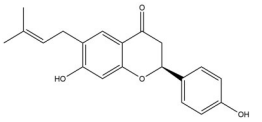
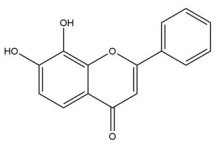
尽管已有多种天然化合物被报道具有抗 Hla 活性，但该领域仍面临以下关键局限：首先，目前已开展系统研究的化合物种类仍相对有限，相关结构信息与构效关系数据积累不足，制约了其作为 Hla 抑制剂的深入开发。其次，多数研究仅停留在表型活性验证阶段，化合物发挥抑制作用的具体分子靶点与作用机制尚不明确。此外，部分抑制剂不仅作用于 Hla，还可影响其他毒力因子，体现出多靶点特性，然而其协同作用机制及相关调控网络仍有待深入阐明。

3.4 其他

除上述治疗策略，有研究证实模拟细胞膜的人造纳米粒子(例如脂质体)在体外和体内均具有阻断细菌毒素的潜力。成孔毒素是最常见的细菌毒力蛋白，在细菌感染的发病机制中起重要作用；因此，PFT 是细菌感染中极具吸引力的治疗靶点。受成孔毒素(pore-forming toxins, PFTs)的成孔过程和机制的启发，有研究设计了一种集成的混合纳米囊泡——红脂质体(red blood cell membrane-liposome, RM-PL)，通过融合天然红细胞(red blood cell, RBC)膜和人工脂质膜实现 PFT 解毒；当脂质和红细胞膜整合到杂化纳米囊泡结构中时可实现功能互补；红细胞膜赋予 RM-PLs 解毒能力，而聚乙二醇化脂质膜稳定 RM-PLs，大幅提升红细胞膜的解毒效率；以 Hla 为模型 PFT 开展的实验证明，RM-PLs 不仅能显著降低 Hla 在体外对红细胞的毒性，还能在体内有效捕获中和 Hla，拯救小鼠免受 Hla 诱导的组织损伤[121]。甘草酸常被用作药物递送载体，其与低生物利用度的槲皮素形成新型纳米制剂甘草酸-槲皮素复合物(glycyrrhizic acid-quercetin complex, GAQ)，被证明对金黄色葡萄球菌主要毒性因子 Hla 表现出抗菌和抗溶血活性[122]。由此可见，纳米治疗策略展现出巨大的应用潜力。

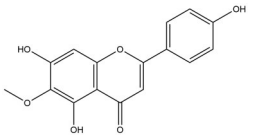
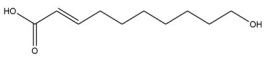
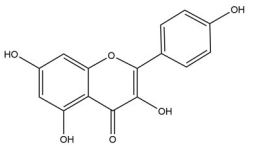
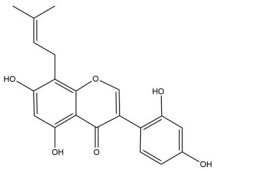
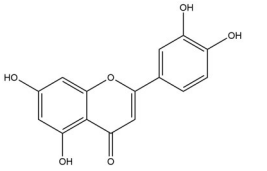
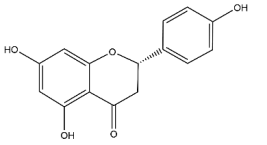
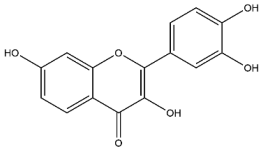
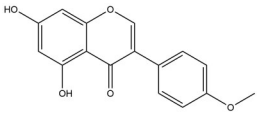
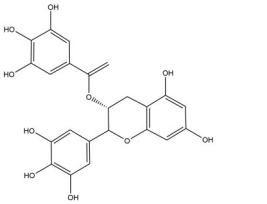
表3　2019–2025年天然化合物Hla抑制剂汇总

Table 3　Summary of natural compound Hla inhibitors from 2019 to 2025

Compounds	Sources	Structure	Mechanism	References
Norwogonin	*Scutellaria baicalensis*		Targeting AgrA to inhibit Hla production	[20]
Cinnamaldehyde	Cinnamon essential oil		Acting as a β-lactam adjuvant, targeting SarA to suppress Hla *via* downregulation of *mecA*	[96]
Citral	*Litsea cubeba* essential oil		Interfering with the quorum sensing (QS) system to inhibit Hla expression	[97]
Schisandrone	Lignans		Inhibiting Hla expression	[98]
Isosakuranetin	Bergamot		Inhibiting the transcription and expression of Hla *via* regulation of upstream RNAIII	[99]
Ampelopsin	*Ampelopsis grossedentata*		Unclear	[100]
Flavone	Edible plants		Unclear	[101]
Echinatin	Licorice		Suppressing the Agr system, thereby inhibiting Hla expression	[102]
Bavachin	*Psoralea corylifolia*		Inhibiting Hla expression	[103]
7,8-dihydroxyflavone	Various foods		Inhibiting Hla expression	[104]

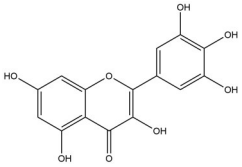
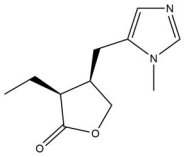
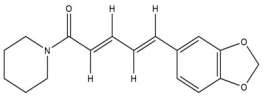
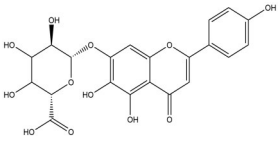
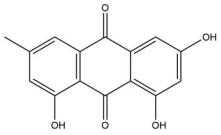
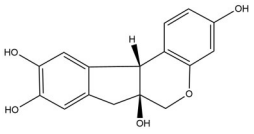
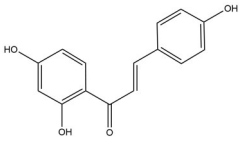
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(续表3)

Compounds	Sources	Structure	Mechanism	References
Hispidulin	*Onopordum acanthium*		Targeting the AgrAC system	[105]
10-hydroxy-2-decenoic acid (10-HDA)	Royal jelly		Unclear	[106]
Kaempferol	Various plants		Inhibiting Hla expression	[107]
2,3-dehydrokievitone	Lupine root		Inhibiting Hla expression	[108]
Andrographis paniculata lactone	Labdane diterpenoids isolated from the stems and leaves of *Andrographis paniculata*		Downregulating the transcription of the Hla gene and its highly associated genes (*clfA* and *fnbA*) to inhibit Hla expression	[109]
Luteolin	Various plants and foods		Downregulating the *hla* gene to inhibit Hla expression	[110]
Naringenin	Oak tree		Targeting AgrB to inhibit Hla secretion	[38]
Fisetin	*Rhus succedanea*		Targeting AgrB to inhibit Hla secretion	[38]
6-ES	*Bocconia frutescens*		Unclear	[111]
BiochaninA	Red clover, cabbage, and alfalfa		Inhibiting Hla expression	[112]
Epigallocatechin gallate	Green tea		Inhibiting Hla expression and heptamer pore formation	[113]

(待续)

(续表3)

Compounds	Sources	Structure	Mechanism	References
Lycopene	Tomato		Inhibiting Hla expression	[114]
Myricetin	Vegetables and fruits		Inhibiting Hla expression	[115]
Pilocarpine	*Peganum harmala* seeds		Inhibiting Hla expression	[116]
Piperine	Black pepper		Inhibiting Hla expression	[117]
Scutellarin	Herbal medicines		Targeting caseinolytic protease P (ClpP) to inhibit Hla	[118]
Emodin	*Polygonum cuspidatum*		Unclear	[119]
Brazilin	Dried heartwood of *Caesalpinia sappan*		Targeting SaeR to inhibit Hla	[21]
Isoliquiritigenin	Licorice		Inhibiting Hla expression	[120]

4 总结与展望

金黄色葡萄球菌及其耐甲氧西林菌株(MRSA)兼具高致病性与耐药性，已成为全球抗生素耐药防控的核心难题。耐药性与致病性密切相关，二者在菌株进化与传播中常伴随发生：MRSA 等耐药克隆株在获得耐药基因的同时，通常携带高表达毒力因子；抗生素选择性压力也可经由 Agr 等全局调控网络影响毒力基因表达。因此，靶向 Hla 的抗毒力策略可在抑制致病性的同时规避传统杀菌药物的选择压力，为应对耐药与致病的双重挑战提供新的干预思路。目前 Hla 在结构解析、致病机理研究以及防控治疗策略开发等方面已取得显著进展。然而，针对 Hla 的深入研究与治疗策略转化仍面临诸多机遇与挑战。首先，需进一步阐明 Hla 在复杂感染微环境中与其他毒力因子的协同作用机制，以及其与宿主免疫系统互作的精细调控网络。其次，现有抑制剂大多处于临床前研究阶段，尚未有实现规模化生产与临床应用的有效药物。

未来研究应致力于利用结构生物学手段解析 Hla 与抑制剂复合物的三维结构，指导合理化药物设计；开发联合疗法，将抗毒力策略与抗生素联用，在清除细菌的同时中和其毒性，实现协同增效的治疗效果；探索基于纳米技术的靶向递送系统，提高治疗药物的生物利用度和病灶靶向性；关注宿主导向疗法，通过调节宿主对 Hla 损伤的应答通路减轻组织病理损伤。本课题组长期致力于金黄色葡萄球菌抗毒力策略研究，已在 Hla 抑制剂筛选、作用机制解析以及构效关系研究等方面取得初步进展，未来将进一步聚焦 Hla 与宿主受体互作的关键界面，开展基于结构的精准药物设计，并探索与现有抗生素的协同治疗方案。总之，以 Hla 为靶点的抗毒力治疗，作为传统抗生素疗法的有力补充，有望为应对耐药性金黄色葡萄球菌感染提供全新的、更具潜力的解决方案。

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孙婷婷：负责综述初稿撰写、调查研究；王新宇：提供资源；刘洋：参与文献的整理与筛选；李應英：验证复核参考资料准确性真实性；王宇星：对综述进行润色修改；徐飞：总体构思、主题选择，监督管理，提供该领域内的专业见解和建议。

作者利益冲突公开声明

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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