

# 葡萄球菌与宿主免疫系统互作及免疫逃逸机制与研究进展

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**摘要:** 葡萄球菌与宿主免疫系统的动态互作过程决定了其致病特点的多样性。在感染的侵袭阶段, 葡萄球菌通过释放  $\alpha$ -毒素、蛋白酶及超抗原, 破坏中性粒细胞、降解补体蛋白, 并诱导免疫应答过度活化, 进而突破宿主固有免疫屏障。当侵入定殖后, 葡萄球菌通过形成生物被膜建立物理屏障, 或形成小菌落变异体减弱免疫系统识别, 或侵入宿主细胞逃逸免疫清除。葡萄球菌急性期通过毒力因子分泌, 表现为主动攻击的感染特点, 慢性持续性感染阶段, 通过免疫逃逸表现为被动防御的感染特点。基于上述机制, 新型防治策略需同时抑制毒力因子产生, 并阻断免疫逃逸途径。结合课题组前期工作, 本文系统梳理了葡萄球菌-宿主免疫系统互作及免疫逃逸机制, 为防治葡萄球菌感染提供了参考。

**关键词:** 葡萄球菌; 宿主; 互作; 免疫逃逸

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## Research advances in *Staphylococcus*-host immune system interactions and immune evasion mechanisms

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**Abstract:** The dynamic interactions between *Staphylococcus* and the host immune system determine the diversity of the pathogenic characteristics of *Staphylococcus*. During the invasive phase of infection, *Staphylococcus* breaches the host's innate immune barriers by releasing  $\alpha$ -toxin, proteases, and superantigens, which compromise neutrophils, degrade complement proteins, and induce hyperactivation of immune responses. Following invasion and colonization, *Staphylococcus* establishes physical barriers through biofilm formation, evades immune recognition by generating small colony variants (SCVs), or infiltrates host cells to escape immune clearance. In acute infections, the pathogen exhibits aggressive traits via virulence factor secretion, whereas during chronic persistent infections, it adopts passive defense mechanisms through immune evasion. On the basis of these mechanisms, novel prevention and therapeutic strategies must simultaneously inhibit virulence factor production and block immune evasion pathways. Integrating our previous studies, this article systematically reviews the *Staphylococcus*-host immune system interactions and immune evasion mechanisms, aiming to provide insights for combating staphylococcal infections.

**Keywords:** *Staphylococcus*; host; interaction; immune evasion

引起医院内感染的葡萄球菌菌种主要有金黄色葡萄球菌(*Staphylococcus aureus*, SA)和表皮葡萄球菌(*Staphylococcus epidermidis*, SE), 此类病原菌的致病性主要依赖于定殖因子、侵袭性酶、毒素及其与宿主免疫系统的互动与演进过程<sup>[1]</sup>。在感染早期, SA 通过分泌成孔毒素(pore-forming toxins, PFTs)破坏宿主吞噬细胞膜, 直接杀伤免疫细胞; 葡萄球菌超抗原可高效活化 T 细胞受体, 引发细胞因子风暴, 过度耗竭适应性免疫应答; 其分泌的葡萄球菌超抗原样蛋白家族(*Staphylococcal superantigen-like*, SSL)可抑制中性粒细胞的趋化作用<sup>[2-4]</sup>。当宿主吞噬细胞启动吞噬作用时, 葡萄球菌通过高表达过氧化氢酶(KatA)和超氧化物歧化酶(superoxide

dismutase, SOD)等活性氧(reactive oxygen species, ROS)清除酶系统, 清除吞噬细胞呼吸暴产生的活性氧, 从而抵抗宿主固有免疫杀伤作用<sup>[5-6]</sup>。随着感染微环境形成, SA 和 SE 可通过调控宿主细胞代谢网络, 诱导巨噬细胞(macrophages, M $\Phi$ )向 M2 抗炎表型极化, 并招募髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)构建免疫抑制微环境, 同时依赖细胞间多糖黏附素(polysaccharide intercellular adhesin, PIA)抵抗免疫清除<sup>[7-8]</sup>。葡萄球菌还可通过形成小菌落变异(small colony variants, SCVs)实现生存策略转变, 表现为下调毒素因子的表达, 由高侵袭性感染特点向低代谢隐匿状态的转换<sup>[9]</sup>。另外, 有研究发现葡萄球菌可劫

持宿主自噬通路, 利用自噬小体作为生存微环境, 并借助吞噬细胞实现广泛播散, 这一类似“特洛伊木马”的胞内寄生策略为理解复发性感染提供了新的视角<sup>[10-11]</sup>。基于上述机制, 本文从葡萄球菌-宿主动态互作角度, 系统阐述葡萄球菌与宿主免疫系统互作及免疫逃逸的研究进展。

## 1 葡萄球菌急性感染的毒性侵袭策略

SA 具有丰富的毒力因子储备, 这些具有免疫调控功能的毒力因子主要包括分泌型毒素和胞外侵袭酶。分泌型毒素如 PFTs 通过形成跨膜孔道直接溶解靶细胞; 而超抗原则通过耗竭 T 细胞克隆以介导免疫抑制; 在胞外侵袭酶中, 核酸酶可降解中性粒细胞胞外诱捕网(neutrophil extracellular traps, NETs), 过氧化物酶可清除 ROS, 均有利于维持生存优势。此外, SA 产生的膜囊泡(membrane vesicles, MVs)不仅能递送毒素以激活核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体 3 (nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3, NLRP3)炎症小体, 进而触发焦亡, 还能改变自身蛋白组分来中和脂肪酸, 最终形成系统性免疫逃逸网络<sup>[12-14]</sup>。

### 1.1 成孔毒素 PFTs 攻击免疫系统

PFTs 是葡萄球菌的重要毒力因子, 可通过识别靶细胞膜并诱导多聚体组装和构象变化形成桶状孔道。根据跨膜结构差异, PFTs 可分为  $\alpha$ -PFT 和  $\beta$ -PFT 两类。孔道形成后导致靶细胞金属离子外流和水分子内流, 使细胞膨胀破裂。同时, 其他毒素因子也能通过孔道进入胞内引起细胞裂解。PFTs 不仅能直接杀伤免疫细胞和引发组织损伤, 还能促进细菌逃逸宿主免疫防御(如吞噬体逃逸)<sup>[2]</sup>。

葡萄球菌  $\alpha$ -溶血素( $\alpha$ -hemolysin, Hla)属  $\beta$ -成孔毒素, 通过与宿主细胞膜上的磷脂酰胆碱和鞘磷脂结合, 形成七聚体跨膜孔道, 引发细胞渗透性裂解(图 1)。Hla 的主要靶点是去整合素和金属

蛋白酶 10 (a disintegrin and metalloprotease 10, ADAM10), 通过 ADAM10 可激活单核细胞中的 NLRP3 炎症小体, 促使 IL-1 $\beta$  大量释放, 导致重度炎症并引发细胞死亡。研究表明, 敲除髓系细胞 ADAM10 基因能显著降低小鼠肺部 IL-1 $\beta$  水平, 减少小鼠死亡率<sup>[15-16]</sup>。进一步研究发现, Hla 关键位点的乳酸化修饰对 SA 维持高毒力至关重要, *SAPIG1173* 及 *SAPIG2573* 基因编码的酰基转移酶能调控 Hla 的乳酸化修饰, 酰基转移酶基因敲除的 SA 在小鼠皮肤脓肿及肺炎模型中表现出显著的致病缺陷<sup>[17]</sup>。除促炎作用外, Hla 通过 ADAM10 依赖性途径抑制适应性免疫。Teymournejad 等<sup>[18]</sup>发现, SA (USA300)分泌 Hla 可减少淋巴结中 T 细胞及树突状细胞数量, 而  $\Delta$ hla 突变株感染可逆转由 Hla 介导的免疫抑制作用, 并显著提升 IL-17A、IFN- $\gamma$  分泌水平及调节性 T 细胞(regulatory T cells, Treg)增殖。类似地, Lee 等<sup>[19]</sup>发现, Hla 缺失虽不影响体液免疫应答强度, 但可显著增加记忆性 T 细胞数量, 提示 Hla 通过抑制抗原特异性 T 细胞增殖减弱免疫记忆形成。

Panton-Valentine 杀白细胞毒素(Panton-Valentine leukocidin, PVL)由 LukS-PV 和 LukF-PV 这 2 种亚基组成, 通过特异性结合宿主细胞表面的补体成分 C5a 及其受体 C5L2 引发多形核白细胞(polymorphonuclear leukocytes, PMN)和 M $\Phi$  裂解。由于淋巴细胞不表达上述受体, 因此对 PVL 作用具有耐受性<sup>[20]</sup>。LukS-PV 亚基选择性地作用于 C5aR 高表达的白细胞亚群(包括 PMN、Gr2<sup>+</sup>细胞及 CD11b<sup>+</sup>单核细胞), 而对 C5aR 低表达的 CD19<sup>+</sup> B 淋巴细胞仅表现出轻微的细胞毒性<sup>[21]</sup>。 $\gamma$ -溶血素 ABC ( $\gamma$ -hemolysin ABC, HlgABC)毒素由 HlgA、HlgB、HlgC 亚基构成复合体, 其中 HlgA 可同时识别 C5aR 及 C-X-C 基序趋化因子受体 1 (C-X-C motif chemokine receptor 1, CXCR1)、C-X-C 基序趋化因子受体 2 (C-X-C motif chemokine receptor 2, CXCR2)、C-C 基序趋化因子受体 2 (C-C motif chemokine

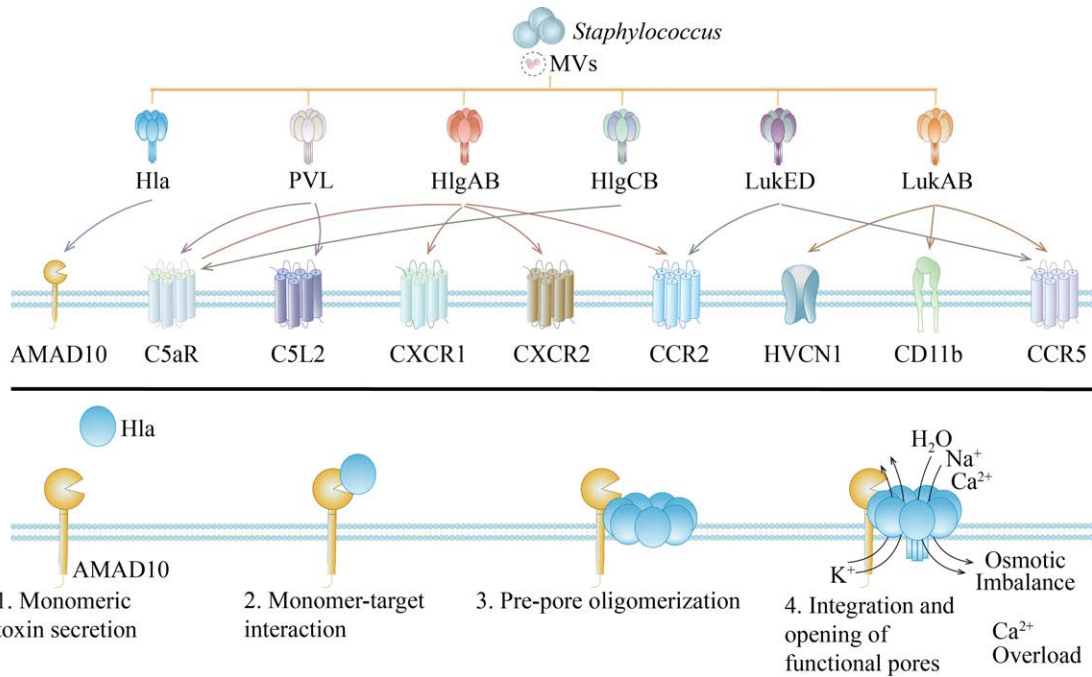


图 1 葡萄球菌成孔毒素的成孔机制模式 MV: 膜囊泡; AMAD10: 去整合素和金属蛋白酶 10; Hla:  $\alpha$ -溶血素; PVL: 杀白细胞毒素; HlgAB:  $\gamma$ -溶血素 AB; HlgCB:  $\gamma$ -溶血素 CB; LukED: 白细胞毒素 ED; LukAB: 白细胞毒素 AB; C5aR: 补体 C5a 受体; C5L2: 补体 C5a 受体样 2; CXCR1: C-X-C 基序趋化因子受体 1; CXCR2: C-X-C 基序趋化因子受体 2; CCR2: C-C 基序趋化因子受体 2; HVCN1: 氢电压门控通道 1; CD11b: 分化簇 11b; CCR5: C-C 基序趋化因子受体 5。

Figure 1 Mechanistic model of pore formation by *Staphylococcal* pore-forming toxins (PFTs). MV: Membrane vesicles; AMAD10: A disintegrin and metalloprotease 10; Hla:  $\alpha$ -hemolysin; PVL: Pantan-Valentine leucocidin; HlgAB: Gamma-hemolysin AB; HlgCB: Gamma-hemolysin CB; LukED: Leukocidin ED; LukAB: Leukocidin AB; C5aR: C5a receptor; C5L2: C5a receptor-like 2; CXCR1: C-X-C motif chemokine receptor 1; CXCR2: C-X-C motif chemokine receptor 2; CCR2: C-C motif chemokine receptor 2; HVCN1: Hydrogen voltage-gated channel 1; CD11b: Cluster of differentiation 11b; CCR5: C-C motif chemokine receptor 5.

receptor 2, CCR2)等趋化因子受体,表现出广泛的受体结合特性<sup>[22]</sup>。另外, HlgABC 对 CD11b<sup>+</sup> 单核细胞的裂解效应与靶细胞受体表达水平无显著相关性,该毒素对不表达 C5aR 的 NK 细胞仍具有显著杀伤活性,提示其作用可能通过非经典受体途径实现<sup>[21]</sup>。

白细胞毒素 AB (leukocidin AB, LukAB) 通过与 PMN 表面的  $\alpha M/\beta 2$  整合素受体(CD11b)结合,诱导其死亡<sup>[23]</sup>。Perelman 等<sup>[24]</sup>发现, SA CC30、CC45 产生 LukAB 还能与人吞噬细胞和 B 细胞膜上高表达的氢电压门控通道 1 (hydrogen voltage-gated channel 1, HVCN1)受体结合,引起细胞裂解,尽管 T 细胞中 *HVCN1* 低表达,但

LukAB 能通过 CD11b 杀伤树突状细胞(dendritic cells, DCs),抑制其抗原呈递和共刺激分子表达,进而抑制 CD4<sup>+</sup> T 细胞的活化与增殖; LukAB 还可激活半胱天冬酶介导的程序性细胞死亡途径,导致 DCs 死亡。此外 Ilmain<sup>[25]</sup>等发现, CD11b 缺失时 LukAB 仍通过 HVCN1 受体发挥细胞毒性,提示 HVCN1 是 LukAB 功能的核心调控位点。

## 1.2 SSL 蛋白家族的免疫调控作用

SSL 由结构同源但无典型超抗原活性的 14 个成员组成,多数 SSL 通过靶向关键环节介导免疫逃逸。SSL5 和 SSL11 可阻断 PMN 表面 P-选择素糖蛋白配体 1 (P-selectin glycoprotein ligand-1, PSGL-1)与内皮细胞 P-选择素的相互作用,抑制

PMN 跨内皮迁移,也可通过抑制基质金属蛋白水解酶(matrix metalloproteinase-8/9, MMP-8/9)活性,阻碍 PMN 穿透细胞外基质;此外,它们通过消除 MMP 介导的 IL-8 趋化信号级联放大效应,进一步阻碍 PMN 趋化功能<sup>[26]</sup>。SSL10 不仅能结合 CXCR4 受体阻滞免疫细胞迁移,还能通过阻断 IgG-C1q 互作抑制补体经典途径激活,同时干扰凝血级联反应并调控丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)/细胞外信号调节激酶 2 (extracellular signal-regulated kinase 2, ERK2)炎症信号通路,最终激活受体相互作用丝氨酸/苏氨酸蛋白激酶 3 (receptor-interacting serine/threonine-protein kinase 3, RIPK3)依赖性凋亡通路,加速免疫细胞死亡<sup>[27]</sup>。

部分 SSL 成员呈现免疫激活特性,如 SSL13 通过甲酰肽受体 2 (formyl peptide receptor 2, FPR2)激活 PMN 呼吸暴发,并诱导肥大细胞释放  $\beta$ -己糖胺酶引发超敏反应;SSL3 与 CD43 结合增强肥大细胞黏附与活化<sup>[28-30]</sup>。这种免疫抑制与激活的双向调节作用,使 SSL 家族能够动态平衡宿主的炎性微环境,有利于葡萄球菌在急性侵袭期和慢性持续期提供生存优势。

### 1.3 超抗原介导免疫逃逸

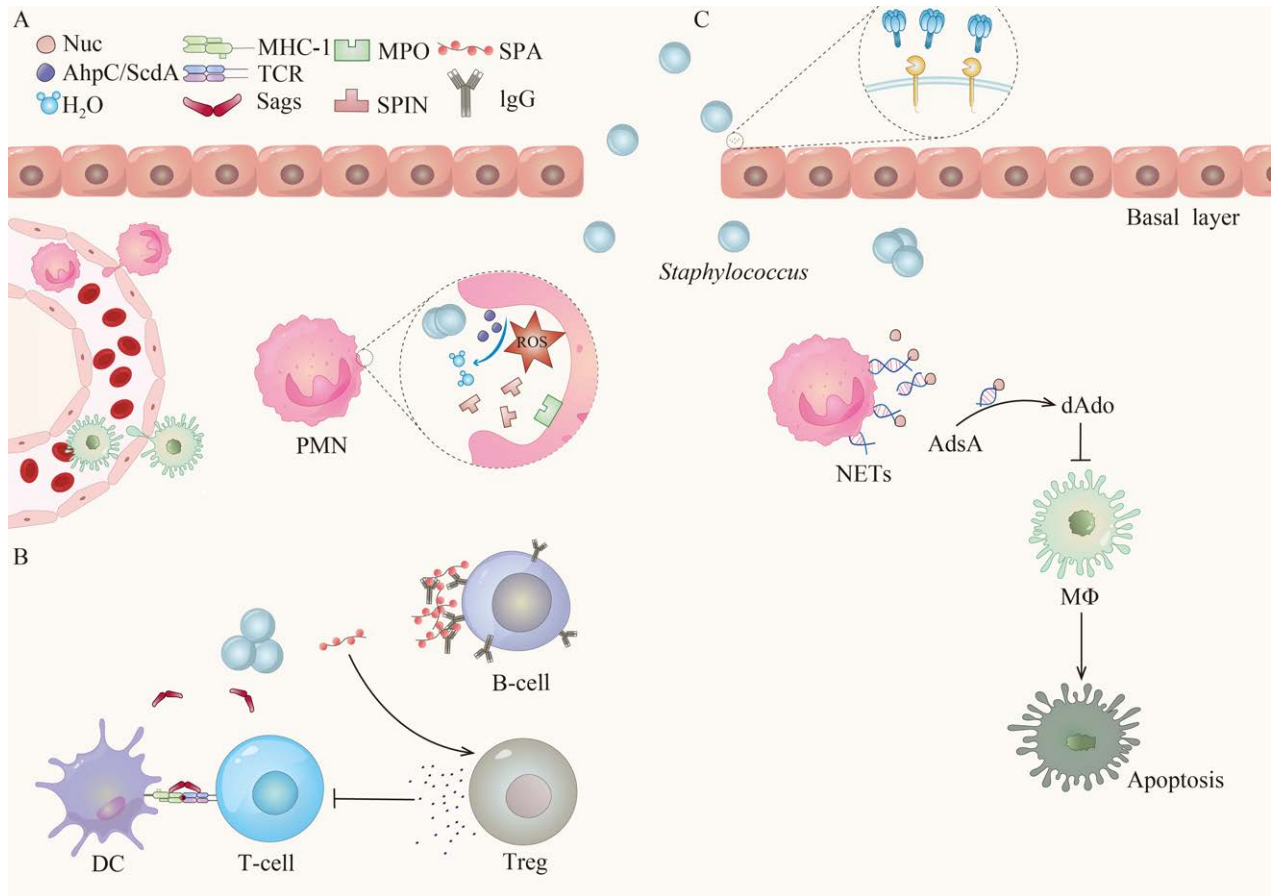
葡萄球菌致热毒素超抗原(superantigens, SAgS)是由 SA 分泌的关键毒力因子,目前已鉴定出 26 种,主要包括中毒性休克综合征毒素-1 (toxic shock syndrome toxin-1, TSST-1)、肠毒素(*Staphylococcal enterotoxins*, SEs)及其类似物(*Staphylococcal enterotoxin-like toxins*, SEIs 等);SAgS 通过同时交联抗原呈递细胞(antigen-presenting cell, APC)的 MHC II 分子和 T 细胞受体(T cell receptor, TCR) V $\beta$  链可变区,引发促炎因子大量释放,导致全身性炎症反应并引发 T 细胞耗竭<sup>[31]</sup>。另外, Tuffs 等<sup>[32]</sup>基于 MHC II 转基因小鼠模型的研究表明, SAgS 通过诱导 CD4<sup>+</sup> T 细胞过度分泌 IFN- $\gamma$ , 进而抑制肝脏 M $\Phi$  的吞噬杀菌功能,为细菌增殖提供微环境,而这一效应在人类原代 M $\Phi$  模型中也同样存在。Noli 等<sup>[33]</sup>

研究进一步揭示, SAgS 显著增加了 PMN 和 M $\Phi$  表面 CD14、CD40 及 CD86 的表达水平,而不会提升其吞噬功能,同时 SAgS 以剂量依赖性地抑制 PMN/M $\Phi$  的吞噬活性并诱导大部分细胞凋亡,存活的 PMN/M $\Phi$  由于 CD86 持续性高表达,当它们通过细胞间接触 Th1 细胞时,会显著诱导 Th1 细胞凋亡,加剧机体免疫抑制状态。

葡萄球菌蛋白 A (*Staphylococcal protein A*, SPA)可广泛激活 VH3 家族阳性(VH3<sup>+</sup>)初始 B 细胞,并促使 B 细胞在成熟阶段优先结合 SPA 表位,从而显著抑制 B 细胞对其他 SA 抗原的免疫应答<sup>[34]</sup>。同时, SPA 与 IgG 的 Fc/Fab 共同结合可形成交联型免疫复合物,直接诱导 VH3<sup>+</sup> B 细胞坏死;当其仅结合 Fc 段时,可阻断 IgG 六聚化及补体 C1q 募集,显著抑制补体介导的杀菌作用<sup>[35-36]</sup>。进一步研究发现, SPA 可激活 APC 分泌免疫抑制因子,并通过旁分泌诱导 Treg 分化;当阻断 APC 的 PD-L1 信号通路后, SA 诱导的 Treg 增殖被显著抑制,提示 SPA 可能通过 PD-L1 信号通路调控 Treg 分化,进而抑制 T 细胞应答,有利于 SA 的免疫逃逸<sup>[37]</sup>。

### 1.4 侵袭性酶 Nuc 促进免疫逃逸

PMN 通过形成 NETs 捕获葡萄球菌。NETs 由 DNA、组蛋白、颗粒蛋白和胞质蛋白构成,其形成可由 SA 产生的 PVL 和 HlgAB 所诱导。SA 分泌的核酸酶(nuclease, Nuc)可通过水解 NETs 的 DNA 骨架降解其空间结构,帮助 SA 躲避 PMN 捕获<sup>[38]</sup>。Sultan 等<sup>[39]</sup>发现, Nuc 在 SA (USA300) 生物膜形成初期高表达,通过分解生物膜中的 DNA 来阻断 TLR9 介导的免疫识别。此外, Nuc 将 DNA 降解为脱氧腺苷一磷酸(deoxyadenosine monophosphate, dAMP)后,腺苷合酶 A (adenosine synthase A, AdsA)进一步催化其转化为脱氧腺苷(deoxyadenosine, dAdo), dAdo 通过激活腺苷受体触发半胱天冬酶-3 (caspase-3)依赖性凋亡通路,直接诱导 M $\Phi$  程序性死亡;同时, AdsA 还可以生成脱氧鸟苷(deoxyguanosine, dGuo),进一步增强细胞毒性,加速 M $\Phi$  死亡进程<sup>[40]</sup>(图 2)。



**图 2 葡萄球菌对宿主免疫系统的主动攻击** A: 超抗原桥接抗原呈递细胞-MHC 复合物与 T 细胞受体触发 T 细胞克隆耗竭; B: 葡萄球菌蛋白 A 通过 B 细胞受体交联诱导 B 细胞耗竭, 其免疫复合物同步引发 B 细胞坏死性凋亡及 Treg 介导的 T 细胞抑制; C: 核酸酶水解 NETs 产生脱氧腺苷一磷酸, 与腺苷合酶 A 共同作用生成脱氧腺苷, 诱导 MΦ 焦亡。MHC-1: 主要组织相容性复合体 I 类分子; MPO: 髓过氧化物酶; AhpC: 烷基过氧化氢还原酶 C 亚基; ScdA: 铁硫簇修复蛋白; Sags: 超抗原; SPIN: 葡萄球菌过氧化物酶抑制剂; PMN: 多形核白细胞; Treg: 调节性 T 细胞; DC: 树突状细胞; AdsA: 腺苷合酶 A; NETs: 中性粒细胞胞外捕获网。

Figure 2 Active attack of *Staphylococcus* against the host immune system. A: Superantigens (Sags) bridge antigen-presenting cell-major histocompatibility complex (APC-MHC) with T cell receptor (TCR) to induce T cell clonal exhaustion; B: *Staphylococcal* protein A (SPA) triggers B cell exhaustion via B cell receptor (BCR) cross-linking, while its immune complexes simultaneously initiate B cell necroptosis and Treg-mediated suppression of T cells; C: Nuclease (Nuc) hydrolyzes NETs to produce deoxyadenosine monophosphate (dAMP), which cooperates with adenosine synthase A (AdsA) to generate deoxyadenosine (dAdo) driving macrophage pyroptosis. MHC-1: Major histocompatibility complex class I; MPO: Myeloperoxidase; AhpC: Alkyl hydroperoxide reductase subunit C; ScdA: Iron-sulfur cluster repair protein; Sags: Superantigens; SPIN: *Staphylococcus* peroxidase inhibitor; PMN: Polymorphonuclear leukocyte; Treg: Regulatory T cells; DC: Dendritic cell; AdsA: Adenosine synthase A; NETs: Neutrophil extracellular traps.

## 2 葡萄球菌感应并清除宿主 ROS/RNS

PMN 释放的 ROS 和活性氮(reactive nitrogen species, RNS)是重要的抗菌效应分子。NADPH 氧化酶催化生成的超氧化物( $O_2^-$ )和  $H_2O_2$  可直接杀灭病原菌,而 RNS 通过 NO 干扰病原菌代谢<sup>[41-42]</sup>。葡萄球菌通过呼吸相关双组分系统(staphylococcal respiratory response AB system, SrrAB)对抗宿主产生的 ROS/RNS,显著增强其氧化应激耐受能力<sup>[6]</sup>。在有氧条件下,SA (USA300)通过 SrrAB 上调过氧化氢酶基因 *kata*、烷基过氧化氢还原酶基因 *ahpC* 及硫铁簇修复蛋白基因 *scdA* 表达,加速内源性  $H_2O_2$  分解并修复氧化损伤蛋白;同时,SA 通过 DNA 保护蛋白(DNA protection during starvation, Dps)抑制芬顿反应(Fenton)以减少羟自由基( $\cdot OH$ )生成<sup>[43]</sup>。此外,Zhao 等<sup>[44]</sup>研究表明,表皮葡萄球菌 SE1457 SrrAB 能感应环境中  $H_2O_2$  和过氧化氢异丙苯的浓度变化,*srrAB* 基因缺失可显著降低其解毒 ROS 的能力,进而降低 Ana-1 巨噬细胞内的存活率,而 *srrAB* 互补株的 ROS 抗性及其胞内存活能力均恢复至野生型水平,证实 SrrAB 通过正调控 ROS 清除相关基因(*kata*, *ahpC*, *scdA*, *serp1797*, *serp0483*)的转录,既能清除细菌生长代谢过程中产生的内源性 ROS,又能抵御宿主免疫细胞呼吸暴发产生的外源性 ROS 的氧化杀伤,以达到适应环境及引起感染的目的。厌氧条件下,SrrAB 进一步激活  $\beta$ -1,6-N-乙酰葡萄糖胺多糖 (poly- $\beta$ -1,6-n-acetylglucosamine, PIA)合成关键基因 *icaA*,促进 PIA 生物合成并形成物理屏障,以抵抗宿主非 ROS 依赖性的杀伤机制<sup>[45]</sup>。针对宿主释放的 NO, SrrAB 上调黄素血红蛋白基因 *hmp* 表达,利用黄素腺嘌呤二核苷酸(flavin adenine dinucleotide, FAD)将 NO 催化为硝酸盐( $NO_3^-$ ),协助 SA 抵抗亚硝化应激;基因敲除后显示,  $\Delta$ *srrAB* 突变株对 NO 的敏感性较  $\Delta$ *hmp* 突变株显著升高,提示 SA 存在不依赖 Hmp 的 NO 抵抗途径<sup>[46-47]</sup>。Leitgeb 等<sup>[48]</sup>

发现,除 SrrAB 外,葡萄球菌过氧化物酶抑制剂(*Staphylococcus* peroxidase inhibitor, SPIN) C 端锚定髓过氧化物酶(myeloperoxidase, MPO)后,将 N 端折叠插入 MPO 的底物通道,通过空间位阻选择性阻断大分子底物运输,从而抑制强氧化剂次氯酸(hypochlorous acid, HOCl)生成,进一步协助 SA 逃逸 PMN 的氧化杀伤。

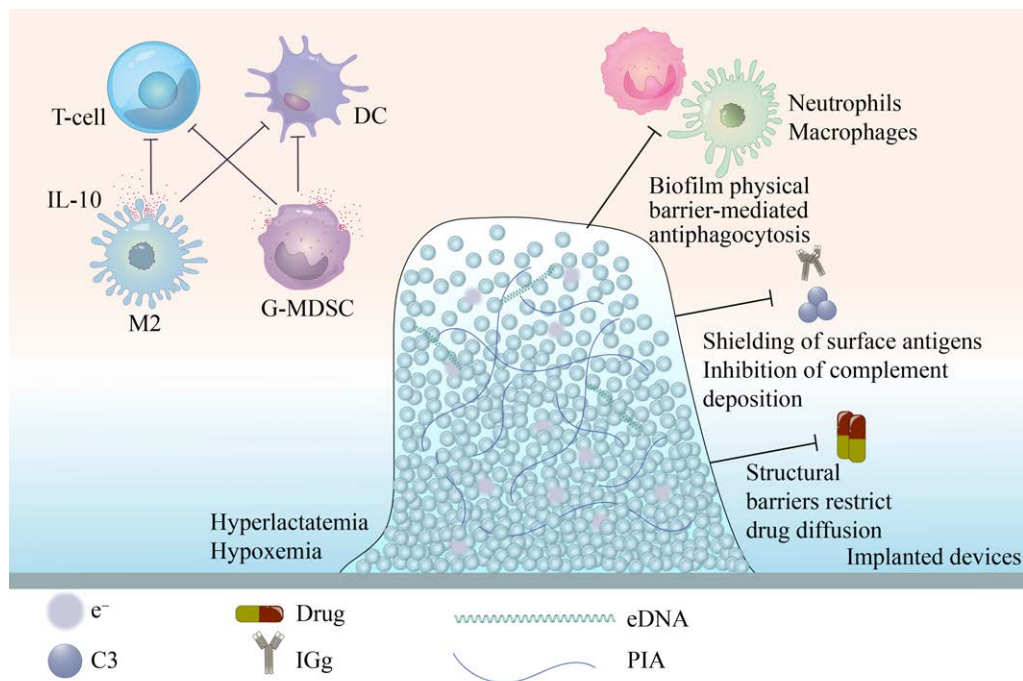
## 3 改变细胞代谢有利于免疫逃逸

衣康酸(itaconic acid, ITA)是一种由免疫应答基因 1 (*lrg1*)编码的顺乌头酸脱羧酶(*cis*-aconitate decarboxylase 1, ACOD1)催化产生的代谢物, Tomlinson 等<sup>[49-50]</sup>利用 SA (USA300)构建的小鼠肺炎模型发现, *lrg1* 缺失小鼠的细菌载量显著低于野生型感染小鼠,SA 能诱导 PMN 产生大量 ITA,后者通过共价修饰 NADPH 氧化酶关键亚基(胞质因子 Ncf2、Ncf4、Rho GTP 酶 Rac2),直接抑制小鼠 PMN 氧化暴发;另一方面,ITA 通过抑制 PMN 糖酵解活性减少 ATP 生成,导致 PMN 能量耗竭及功能紊乱,进而减弱对 SA 的杀灭作用;此外,研究人员通过 RT-qPCR 和 RNA-Seq 发现,ITA 可抑制 SA 糖酵解关键酶 Fba (阻断果糖-1,6-二磷酸分解)和 TCA 循环酶 AcnA (阻断柠檬酸代谢),导致 SA 糖酵解与能量生成受阻,但 SA 能通过上调乳酸脱氢酶基因 *ldh1* 和丙酮酸羧化酶基因 *pyc* 的表达来积累葡萄糖;<sup>13</sup>C-葡萄糖标记和同位素示踪显示,SA 将积累的葡萄糖重新分配至 UDP-N-乙酰氨基葡萄糖的合成,促进 EPS 产生及生物膜形成,最终逃避宿主免疫清除。

SA 形成的生物膜通过代谢消耗降低局部组织的氧分压,导致免疫细胞中的缺氧诱导因子-1 $\alpha$  (hypoxia-inducible factor 1-alpha, HIF1 $\alpha$ )降解减少, HIF1 $\alpha$  蛋白通过结合糖酵解基因的缺氧反应元件(hypoxia-responsive element, HRE),显著增强糖酵解代谢通量,促使粒细胞型髓源性抑制细胞(granulocytic myeloid-derived suppressor cells, G-MDSCs)转化为抗炎表型,通常来说 HIF1 $\alpha$  在 PMN 和 M $\Phi$  中表现为促炎作用,但 G-MDSCs

却会通过 HIF1 $\alpha$  负向调控 IFN- $\alpha/\gamma$  及 TNF-NF- $\kappa$ B 通路维持抗炎表型, 减弱 PMN 等免疫细胞对生物膜的氧化杀伤能力; 在 HIF1 $\alpha$  缺陷模型中, G-MDSCs 的促炎功能恢复, 感染骨组织与植入物的细菌载量显著降低, 提示 HIF1 $\alpha$  是 SA 生物膜慢性感染的关键调控因子<sup>[51]</sup>。此外, 研究发现, G-MDSCs 通过糖酵解产生的高浓度乳酸还会抑制 CD4<sup>+</sup> T 细胞的乳酸外排, 导致细胞氧化还原稳态失衡与代谢紊乱, 干扰 CD4<sup>+</sup> T 细胞的正常免疫功能<sup>[52]</sup>。SA (USA300) 生物膜中的代谢产物乳酸, 还能通过抑制组蛋白去乙酰化酶(histone deacetylases, HDAC), 增加 IL-10 基因启动子区的 H3K27 乙酰化水平, 驱动抗炎因子 IL-10 的过度分泌<sup>[51,53]</sup>。Kak 等<sup>[54]</sup>在 SA (USA300) 诱导的小鼠

颅内感染模型中发现, IL-10 主要由 PMN 和 G-MDSCs 分泌, 其通过抑制 PMN 的杀菌能力和 TNF- $\alpha$  分泌, 同时限制 CD4<sup>+</sup> 和  $\gamma\delta$ T 细胞的招募与活化, 减少 IL-17、IFN- $\gamma$  及 C-X-C 基序趋化因子配体 10 (C-X-C motif chemokine ligand 10, CXCL10) 等促炎因子的产生, 从而削弱免疫应答 (图 3); SA 感染 IL-10 缺陷小鼠后, 脑组织及帽状腱膜区淋巴细胞浸润显著增加, 并伴随 IFN- $\gamma$  和 TNF 水平升高及细菌载量降低, 进一步验证 IL-10 是维持生物膜持续感染的核心因子。进一步研究发现, 在 SA (USA300) 引发的假体周围感染模型中, G-MDSCs 可转化为 F4/80<sup>+</sup>MHCII<sup>+</sup> 表型, 表现出更强的 T 细胞抑制能力, 揭示 SA 生物膜通过 G-MDSCs 表型转化实现免疫逃逸的新机制<sup>[55]</sup>。



**图 3 葡萄球菌生物膜介导的免疫逃逸** 生物膜形成导致局部缺氧及乳酸堆积, 诱导粒细胞型髓源性抑制细胞与 M2 巨噬细胞协同释放免疫抑制因子 IL-10, 形成免疫抑制微环境; 生物膜形成的物理屏障阻断吞噬细胞的攻击, 减少补体与抗体的结合, 减少药物渗透。DC: 树突状细胞; M2: M2 型巨噬细胞; G-MDSCs: 粒细胞-髓源性抑制细胞。

Figure 3 Biofilm-mediated immune evasion in *Staphylococcus*. Biofilm formation leads to local hypoxia and lactic acid accumulation, driving granulocytic myeloid-derived suppressor cells (G-MDSCs) and M2 macrophages to synergistically release IL-10, thereby establishing an immunosuppressive microenvironment; Biofilm formation physically blocks phagocytic attacks, reduces the possibility of complement-antibody binding, and impairs the drug penetration. DC: Dendritic cell; M2: M2 macrophage; G-MDSCs: Granulocytic-myeloid-derived suppressor cells.

综上, SA 通过重塑宿主代谢网络与免疫抑制微环境, 实现多重免疫逃逸及慢性感染的维持。

## 4 形成生物膜隐匿定殖抵抗清除

PMN 向感染灶迁移需要经历内皮滚动、黏附及跨内皮渗出等过程, 这一时间差为病原菌增殖提供了关键机会<sup>[56]</sup>。Alhede 等<sup>[57]</sup>发现, 葡萄球菌聚集体的直径在 96 孔板中每增加 1  $\mu\text{m}$ , 其被有效吞噬的概率降低约 41%, 当聚集体直径超过 5  $\mu\text{m}$  时, 单个 PMN 已无法完成吞噬清除。Pettygrove 等<sup>[58]</sup>在 SA (AH2547)体外玻片模型中证实, SA 聚集体形成后可快速抵抗 PMN 的清除, 成熟的葡萄球菌聚集体通过破坏 PMN 细胞膜完整性引发其裂解, 并且该效应具有明确面积依赖性: 当聚集体面积超过 50  $\mu\text{m}^2$  时可引发显著细胞膜损伤, 而面积超过 75  $\mu\text{m}^2$  时导致 PMN 完全裂解<sup>[58]</sup>。未被及时清除的葡萄球菌将定殖于宿主血浆及胞外基质蛋白包被的植入物表面, 为生物膜形成创造有利条件。

葡萄球菌通过识别黏附基质分子的微生物表面成分(microbial surface components recognizing adhesive matrix molecules, MSCRAMMs)与宿主胞外基质(extracellular matrix, ECM)或非生物植入物表面特异性结合, 实现初始定殖<sup>[59]</sup>。随后在生物膜成熟阶段, PIA 可形成三维网状结构来包被病原相关分子模式(pathogen-associated molecular patterns, PAMPs), 减少免疫球蛋白及补体 C3b 的沉积, 从而抑制宿主免疫识别<sup>[7]</sup> (图 3)。在生物膜介导的免疫逃逸过程中, *ica* 操纵子的表达调控具有核心地位, Wu 等<sup>[60]</sup>研究发现, 万古霉素耐药相关系统(vancomycin resistance-associated sensor-regulator system, *VraSR*)通过 *ica* 途径正调控表皮葡萄球菌(*Staphylococcus epidermidis*)生物膜形成, 当 *vraSR* 基因缺失时, PIA 合成减少导致生物膜结构疏松, *vraSR* 突变株体内生物膜形成能力均显著减弱, 并且生物膜内死菌数比例增加; 上述结果提示, 通过靶向干预 *VraSR* 通路可部分控制生物膜介导的慢性感染。此外,

葡萄球菌荚膜多糖作为细胞壁的重要组成部分, 既参与生物膜形成, 也能显著减少补体 C3 与细菌的结合, 并且高表达荚膜多糖可有效减少非特异性免疫杀伤, 保护细菌免受免疫系统攻击<sup>[61-62]</sup>。此外, 葡萄球菌分泌的胞外纤维蛋白原结合蛋白(extracellular fibrinogen-binding protein, Efb)通过结合细菌表面的补体 C3b 和纤维蛋白原, 在细菌周围形成一层纤维蛋白原屏障, 有助于葡萄球菌抵抗吞噬<sup>[63]</sup>。另外, 宿主补体系统与葡萄球菌的交互具有双向性, 补体成分不仅参与宿主防御, 还能直接调节细菌代谢。Jin 等<sup>[64]</sup>发现, 补体 C3 可直接调控 SA (USA300)的基因表达谱(如 *proC*、*hrcA* 等), 影响细菌代谢通路与应激反应; 该研究还发现 C3 缺陷能显著抑制小胶质细胞的抗菌功能, 提示在血脑屏障破坏的感染中, C3 可能同时承担神经免疫监视与病原代谢调控的双重功能。补体系统与病原体间的交互, 揭示了葡萄球菌感染微环境中免疫逃逸与宿主免疫拮抗的动态平衡机制。

## 5 形成 SCVs 逃避免疫识别

葡萄球菌在宿主压力环境中可转化为 SCVs, 该表型变异与慢性感染高度相关。SCVs 形成机制与电子传递链功能障碍、胸苷酸合成异常及  $\sigma\text{B}$  因子(sigma B factor, SigB)应激通路激活相关<sup>[65-67]</sup>。SCVs 通过抑制 RNA III 依赖的毒素分泌维持潜伏感染, 同时上调纤维连接蛋白(fibronectin-binding protein, FnBP)表达, 以利于侵入宿主细胞。实验表明, SA LS1、SH10008325-4 侵染小鼠 MLO-Y4 骨细胞时, SCVs 比例显著增加, 并且由于骨细胞自身产生的抗菌肽不足, 导致其无法有效清除胞内 SA; 此外, SA 感染的骨细胞还会分泌大量的前列腺素 E2 (prostaglandin E2, PGE2), 激活 Wnt/ $\beta$ -catenin 信号通路抑制细胞凋亡, 为胞内菌存活提供微环境<sup>[68-69]</sup>。Siwczak 等<sup>[70]</sup>研究表明, M2 型巨噬细胞极化也能促进 SCVs 形成, 并且由于 M2 型巨噬细胞自身杀菌能力较弱, 同时被吞噬的 SCVs 又会抑制 HIF-1 $\alpha$

生成, 这两方面因素共同减弱了宿主的抗菌免疫反应, 为 SCVs 创造了更利于存活的环境。

Painter 等<sup>[71]</sup>发现 SCVs 对中性粒细胞氧化暴发的抵抗能力显著强于野生型, 这可能是由于 SCVs 的铁含量较低, 减弱了 Fenton 反应, 进而有助于抵抗氧化暴发。此外, Wong 等<sup>[72]</sup>利用  $\Delta hemB$  8325-4 突变体构建的 SCVs 发现, SCVs 能够激活宿主糖酵解途径, 升高 ROS 水平, 进而诱导受体互作蛋白激酶(receptor-interacting protein kinase, RIPK)依赖的坏死性凋亡(necroptosis); 另外, 此类坏死性死亡模式反而促进了 SCVs 的播散与定殖, 同时 SCVs 通过上调 *fumC* 基因表达来增强富马酸酶活性, 抑制富马酸累积介导的免疫训练。最后, Kittinger 等<sup>[73]</sup>通过对临床分离的胸苷营养缺陷型 SA-SCV (thymidine auxotrophic *Staphylococcus aureus* small colony variant, td-SA-SCV)进行长期观察, 发现 12 株 td-SA-SCV 中有 7 株出现表型回复现象, 提示 SCVs 具有根据环境压力动态调整生存策略的生物学特性。

## 6 利用自噬存活并传播

自噬是吞噬细胞清除胞内病原体的重要机制, 通过形成酸化吞噬溶酶体发挥抗菌效应。SA (ATCC29213)感染 M $\Phi$  后可阻断自噬通量, 利用滞留的自噬体作为增殖场所, 经自噬抑制剂氯喹处理后胞内菌载量显著升高, 证实自噬体聚集有利于细菌存活<sup>[74]</sup>。进一步研究表明, 这一过程可能与 Agr 群体感应系统调控相关。Tranchemontagne 等<sup>[75]</sup>发现, SA (USA300)在自噬体低 pH 环境下可上调 *agr* 系统表达以维持存活, 其分泌的 Hla 或酚溶性调节蛋白  $\alpha$  (phenol-soluble modulins alpha, PSM $\alpha$ )可能协助细菌逃离自噬体, 进入胞质复制。然而, Flannagan 等<sup>[76]</sup>提出不同机制: SA (USA300)在完全酸化的溶酶体相关膜蛋白 1 (lysosome-associated membrane protein 1, LAMP-1)阳性吞噬溶酶体中通过葡萄球菌毒力调控双组分系统(GraS-GraR two-component regulatory system,

GraXRS)激活应激反应, 使其耐受抗菌肽等效应分子, 并持续增殖。即使 *agr* 和 *saeR* 突变株仍保留复制能力, 但当囊泡破裂、pH 升高时菌体存活率急剧下降, 提示 GraXRS 及其所处的酸性微环境是 SA 生存的必要条件。此外, M $\Phi$  胞内的 SA 通过大量消耗葡萄糖和氨基酸诱导宿主细胞饥饿应激, 激活 AMP 依赖蛋白激酶/细胞外信号调节激酶(AMP-activated protein kinase/extracellular signal-regulated kinase, AMPK/ERK)通路诱导自噬, 自噬降解产物为细菌生存提供代谢底物, 同时自噬体内的 SA 通过维持 M $\Phi$  的胞饮作用, 持续获取胞外营养来维持后续的增殖; 当 SA 在 M $\Phi$  内达到临界数量时, SA 通过 Sae 系统调控白细胞毒素 LukAB/PVL 表达, 以实现免疫逃逸<sup>[77-79]</sup>。释放的菌体可被邻近 M $\Phi$  再次吞噬, 形成持续感染。因此, M $\Phi$  被视为 SA 体内感染、播散的“特洛伊木马”。

Prajsnar 等<sup>[80]</sup>利用斑马鱼幼虫模型研究 SA (SH1000)感染发现, PMN 依赖 NADPH 氧化酶产生的 ROS, 可诱导 LC3 相关吞噬作用(LC3-associated phagocytosis, LAP), 将 SA 包裹于非酸化单层膜囊泡内, 当敲除 *cyba/p22phox* 基因或使用二苯基碘(diphenyliodonium, DPI)抑制 ROS 生成时, LC3 无法锚定至吞噬体膜, 提示 ROS 是 LAP 形成的必需信号分子; 而 ATG5/ATG16L1 双敲除模型可完全阻断 LAP 通路, 导致 LC3 标记的菌囊泡数量显著减少, 并显著增强幼虫宿主的抗感染能力, 证实 LAP 为 SA 提供关键生存微环境。Mulcahy 等<sup>[81]</sup>研究发现, 携带有 SA (PS80)的 PMN 因自噬通量受阻导致自噬体异常堆积, 堆积的自噬体可激活 p53 信号通路, 并伴随抗凋亡因子 *bcl2*、*mcl1* 和 *bcl2a1* 转录水平升高, 这些因子通过抑制线粒体膜去极化和阻断半胱天冬酶-3 (caspase-3)活化延缓了细胞死亡, 从而延长 SA 的胞内增殖时间(图 4)。另外, SA 在人吞噬细胞中的存活能力显著强于凝固酶阴性葡萄球菌(coagulase-negative staphylococci, CoNS), 实验表明, 抑制

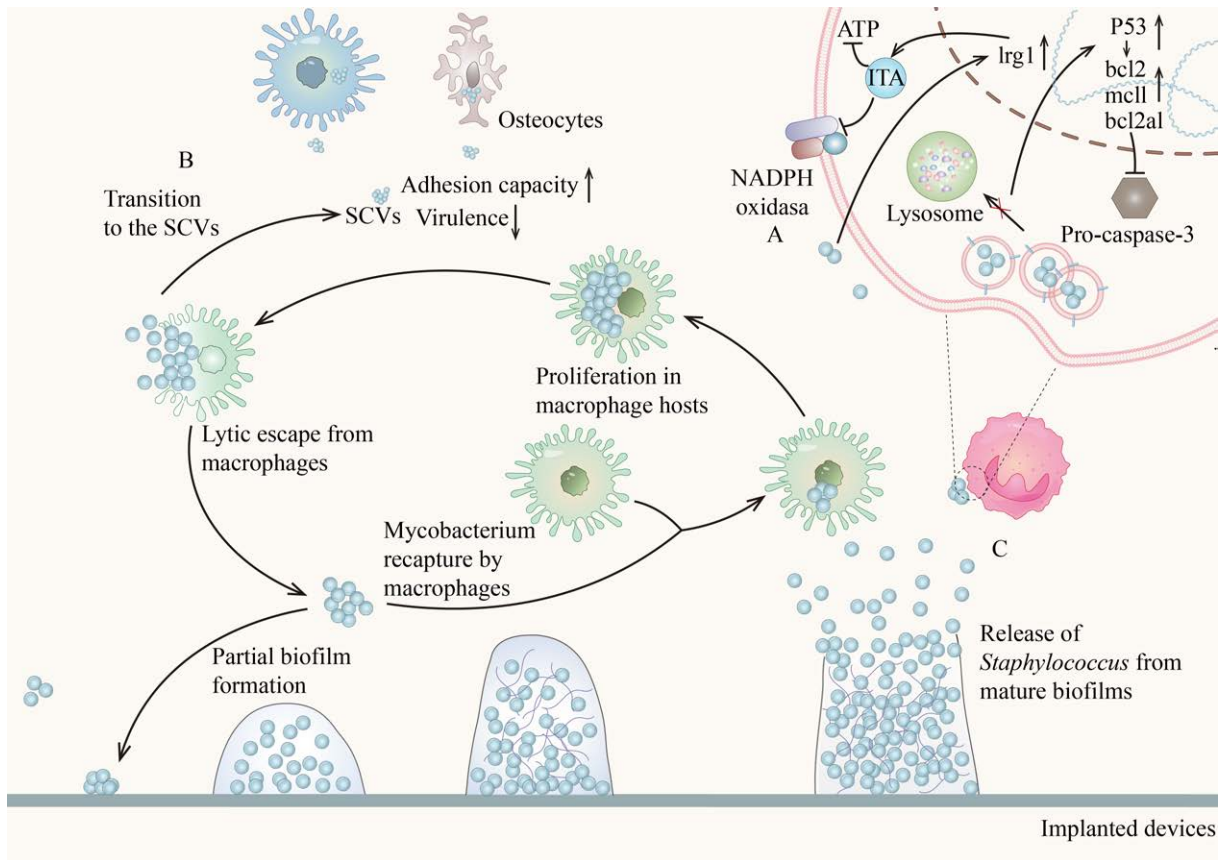


图 4 葡萄球菌的胞内存活与播散 A: 葡萄球菌诱导 PMN 合成 ITA, 拮抗 ROS 生成, 并阻遏线粒体 ATP 合成; B: SCVs 通过降低毒力和增强黏附来介导内化, 逃逸宿主的免疫监视; C: 葡萄球菌在吞噬溶酶体中实现胞内存活与增殖, 通过吞噬细胞迁移进行播散。

Figure 4 Intracellular survival and phagocytosis-mediated spread of *Staphylococcus*. A: *Staphylococcus* induces PMN to synthesize ITA to counteract ROS generation and suppresses mitochondrial ATP synthesis; B: SCVs reduce virulence and enhance adhesion-mediated internalization to evade host immune surveillance; C: *Staphylococcus* achieves intracellular survival and proliferation within phagolysosomes, disseminating through phagocyte migration pathways.

吞噬体酸化(如巴菲霉素处理)能显著改善表皮葡萄球菌等 CoNS 的胞内存活能力, 提示低 pH 环境是清除 CoNS 的关键因素<sup>[82]</sup>。

## 7 结语与展望

葡萄球菌与宿主的博弈本质上是毒力策略与免疫监视的动态平衡过程, 本综述揭示了这一相互作用的核心特征, 即葡萄球菌通过动态调控毒力因子表达, 建立病原体的多层次攻击与防御体系, 而宿主则通过改变代谢模式与免疫细胞分化进行反制。从 PFTs 介导的细胞焦亡到自噬

小体庇护的胞内存活, 从 ROS 清除系统的快速应激到生物膜微生态的慢性适应, 葡萄球菌展现出从分子作用到群体行为的协同进化机制。然而, 体外模型虽为解析葡萄球菌-宿主互作提供了重要基础, 但其简化设计难以复制组织微环境中免疫-代谢网络的动态互作。动物模型的跨物种免疫应答差异, 也可能会导致关键机制的误判。基于现有动物感染模型的研究为葡萄球菌感染防控策略提供了重要启示, 例如, 针对细胞壁锚定蛋白(cell wall-anchored protein, CWA) 的亚单位疫苗设计, 抑制细菌初始定殖和侵入宿

主细胞;调控自噬通量限制细菌增殖微环境的建立;选择具有更高渗透性的抗生素,以增强药物在吞噬溶酶体中的杀菌效能。未来需要构建更贴近人体免疫代谢特征动物模型,以深入解析葡萄球菌-宿主的互作机制,精准优化治疗策略。

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付斌: 查询文献, 撰写文章, 图表绘制; 李明珠: 撰写文章, 审阅; 宋树佳、李福星: 图表绘制, 审阅; 陈佳乐: 数据管理, 审阅; 尚爽婕: 方法论, 审阅; 武有聪: 选题与设计, 指导并修改文章, 获取基金。

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作者声明绝无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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