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细菌生物膜耐药机制与纳米生物治疗研究*

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摘要 由细菌生物膜造成的耐药是感染性疾病的临床挑战，严重危害人类健康。细菌定植在机体后产生胞外基质形成生物膜，其具有结构致密、高黏附性、药物低渗等特征，是临床传统药物治疗感染性疾病失败的关键原因。因此，亟待开发抗细菌生物膜感染的新型治疗策略，应对日益严峻的耐药感染。纳米生物材料具有特异靶向、智能递送、载药量高、毒副性低、穿透性强等优势，被广泛用于细菌生物膜相关感染的治疗。本文阐述了细菌生物膜的生物学特性及其耐药分子机制，介绍了纳米生物材料通过破坏成熟生物膜、阻断细菌通信、抑制细菌代谢和增强生物膜渗透等策略治疗细菌感染的进展，并展望了纳米材料生物治疗的发展趋势与转化前景。

关键词 细菌生物膜，耐药机制，纳米药物，生物治疗
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细菌造成持续感染和器官衰竭，已成为全球第二大死因。据世界卫生组织报道，全球每年有约700万人死于病原体感染，其中3/4患者的死亡与细菌感染直接相关，预计到2050年，细菌感染造成的死亡将达到1 000万人/年[1]。其中，多数感染都与细菌生物膜的形成有关。细菌在中枢神经、眼部、呼吸道、肝脏、骨骼、口腔、皮肤软组织、心血管、胃肠道以及泌尿系等人体主要部位均可形成生物膜，生物膜促进细菌在感染部位的定植与生长繁殖，产生大量代谢产物刺激机体炎症因子释放，引发机体血管扩张和免疫细胞浸润，造成组织炎症反应。而且，细菌生物膜还会阻碍药物渗透，使炎症反应持续激活，导致感染难以治愈[2-4]。例如，脑膜炎链球菌（*Streptococcus meningitidis*，*S. meningitidis*）、肺炎链球菌（*Streptococcus pneumoniae*，*S. pneumoniae*）、流感嗜血杆菌（*Haemophilus influenzae*，*H. influenzae*）等细菌在中枢神经形成生物膜造成脑膜炎，金黄色葡萄球菌（*Staphylococcus aureus*，*S. aureus*）、铜绿假单胞菌（*Pseudomonas aeruginosa*，*P. aeruginosa*）、*S. pneumoniae*等可在眼部形成生物膜造成角膜炎，*H. influenzae*、*S. pneumoniae*、结核分枝杆菌（*Mycobacterium tuberculosis*，*M. tuberculosis*）等可在呼吸道形成生物膜引发肺炎[5-7]（图1）。

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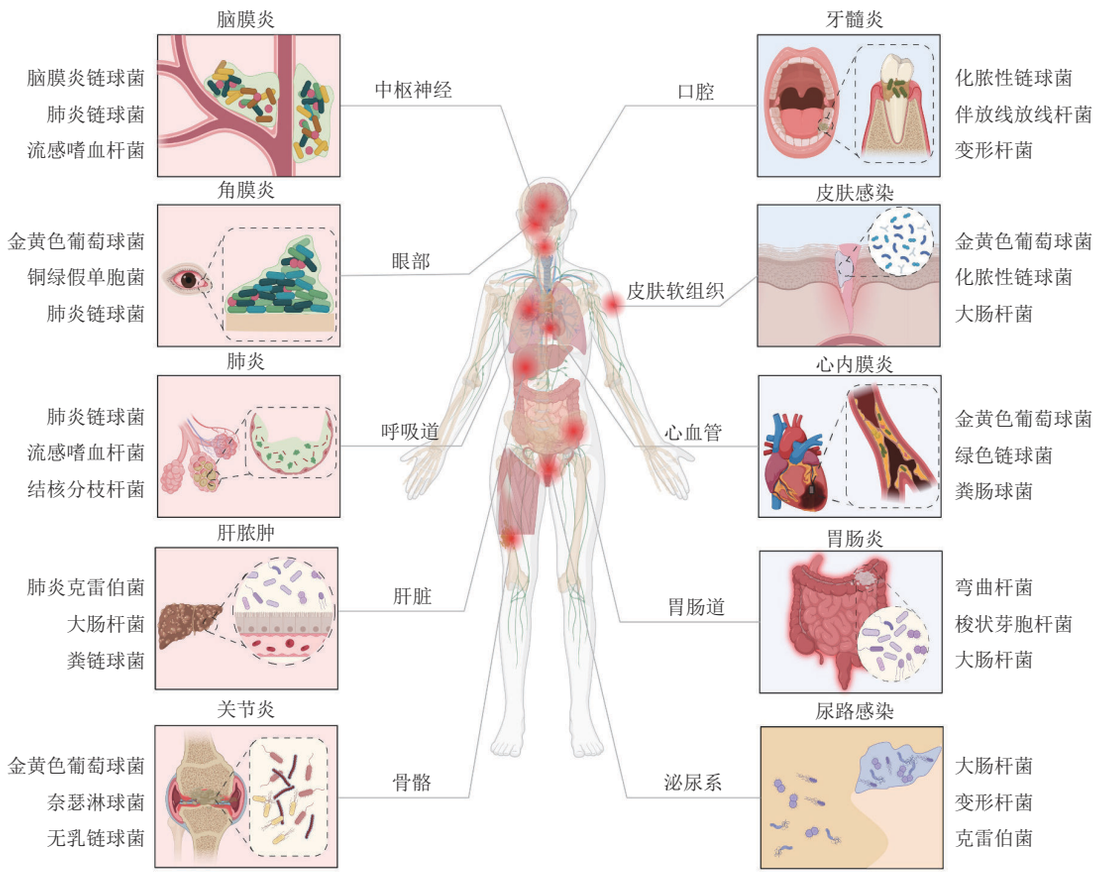

Fig. 1　Biofilm colonization sites and infectious symptoms of pathogenic bacteria

图1　相关病原菌的生物膜定植部位及其引发的感染症状

细菌黏附和定植于生物或非生物表面后，依靠自身合成的蛋白质、多糖、胞外DNA（extracellular DNA，eDNA）等非水溶性胞外聚合物基质（extracellular polymeric substances，EPS）相互交联形成结构致密的生物膜。带负电的生物膜具有较强的疏水性，能够通过静电吸附和物理屏蔽阻碍抗生素的渗透和免疫细胞的浸润，是细菌天然的耐药物理屏障。此外，生物膜还可诱导细菌代谢静止、应激反应与细菌群体感应（quorum sensing，QS）或上调细菌外排泵的表达水平，加重耐药[8-11]。最终，细菌生物膜得以在人体中长期定植，引发难以消除的局部炎症、慢性感染，严重时会导致脓毒血症、器官衰竭乃至死亡[12-13]。

目前，临床上治疗耐药细菌多采用多黏菌素、环丙沙星、万古霉素等抗生素，但这些抗生素无法有效渗透或清除生物膜，并且存在严重的毒副作用[14-15]。因此，亟需开发能够有效破坏细菌生物膜的抗生素替代药物，缓解耐药细菌导致的持续感染与器官衰竭等症状。随着纳米医学与生物工程的快速发展，纳米生物材料迅速崛起，已经广泛应用于细菌感染治疗。纳米生物材料不仅具有纳米尺度结构及生物相容活性，还能通过靶向药物输送、提高药物驻留、刺激药物释放等功能设计，实现对耐药细菌生物膜的高效干预与精准治疗，具有巨大的临床产业转化和应用前景[16-19]。例如，纳米生物材料能够诱导膜基质的分散、干预膜内细菌信号传递、阻断细菌能量供应，还能利用其高载药能力与自驱动性能提高药物在细菌生物膜部位的高效递送和深层渗透[20-23]。因此，通过纳米生物材料破坏生物膜耐药分子机制和提高生物膜清除效率，可实现对耐药细菌感染的高效治疗[24-25]。

本文详细介绍了细菌生物膜的生物学特性及其

在耐药细菌感染中的重要分子机制，总结了纳米生物材料在细菌生物膜清除与抗感染治疗中的应用，阐述了其在破坏生物膜基质、干预细菌信号传递/代谢治疗细菌感染中的优势。此外，介绍了能源驱动型微纳机器人在药物主动递送与生物膜清除中的进展，以期为耐药细菌感染引起的临床治疗难题提供关键理论依据和技术手段。

1 生物膜造成细菌耐药的分子机制

生物膜作为天然的物理屏障，能够从多种机制上保护细菌免受抗生素的杀伤和宿主免疫系统的清除，造成持续性耐药与系统性感染[16]。长时间的抗生素治疗不仅无法改善由细菌生物膜造成的耐药症状，还会引发肝肾损害、过敏反应、菌群紊乱、反复感染等危害[26]。因此，深入探究细菌生物膜保护细菌及抵抗药物机制，对于遏制细菌耐药态势和避免反复感染具有重要意义。

1.1 胞外基质造成天然物理屏障

浮游细菌附着在生物或非生物表面后，通过有组织的细菌种群（单物种或多物种）聚集形式，以及生理、代谢和表型变化，实现从浮游菌到生物膜内定植的转变。细菌可以通过促进自身鞭毛和菌毛的合成组装与功能激活，增强自身在介质表面的运动与黏附，诱导细菌生物膜的形成与成熟[27-29]。此外，细菌通过分泌多糖、蛋白质、eDNA等物质，促进彼此紧密交联形成EPS将细菌包裹在内，为其生长繁殖提供天然物理屏障[30]，同时帮助细菌对抗生素产生耐受抵抗及避免宿主免疫细胞吞噬清除，导致耐药加重和持续感染。

1.2 群体感应（QS）诱发细菌环境适应

外环境压力改变或细菌数量增加时，细菌通过合成并释放信号分子增强细菌群体间相互联系和细胞间信号通信，这种机制称为QS系统[31]。QS系统普遍存在于革兰阳性菌和革兰阴性菌中，是调控和协调细菌毒力基因表达与生物膜形成的重要机制。而生物膜能够进一步聚拢和固定浮游细菌，提高细菌QS信号分子的富集，强化细菌种群间信息交流，促使细菌对外界胁迫因素做出快速应激反应，增强对抗菌药物和免疫细胞的抗性[32]。

1.3 代谢适应促进细菌长期生存

当暴露于抗生素环境中时，生物膜中的细菌会通过调节自身的代谢耐受性机制应对抗生素的干预。由于外来抗生素或其他物质在生物膜部位的富集，生物膜外层的细菌会产生适应性突变（如上调外排泵与β内酰胺酶表达等）以抵抗抗生素治疗，维持正常的生理活动和代谢过程[33-34]。另一方面，得益于致密的EPS结构，大部分外界营养物质、氧气或药物被挡在生物膜外或膜表层，导致营养物质与氧气等细菌必需物质在生物膜内产生空间分布梯度差异，导致生物膜深层微环境改变（氧含量、pH等），促使膜深层的细菌代谢活性被抑制。细菌在恶劣生理环境下会关闭自身蛋白质合成与生理代谢通路，还能应激性释放DNA修复基因对自身DNA进行损伤修复[35-39]，维持生物膜深层细菌的长期生存。适应性应激反应的激活会进一步诱导细菌休眠，增强抗生素耐药性，同时上调细菌毒力因子与耐药基因表达水平，是导致临床持续性、反复性感染的根本原因之一。

1.4 细菌耐药减弱药物杀伤效能

细菌在宿主体内定植并演化形成生物膜以后，细菌能够凭借生物膜EPS的致密结构和独特理化性质，提高对抗生素药物与宿主免疫细胞的耐受能力。EPS中70%~80%的成分由蛋白质、多糖、eDNA等物质构成[25, 30]。妥布霉素和多黏菌素等多种带正电荷抗生素易于与胞外基质中的多糖、eDNA等带负电荷成分产生静电吸附，不仅阻碍药物在膜内的主动扩散，还会导致膜内细菌有充足时间来产生适应性应激，增加细菌耐药性[40]。此外，EPS的微小孔隙与阻滞吸附能力还能够抑制外来物质进入膜内，有助于细菌免受外来抗菌药物或免疫细胞的清剿[41-42]。

2 纳米生物材料在生物膜治疗中的应用

由于生物膜的致密结构、细菌QS及代谢适应等机制的存在，传统的抗生素不仅不能有效治疗生物膜感染，而且还会对机体造成严重的毒副作用。纳米生物材料可通过分散细菌生物被膜、阻断细菌信号传递、抑制细菌能量代谢及能源驱动渗透等策略破坏细菌生物膜，改善细菌生物膜引发的耐药[43-45]。

2.1 破坏物理屏障，分散细菌被膜

生物膜不仅为细菌代谢提供丰富的营养物质和

稳定环境，还能将外界抗生素、抗体、有毒物质等环境胁迫因素排斥在外，为生物膜内的细菌提供了强有力的保护[46]。分解生物膜EPS可以增强生物膜的通透性，瓦解破坏生物膜的三维空间结构，实现细菌的主动暴露与扩散。纳米生物材料联合生物膜基质降解酶（蛋白酶、多糖酶、脱氧核糖核酸酶（deoxyribonuclease，DNase）、纳米酶以及噬菌体裂解酶）靶向水解生物膜物理屏障，有效提高药物在生物膜部位的富集，是实现细菌生物膜清除与抗感染治疗的潜在策略[47]。

胞外蛋白是生物膜EPS的重要组成部分，能够与胞外多糖相互作用维持和强化生物膜的骨架结构，还能作为通道蛋白或转运蛋白在生物膜内及膜外环境之间输送营养物质与代谢产物，对于维持生物膜内细菌代谢与生命活动至关重要，是实现生物膜有效清除的重要靶点。表面涂覆蛋白酶并负载环丙沙星的功能化抗生素纳米凝胶载体，能够利用蛋白酶将EPS中的胞外蛋白进行有效“消化”，随后将环丙沙星递送至生物膜内部造成细菌杀伤。功能化的抗生素纳米凝胶载体可对多种细菌生物膜（如*S. aureus*、*P. aeruginosa*等）造成明显破坏，减少80%以上的生物膜质量和降低99.9%以上的细菌量，具有十分显著的抗菌/抗生物膜效果[48]。以硫化铜为载体负载蛋白酶构建而成的光热纳米颗粒，利用蛋白酶对胞外蛋白的酶促降解特性及硫化铜优异的光热性能，在由牙菌斑生物膜引起的大鼠牙周炎模型中实现有效的细菌杀伤和生物膜分解[49]。

胞外多糖包含了葡聚糖、甘露糖、纤维素等多种组分，可促进浮游细菌的附着和细菌对营养物质的吸收，有利于细菌在膜内的定居与繁殖[50]。此外，胞外多糖作为生物膜内细菌的保护屏障，能够利用其复杂致密的结构特性将外界有毒物质等环境胁迫因子排斥在膜外。因此，靶向降解、清除胞外多糖，同样是破坏细菌物理屏障的重要手段。纤维素是细菌生物膜胞外多糖中的主要组分，对于维持生物膜空间结构的稳定性至关重要。纤维素酶作为纳米级的生物降解酶，不仅能够通过高效降解纤维素产生葡萄糖来破坏生物膜，还能够增强抗生素的抗菌疗效[51-52]（图2a）。负载有α淀粉酶的银纳米颗粒可通过淀粉酶酶促分散胞外多糖，协同银离子自身所具备的高效抗菌能力，降低*S. aureus*和大肠杆菌（*Escherichia coli*，*E. coli*）生物膜的表面黏附程度且去除率超过80%，为缓解抗菌素耐药性提供了新型抗菌策略[53]。装载了α淀粉酶与包含左氧氟沙星的聚多巴胺纳米颗粒的可溶性微针贴片，在近红外光照射下溶解并释放出α淀粉酶以降解胞外多糖，随后将聚多巴胺纳米颗粒递送至生物膜内，协同抗生素实现对*S. aureus*与*P. aeruginosa*生物膜的破坏与菌体的有效裂解[54]。

eDNA作为生物膜内细菌基因水平传递的“基因仓库”，通过细菌主动分泌、细胞溶菌作用等方式释放到胞外，能够与胞外蛋白、胞外多糖相互紧密交联，共同构成生物膜的空间骨架[55]。因此，通过酶促水解eDNA是抑制、分散生物膜以及增强抗菌剂敏感性的关键策略。负载DNase和环丙沙星的pH响应型阳离子纳米胶束，在酸性微环境下释放DNase高效破坏eDNA，协同抗生素化疗实现对*S. aureus*生物膜的靶向、扩散与根除及菌体的高效消杀[56]。

纳米酶是一种具有天然酶活性的新型纳米材料，具有良好的尺寸效应和表面效应，可催化生物体内的氧化还原反应，产生抗菌作用。此外，纳米酶具有成本低、稳定性高、催化活性可调和易于大规模生产等特点，在抗菌抗生物膜感染领域具有广阔的应用前景[57]。负载铁基纳米酶与葡萄糖氧化酶的可溶性微针贴片，在细菌生物膜酸性环境下通过催化过氧化氢（hydrogen peroxide，H_2O_2）产生毒性羟基自由基（hydroxyl radical，•OH）破坏胞外基质的主要成分（eDNA、多糖胞间黏附素（polysaccharide intercellular adhesion，PIA）等蛋白质），诱导生物膜结构解体。产生的•OH造成细菌基因组DNA断裂，加剧细胞结构的破坏，可对耐甲氧西林金黄色葡萄球菌（methicillin-resistant *Staphylococcus aureus*，MRSA）生物膜实现93%以上的清除率[58]（图2b）。噬菌体是以特定细菌为宿主的病毒，能够识别并寄生至宿主细菌中进行繁殖，其裂解细菌的过程不受细菌耐药性影响，已作为传统抗生素的替代治疗方法[59]。嵌合纳米钯（Pd）的M13噬菌体，依靠生物合成的裂解酶分解生物膜的胞外多糖，靶向黏附、包裹细菌，在生物膜酸性微环境的刺激下，具有过氧化物酶活性的Pd能够高效催化产生毒性的羟基自由基（•OH），提高了噬菌体对浮游细菌和生物膜内细菌的抗菌能力，治疗后细菌量减少95%[60]（图2c）。

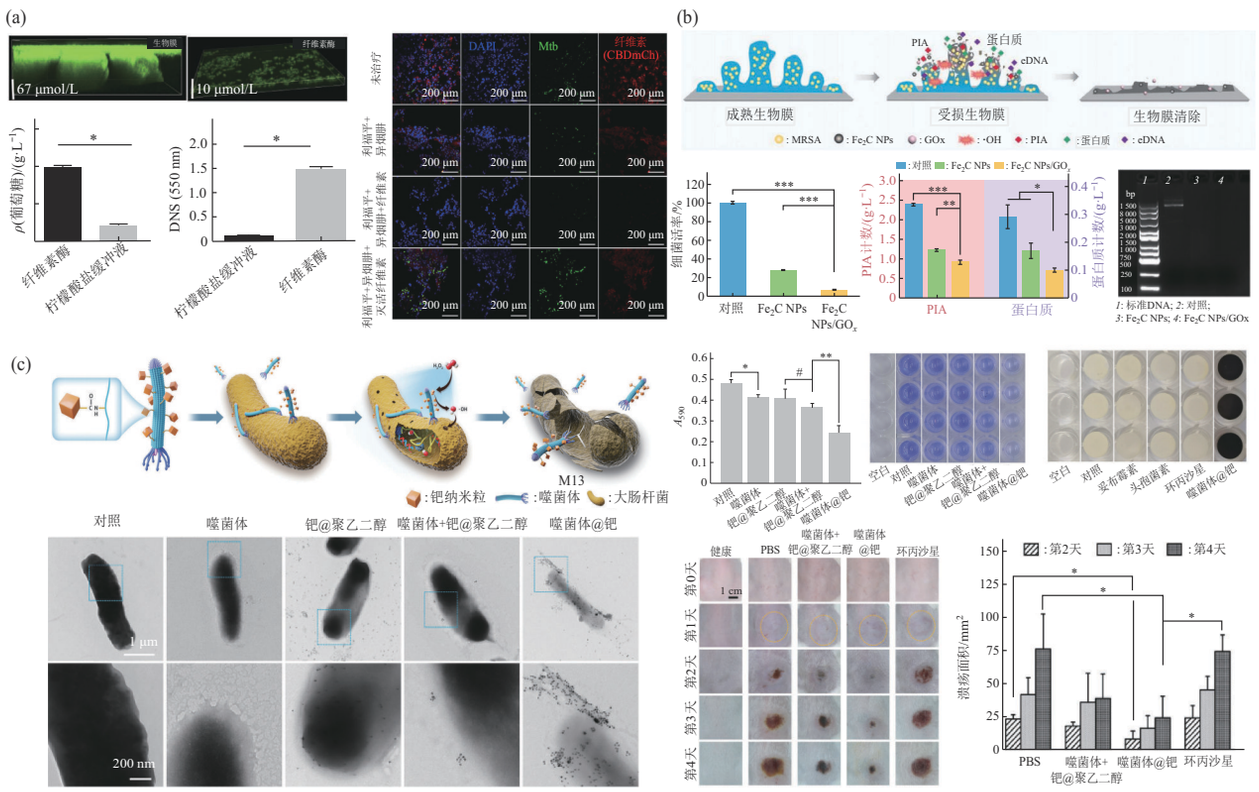

Fig. 2　Nano-biomaterials eradicate bacteria in the biofilm by dispersing extracellular polymeric substances

图2　纳米药物破坏细菌生物膜胞外基质，根除膜内细菌

（a）纤维素酶降解结核分枝杆菌生物膜中纤维素，增强利福平与异烟肼等抗结核药物的疗效[51-52]；（b）搭载铁基纳米酶与葡萄糖氧化酶的可溶性微针，分解生物膜胞外蛋白、多糖黏附素和eDNA，实现对MRSA生物膜的防治一体化[58]；（c）微米级噬菌体负载纳米钯，通过自身裂解酶与催化纳米钯生成羟基自由基，有效瓦解生物膜与杀灭细菌，有效治疗*E. coli*生物膜造成的急性细菌性肺炎和皮下脓肿[60]。

2.2　阻断信号传递，调控细菌稳态

信号传递是细菌面对外部环境变化做出响应的主要手段，能够帮助细菌在不同环境下迅速感知和做出适应性调整，维持生物膜内部稳态与正常的细菌生命活动[61]。其中，QS系统是细菌生物膜中最为重要的信号系统之一，通过调节细菌间信号通讯来调控细菌的行为状态，帮助细菌适应环境变化并做出适应性应激变化，抵御抗生素治疗[62]。因此，阻断细菌QS系统和屏蔽细菌间通讯，是实现细菌生物膜清除与抗感染治疗干预的有效策略。

脂肪酰基高丝氨酸内酯（acyl homoserine lactones，AHL）是细菌QS系统中的自诱导剂，能够作为信号分子感知细菌密度，触发细菌群体的生理和行为变化，调节细菌致病、生物膜形成和抗生素抗性等基因表达，维持生物膜内细菌的生存与繁殖[63-64]。通过在碳纳米颗粒中掺杂锌（zinc，Zn）、氮（nitrogen，N）单原子基团构建具有类内酯酶活性的Zn-N_x-C中心纳米酶，能够高效催化水解AHL（水解效率达77.5%），干扰细菌的QS信号通路，在多药耐药*P. aeruginosa*模型与真实水下船体表面生物膜模型中都证实，该纳米酶能够有效抑制细菌生物膜结构的形成（抑制效率达80.3%）[65]（图3a）。生物碱黄连素（berberine，BBR）可大幅度抑制细菌QS信号分子合成基因（S-核糖同型半胱氨酸酶（luxS）/S-腺苷高半胱氨酸核酸酶（pfS））表达，阻断细菌的QS系统的正常运转，显著下调细菌的毒力基因水平[66]。负载有螺旋藻（*Spirulina platensis*，SP）与BBR的生物活性纳米水凝胶，通过BBR下调细菌QS基因的表达，有效抑制MRSA生物膜的形成，显著下调MRSA中溶血素及丝氨酸蛋白酶等毒力基因的表达，协同SP的光动力治疗在MRSA感染的糖尿病小鼠模型中实现感染伤口的快速愈合与炎症抑制[67]。聚乙二胺（PAMAM）和2,3-二甲基马来酸酐（DA）修饰的生物素-聚乙二醇-聚赖氨酸，能够在静电相互作用下负载姜黄素（curcumin，Cur），制备成具有靶

向性能的pH响应型纳米颗粒（Cur-DA NPs），Cur-DA NPs在酸性生物膜环境下响应性释放Cur，Cur能够显著下调*P. aeruginosa*生物膜内QS系统相关基因（*Rhl*Ⅰ、*Rhl*R、*Las*I、*Las*R）的表达，在活体慢性肺部感染模型中能够显著提高青霉素G、环丙沙星、妥布霉素等抗生素序贯疗法的杀菌性能[68]（图3b）。

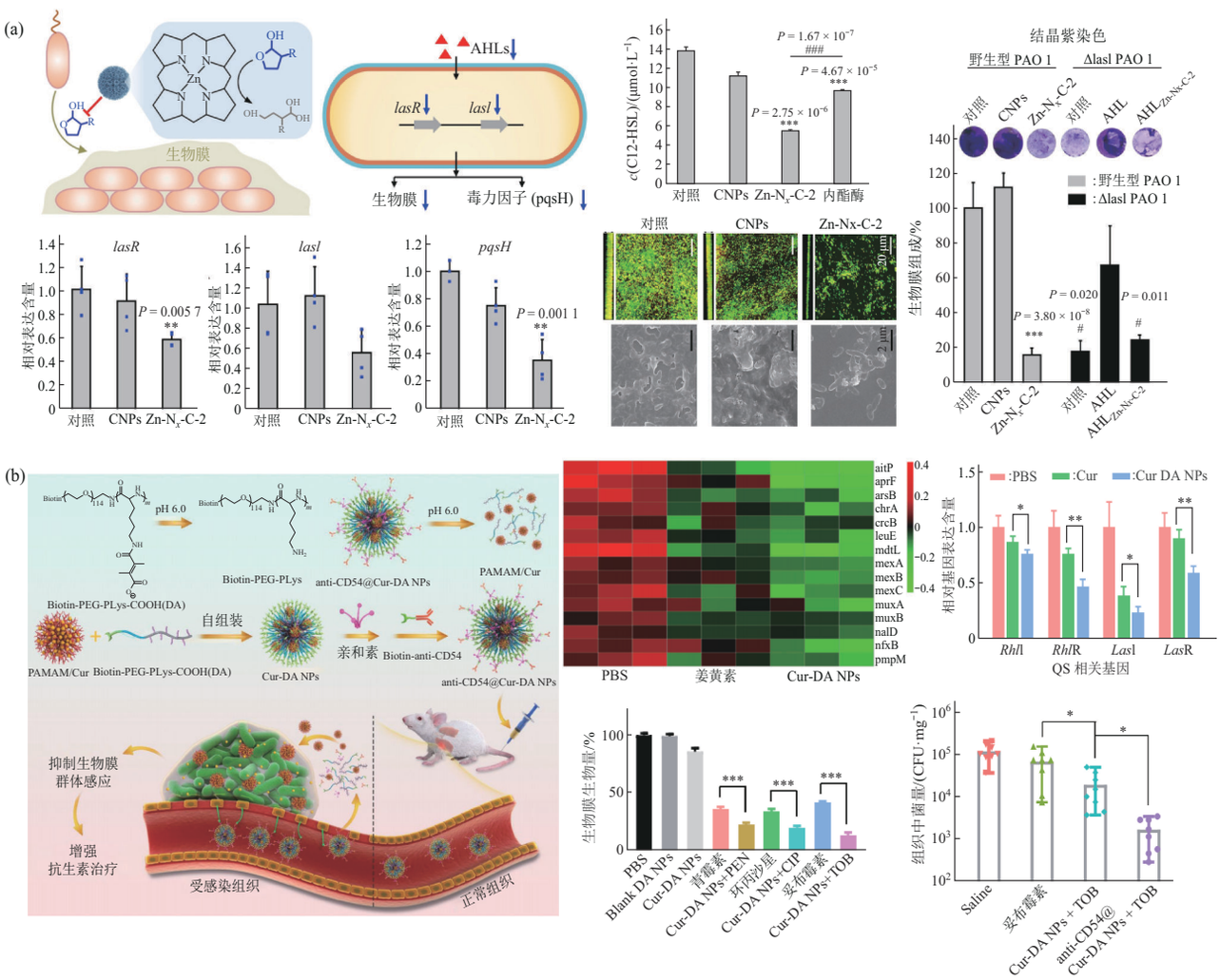

Fig. 3　Nano-biomaterials block intracellular signal transmission to regulate bacterial homeostasis

图3　纳米生物材料阻断膜内信号传递，调控细菌稳态

（a）Zn-N_x-C纳米酶高效水解*P. aeruginosa*的QS自诱导剂分子（AHLs），干扰细菌QS系统基因（*Las*R、*Las*I、*Pqs*H）的表达，最终抑制细菌生物膜形成和导致细菌毒力下降[65]；（b）负载姜黄素的马来酸酐纳米颗粒（DA NPs），在生物膜的酸性环境下响应性释放姜黄素，下调*P. aeruginosa* QS系统相关基因（*Rhl*Ⅰ、*Rhl*R、*Las*I、*Las*R）的表达，抑制生物膜的形成，提高抗生素的杀菌性能[68]。

2.3　抑制细菌代谢，干预细菌生存

代谢稳态对于细菌保持生存活力、维持生物合成、促进能量摄取以及抵抗外界压力至关重要[69]。细菌往往通过铁离子、铜离子、硫元素、葡萄糖等物质的代谢途径从外源环境获取营养物质，而生物膜能够凭借致密结构阻止营养物质扩散与外流，协助膜内细菌维持代谢稳态和生长环境，对宿主造成持续性感染[70-71]。因此，开发阻断细菌代谢通路、破坏细菌生存平衡的新型治疗策略，有利于破坏细菌的代谢稳态，实现细菌生物膜清除与抗感染治疗。

细菌代谢通路作为生命活动能量供应的主要来源途径，对维持细菌正常的生理功能和生长繁殖具有决定性作用。例如，以光敏剂吲哚菁绿与镓离子（Ga^{3+}）为原料构建的超小非抗生素纳米颗粒，其中吲哚菁绿的光动力治疗作用能够有效破坏细菌

壁，促进Ga^{3+}的细菌摄取，而Ga^{3+}作为“特洛伊木马”冒充铁离子竞争抑制细菌中铁代谢通路，阻断细菌的能量来源，导致细菌缺铁性死亡，最终对广谱β内酰胺酶大肠杆菌（ESBL *E.coli*）表现出优异的杀菌性能，显著提高由ESBL *E. coli*引起的感染性肝脓肿和角膜炎的治疗效果[72]。此外，当暴露于*S. aureus*生物膜酸性环境中时，掺杂铜的多金属氧酸盐纳米团簇（Cu-POM）可自组装成大分子，不仅能够在生物膜高谷胱甘肽环境下生成ROS破坏菌体，还能够在近红外光照射下驱动Cu-POM进入细菌细胞，抑制细菌的三羧酸循环和限制能量获取，并促进细胞内过氧化物的积累，导致细菌铜死亡和生物膜解体[73]（图4a）。二硒化锰（$MnSe_2$）纳米颗粒能够在生物膜酸性环境下响应性释放硒离子，并利用同源物诱导机制竞争嵌入至MRSA的硫代谢途径中，破坏MRSA胞内硫相关代谢通路，协同$MnSe_2$的光热致敏效应有效根除MRSA生物膜及裂解菌体[74]。抑制细菌的能量信号传递同样是清除耐药菌生物膜和对抗持续性感染的重要治疗手段。以医用植入钛板（TPs）为载体搭载二维碳化铌纳米片的生物治疗平台（Nb_2C@TP），可以激活辅助调节基因（*agrA*、*agrB*、*sak*、*HtrA*）促进生物膜分离并防止细菌黏附，此外还能下调柠檬酸循环和磷酸化转移酶系统等细菌能量代谢途径直接杀死MRSA，联合光热疗法能够彻底瓦解细菌生物膜和清除细菌[75]（图4b）。

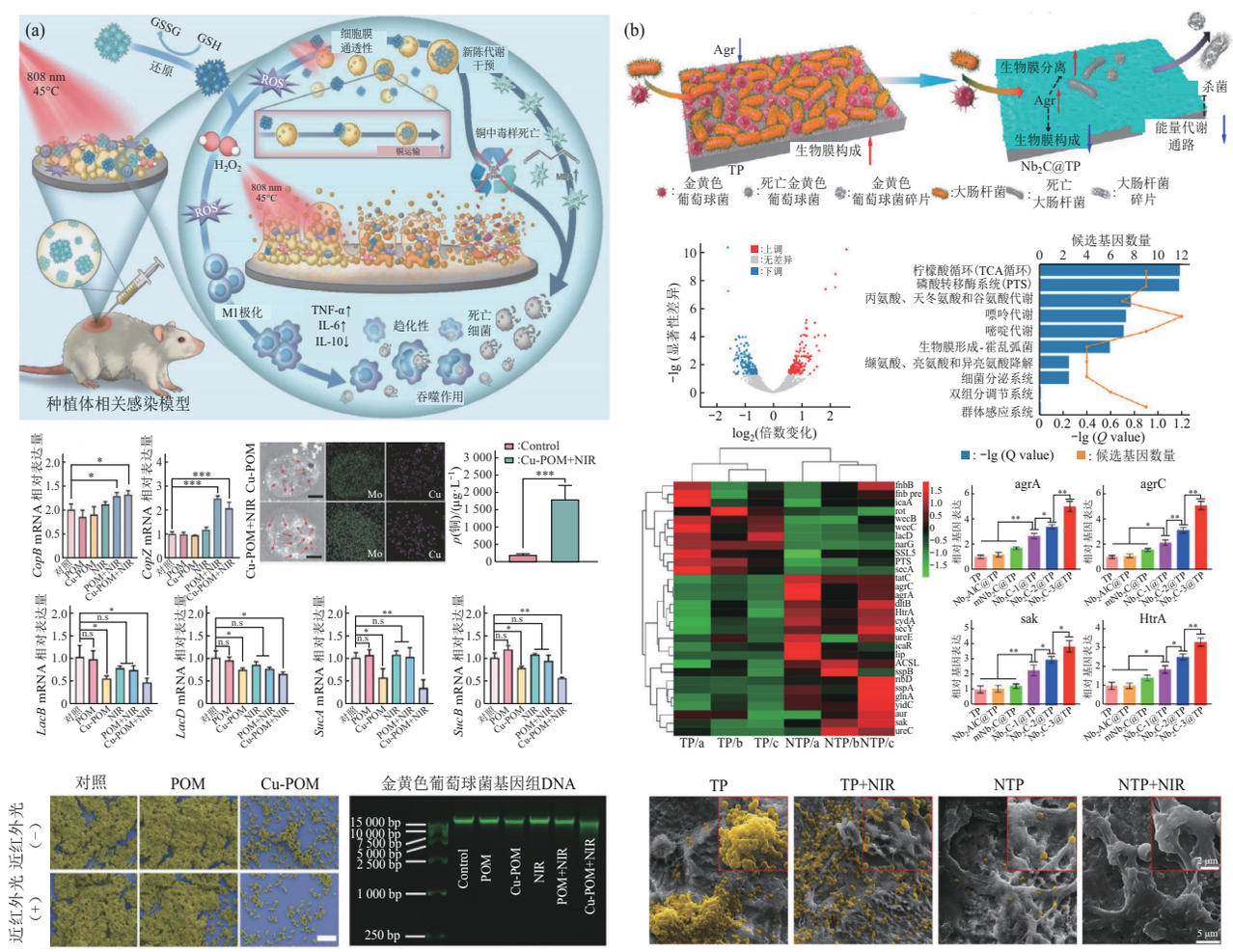

Fig. 4　Nano-biomaterials inhibit bacterial metabolism to interfere with bacterial survival

图4　纳米生物材料抑制细菌代谢，干预细菌生存

（a）掺杂铜的多金属氧酸盐纳米团簇在近红外光照射下，增强细菌代谢和促进Cu-POM进入细菌胞内导致铜超载，铜的积累抑制细菌能量循环，促进胞内H_2O_2积累，诱导机体免疫，实现生物膜降解及细菌铜死亡[73]；（b）医用钛板植入物搭载Nb_2C纳米片，可以激活辅助调节基因（*agrA*、*agrB*、*sak*、*HtrA*）的表达，并通过调控柠檬酸循环、磷酸转移酶系统、丙氨酸/天冬氨酸/谷氨酸代谢等途径，降低细菌能量代谢，抑制细菌生物膜形成[75]。

2.4　能源靶向驱动，促进药物渗透

生物膜具有高黏性、高致密性、强疏水性等特性，能够有效阻碍抗菌药物的渗透与富集。通过口服给药、注射给药、经皮给药、吸入给药及眼部给药等给药方式，纳米生物材料能够以被动靶向（改变纳米生物材料的自身大小尺寸或表面性质）、主动靶向（材料表面修饰特定靶向分子，如抗体、配体或肽等），以及外部能源驱动靶向（生物、化学、超声、磁场）等多种靶向形式，提高纳米生物材料的局部给药效率、生物利用度和局部药物浓度来破坏细菌生物膜[76-79]。微纳机器人凭借外源性/内源性驱动方式，能够穿过常规药物难以逾越的生理屏障（血脑屏障、生物膜等），将药物精准递送至病灶部位[80-84]（图5a）。

超声驱动型微纳机器人利用远程超声系统产生声流，引发超声“空化效应”促进药物在人体组织或生物膜中的可控精准推进，同时产生高频振动与强物理剪切应力，在组织穿透、可控递送、生物安全等方面具备独特优势[85]。Fe_3O_4纳米颗粒负载哌拉西林构建的超声响应型纳米微泡，能够在超声刺激下产生高频振动和强剪切应力物理破坏生物膜，协同哌拉西林实现物理/化学双模式的*P. aeruginosa* EPS降解和生物膜破坏，而Fe_3O_4纳米颗粒的过氧化物酶样活性能够生成ROS促进巨噬细胞M1极化，增强巨噬细胞杀菌能力，有效治疗由*P. aeruginosa*生物膜引起的慢性肺部感染[86]（图5b）。

磁驱动型微纳机器人利用外加磁场产生的强磁力和强扭矩实现定向导航与自主推进，完成药物的精准递送与靶向治疗，具有响应即时、穿透力强、无燃料介入、生物安全性好等优势[87]。基于镓基液态金属（LM）液滴的磁响应纳米材料，能够在低强度旋转磁场作用下改变形状并形成锋利边缘，接触细菌生物膜后即可精准运动至深层生物膜，同时高效剪切破坏生物膜及细菌结构，可杀灭99%的*P. aeruginosa*与*S. aureus*[88]（图5c）。以磁性Fe_3O_4纳米颗粒为载体、负载光活性材料钒酸铋（$BiVO_4$）构建的蜂群磁性微型机器人，具有磁驱动和光动力的双重功能，机器人受到磁场作用可以精准推动Fe_3O_4 NPs携带$BiVO_4$向链球菌、放线菌生物膜深层运动和进行光动力杀菌[89]（图5d）。

气泡驱动型微纳机器人通过催化反应在尾部产生气泡，利用气泡的反推力实现可控驱动，最大速度可达0.1 m/s，为自驱动药物递送至深层生物膜提供了新思路[90]。空心硅藻纳米棒负载二氧化锰纳米颗粒（MnO_2）开发的自驱动抗菌微型机器人（SLAM），能够在H_2O_2的催化下产生氧气微气泡，实现向*E. coli*生物膜的自推进，并通过反复产生、包围、膨胀和破裂氧气泡产生破坏细菌生物膜的空化能量，穿透、破坏和剥离细菌生物膜，使细菌丧失抗生素耐药性，协同抗生素可实现高达99.9%的细菌杀伤效率[91]（图5e）。

3　总结与展望

细菌生物膜能够协助浮游细菌在生物表面定植并形成致密的三维空间结构，成为病原体的天然庇护所，保护细菌免受药物和免疫细胞的攻击与清除，给临床抗细菌感染治疗带来了巨大挑战。纳米生物材料的快速崛起为细菌生物膜清除与抗感染治疗提供了一种全新手段。纳米生物材料具有生物相容性能、特异靶向识别、智能递送释药的特性[92]，通过分散EPS基质屏障、阻断细菌信息交流、抑制细菌代谢、增强药物渗透等策略，瓦解细菌生物膜对抗细菌感染。

然而，目前纳米生物材料对抗细菌生物膜感染仍有诸多关键问题亟待解决。首先，EPS致密结构造成生物膜的空间异质性与代谢异质性，对材料的设计构建、制备过程、理化性质和药物代谢性能等提出严苛要求，严重阻碍了纳米生物材料的破膜抗感染性能，深入探究生物膜的异质性特征及生物膜-材料间互作机制将是重要解决策略。其次，破坏细菌生物膜存在致病菌扩散和传染风险，可能引发其他部位甚至全身性感染，开发生物膜清除和病原体杀灭等功能一体化的生物安全性纳米生物材料，将成为未来的重点突破方向。此外，目前的纳米生物治疗多数为体外生物膜破坏及抗感染研究，迫切需要在小动物和大动物疾病模型水平，开展系统性的活体效果验证与生物安全性评估。综上，利用材料学、生物信息学、感染病学、免疫学与生物医学工程学等多学科的交叉融合，深入解析细菌生物膜的形成过程与机制，开展系统性临床试验评价，有利于打破纳米生物材料的临床转化瓶颈，发掘抗细菌生物膜感染的新思路和新策略。

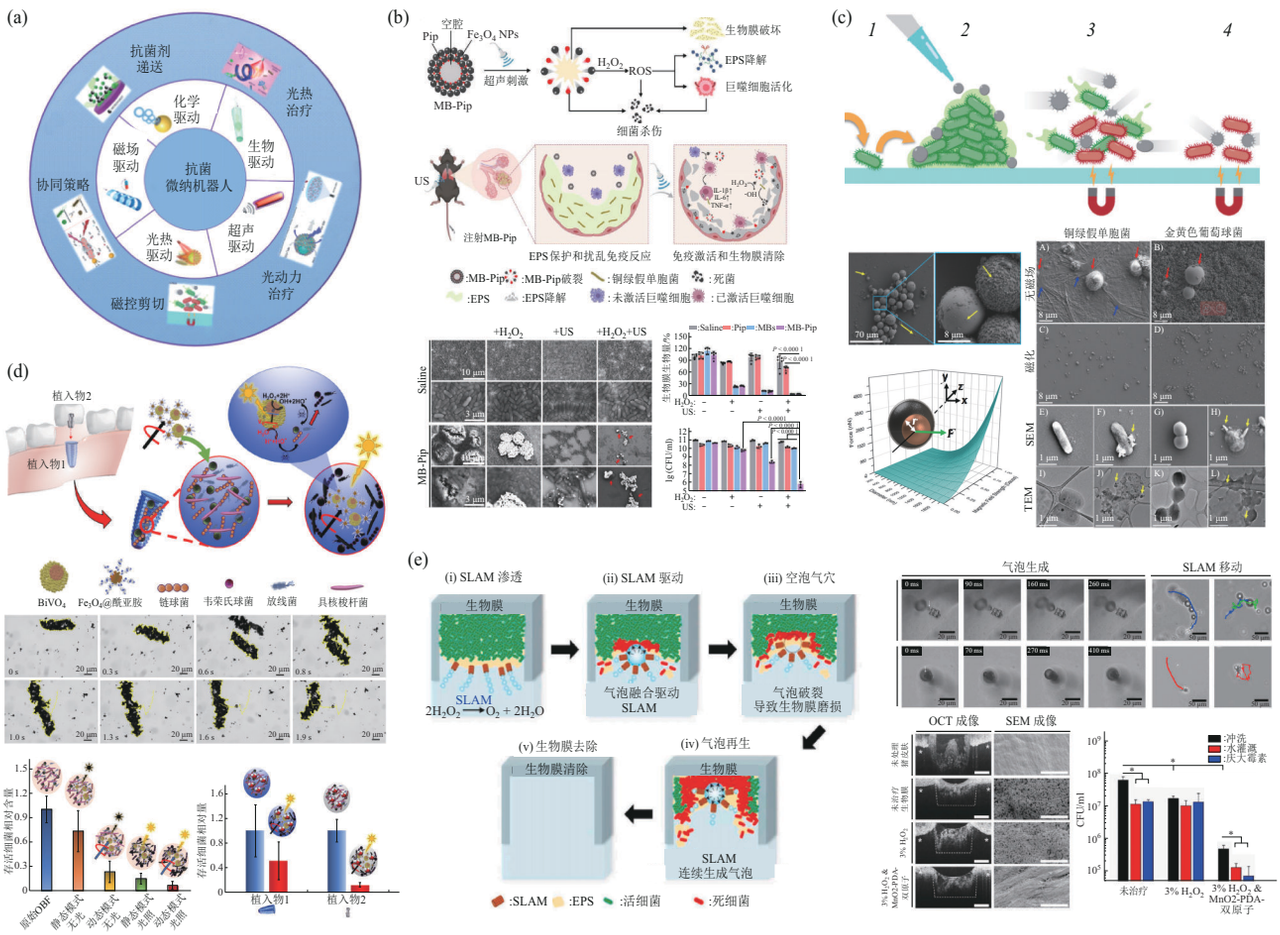

Fig. 5　Nano-biomaterials promote drug penetration in biofilms with energy driven

图5　纳米生物材料通过能源驱动，促进药物渗透

（a）生物、化学、超声、磁光驱动型微纳机器人的示意图[82]；（b）MB-Pip微纳机器人在超声刺激下，产生物理剪切应力破坏生物膜，协同Fe_3O_4 NPs的过氧化物酶样活性产生ROS促进巨噬细胞极化，破坏*P. aeruginosa*生物膜[86]。（c）镓基液态金属的磁响应型纳米液滴，在旋转磁场作用下改变形状形成边缘剪切力切割细菌生物膜，实现对*P. aeruginosa*与*S. aureus*高达99%的杀菌效果[88]；*1*：浮游细菌黏附；*2*：纳米液滴治疗；*3*：磁场作用下纳米液滴破坏生物膜基质，同时物理诱导细菌细胞裂解；*4*：处理区域的生物膜质量较低，大部分细胞失活。（d）负载光活性材料钒酸铋的磁性Fe_3O_4 NPs，精准驱动至细菌生物膜内，在近红外光照射下产生ROS实现光动力杀菌[89]；（e）二氧化锰纳米催化剂负载至棒状空心硅藻颗粒上，利用膜内H_2O_2连续产生含氧气泡，通过气泡破裂形成气泡空穴，破坏生物膜[91]。

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Nanomaterial-based Therapeutics for Biofilm-generated Bacterial Infections*

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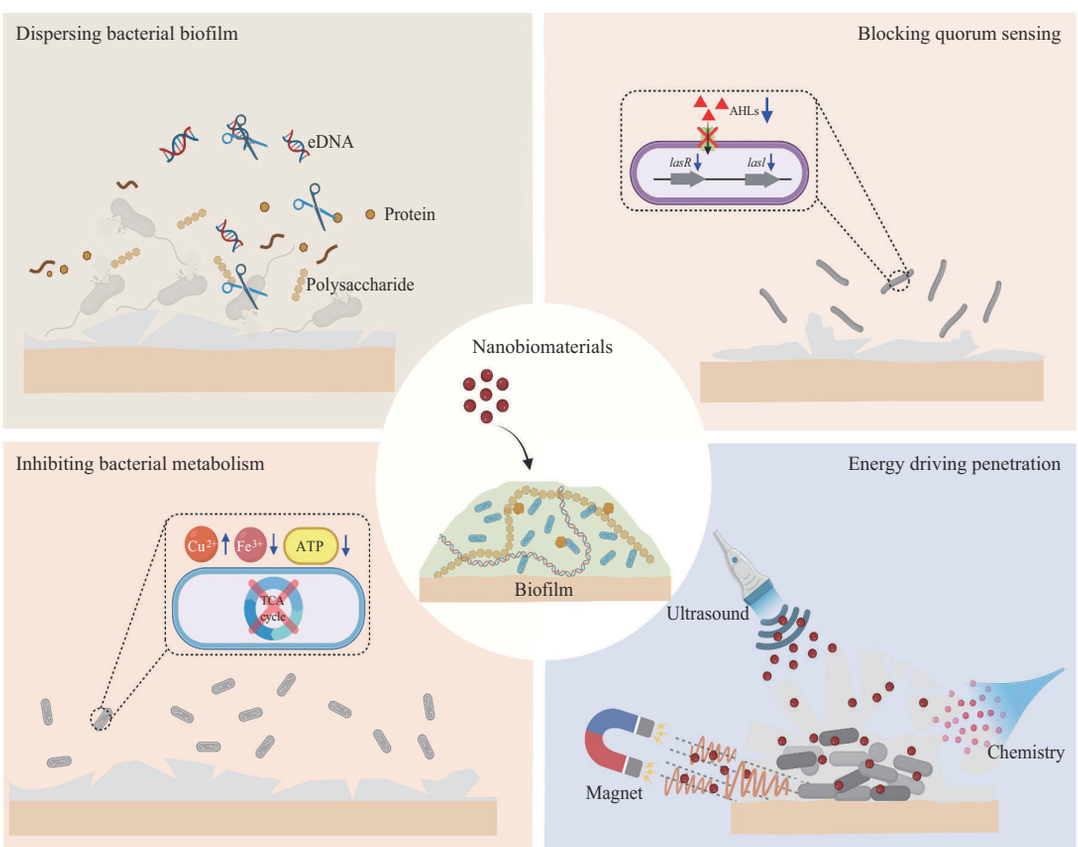
Graphical abstract



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Abstract Bacterial biofilms gave rise to persistent infections and multi-organ failure, thereby posing a serious threat to human health. Biofilms were formed by cross-linking of hydrophobic extracellular polymeric substances (EPS), such as proteins, polysaccharides, and eDNA, which were synthesized by bacteria themselves after adhesion and colonization on biological surfaces. They had the characteristics of dense structure, high adhesiveness and low drug permeability, and had been found in many human organs or tissues, such as the brain, heart, liver, spleen, lungs, kidneys, gastrointestinal tract, and skeleton. By releasing pro-inflammatory bacterial metabolites including endotoxins, exotoxins and interleukin, biofilms stimulated the body's immune system to secrete inflammatory factors. These factors triggered local inflammation and chronic infections. Those were the key reason for the failure of traditional clinical drug therapy for infectious diseases. In order to cope with the increasingly severe drug-resistant infections, it was urgent to develop new therapeutic strategies for bacterial-biofilm eradication and anti-bacterial infections. Based on the nanoscale structure and biocompatible activity, nanobiomaterials had the advantages of specific targeting, intelligent delivery, high drug loading and low toxicity, which could realize efficient intervention and precise treatment of drug-resistant bacterial biofilms. This paper highlighted multiple strategies of biofilms eradication based on nanobiomaterials. For example, nanobiomaterials combined with EPS degrading enzymes could be used for targeted hydrolysis of bacterial biofilms, and effectively increased the drug enrichment within biofilms. By loading quorum sensing inhibitors, nanotechnology was also an effective strategy for eradicating bacterial biofilms and recovering the infectious symptoms. Nanobiomaterials could intervene the bacterial metabolism and break the bacterial survival homeostasis by blocking the uptake of nutrients. Moreover, energy-driven micro-nano robotics had shown excellent performance in active delivery and biofilm eradication. Micro-nano robots could penetrate physiological barriers by exogenous or endogenous driving modes such as by biological or chemical methods, ultrasound, and magnetic field, and deliver drugs to the infection sites accurately. Achieving this using conventional drugs was difficult. Overall, the paper described the biological properties and drug-resistant molecular mechanisms of bacterial biofilms, and highlighted therapeutic strategies from different perspectives by nanobiomaterials, such as dispersing bacterial mature biofilms, blocking quorum sensing, inhibiting bacterial metabolism, and energy driving penetration. In addition, we presented the key challenges still faced by nanobiomaterials in combating bacterial biofilm infections. Firstly, the dense structure of EPS caused biofilms spatial heterogeneity and metabolic heterogeneity, which created exacting requirements for the design, construction and preparation process of nanobiomaterials. Secondly, biofilm disruption carried the risk of spread and infection the pathogenic bacteria, which might lead to other infections. Finally, we emphasized the role of nanobiomaterials in the development trends and translational prospects in biofilm treatment.

Key words bacterial biofilm, resistance mechanism, nanomedicine, biotherapy
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