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金纳米颗粒的抗菌机制研究进展

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摘　要

目前临床上针对细菌感染的主要治疗手段是使用抗生素治疗，但由于过度使用抗生素产生耐药菌的现象，导致抗生素有效率下降，所以新型抗菌手段的研发迫在眉睫，其中金属纳米颗粒的抗菌效果受到广泛的关注，尤其是金纳米颗粒，因其具有低毒性、高比表面积、表面易修饰官能团和优异的抗菌性能。本文旨在总结并讨论金纳米颗粒的抗菌作用机制，这些抗菌机制包括造成细胞壁和细胞膜的损伤、活性氧和氧化应激的产生、三磷酸腺苷水平的降低和DNA的损伤。

关键词

金，纳米颗粒，活性氧，抗菌机制

Advances in Antibacterial Mechanism of Gold Nanoparticles

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Abstract

At present, the main clinical treatment for bacterial infections is the use of antibiotics. However, due to the phenomenon of overuse of antibiotics to produce drug-resistant bacteria, which leads to a decline in the effectiveness of antibiotics, the development of new antibacterial methods is imminent. The antibacterial effect of metal nanoparticles is affected. Wide attention has been paid, especially to gold nanoparticles, due to their low toxicity, high specific surface area, easily modified surface functional groups, and excellent antibacterial properties. This article aims to summarize and discuss the antibacterial mechanisms of gold nanoparticles, which include cell wall and membrane damage, generation of reactive oxygen species and oxidative stress, reduction of adeno-

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sine triphosphate levels, and DNA damage.

Keywords

Gold, Nanoparticles, Active Oxygen, Antibacterial Mechanism

1. 引言

根据世界卫生组织(WHO)的数据，由病原体引起的细菌感染，仍然是人类发病率和死亡率增加的主要原因之一[1]。尽管有一系列令人信服的抗生素，但滥用抗生素已成为一个日益严重的问题，细菌对已经对一种或多种抗生素产生了耐药性[2] [3]。抗生素耐药细菌的增加导致与细菌引起的传染病相关的发病率和死亡率增加[4]。对于某些严重的细菌感染，甚至没有能用的药物[5]。开发针对耐药细菌的新型有效抗菌剂迫在眉睫。在研的新型抗生素中金属纳米颗粒(Metal Nanoparticles, MNPs)的抗菌性能令人振奋[6]。

MNPs 被广泛用于生物应用，包括诊断[7]、药物递送[8]和癌症治疗[9]。然而，抗菌活性是 MNPs 的主要应用之一。已显示出抗菌活性的纳米级材料包括 Au，Ag 和 Cu 以及部分金属氧化物[10]。其中金纳米颗粒(AuNPs)显示出优异的抗菌活性，它可以在表面进行多种修饰[11]，并且 AuNPs 的非常大的比表面积有利于与目标细菌结合[12]。AuNPs 抗菌谱很广，对金黄色葡萄球菌、大肠杆菌、铜绿假单胞菌、白色念珠菌、伤寒沙门氏菌及部分耐药菌群都显示出抗菌能力[13]。此外，金作为低活性的金属，具有非常稳定的化学性质，无毒且具有良好的生物相容性[14]。

AuNPs 的制备和抗菌性能已被广泛研究，但缺乏单独针对抗菌机制发表的全面的摘要。本文综述了金纳米复合材料的可能的抗菌机制。这些抗菌机制主要涉及破坏细胞壁和细胞膜，产生活性氧(ROS)并释放金属离子，从而在细菌细胞中引起损伤等。本综述的目的是深入了解 AuNPs 的可能抗菌机制，为 AuNPs 的研究方向提供想法，同时讨论的相关机制可做新型抗菌药物的研发靶点。

2. 抗菌机制

2.1. AuNPs 造成细胞壁、细胞膜的损伤

细菌具有细胞壁和细胞膜，细胞壁为细菌提供刚性，而细胞膜则能通过生物作用选择性的不让一些物质进入细菌内，膜上磷脂变体还能调节与膜相关蛋白的相互作用，维持细菌内的物质稳定，两者共同保护细菌使其不受伤害[15] [16]。大多数细菌可以根据其细胞壁结构分为两个单独的分类：革兰氏阳性和阴性。革兰氏阳性细菌在其细胞壁中含有一层厚厚的肽聚糖，而革兰氏阴性细菌具有一层薄的肽聚糖层，带有由脂多糖组成的附加外膜。有研究发现，革兰氏阳性菌对 NP 作用机制的抵抗力更强[17]。据推测，不同的细胞壁是这种现象存在的原因[18]。AuNPs 可以通过静电吸附作用吸附在细胞壁上，造成细胞壁的损伤。

AuNPs 能够不断释放金离子，这是一种潜在的杀微生物机制[19]。这些金离子可以粘附在细胞壁和细胞质膜上，膜蛋白是银离子和金离子的重要靶标，粘附的离子可以改善细胞质膜通透性并导致细菌包膜的破坏[20] [21] [22]。有趣的是，AuNPs 的抗菌活性来自于形态特异性，即金纳米棒、金纳米星、金纳米球抗菌效果的差异与金离子的释放量无关[23]。但同一种形态 AuNPs 添加浓度越高，释放的金离子就

越多，抗菌效果就越好[24] [25]。这种现象可能是由于金离子浓度与 AuNPs 物理形态改变相比产生抗菌效果的变化更弱。AuNPs 自身也可通过与细菌细胞壁的静电吸引作用引起损伤，导致细胞壁破裂，细菌死亡[26]。此外 AuNPs 还能够穿透细菌外膜，积聚在内膜中，与细胞的粘附产生其不稳定和损伤，增加膜通透性并诱导细胞内容物泄漏并随后死亡[21]。另有研究表明，AuNPs 表现出去极化的膜电位，而膜完整性没有变化[27]。AuNPs 处理细菌后观察到膜电位变化，细菌内离子失衡，细菌膜电位降低，膜电位的降低意味着细胞膜的损伤，这是细菌细胞死亡的主要原因[18]。

2.2. AuNPs 触发活性氧的产生和氧化应激

ROS 是部分还原氧衍生物，具有很强的氧化能力，它们包括超氧阴离子($O_2^{\bullet-}$)、过氧化氢(H_2O_2)、羟基自由基(•OH)和单线态氧($^1O_2$) [28] [29]。ROS 可以在细胞内产生，这是细菌代谢不可避免的结果，是在基本新陈代谢中形成的，也可以来自环境，将 ROS 维持在适当水平对细胞有积极作用[30]。但过量的活性氧会产生负面影响，触发 ROS 可对细菌造成严重损伤[31]。ROS 的过量产生引起氧化应激，由于氧化，导致大多数生物分子的结构和功能受到影响，如脂质过氧化和蛋白质氧化显着增加[32] [33]。脂质过氧化会导致细菌细胞毒性，因为较高的脂质过氧化会导致多不饱和脂质的氧化降解，导致质膜损伤，膜流动性降低，膜渗漏增加[34]。

AuNPs 已被证明产生自由基，细胞壁上的 ROS 形成是由于 AuNPs 与细胞壁的相互作用，AuNPs 浓度增加导致 ROS 伴随增加[35] [36]。Wei Bing 等人使用产氢超嗜热细菌合成了尺寸可控的 AuNPs，发现 AuNPs 在很宽的 pH 范围内其具有过氧化物酶活性，可以催化 H_2O_2 分解成•OH 和 O_2^- 。对革兰氏阴性和革兰氏阳性细菌均表现出显著的抗菌性能[37]。K Umamaheswari 等人使用葱(大蒜)瓣水提取物作为还原剂的绿色环保的方法合成了 AuNPs，他们观察到用 AuNPs 处理后所有测试的念珠菌物种的 ROS 水平增加，导致细胞膜破坏最终导致细胞死亡，其中在念珠菌细胞上的 ROS 产生更为明显并且在 LDH 测定中也具有更高的吸光度，这表明 LDH 泄漏水平增加，显示 AuNPs 对真菌细胞的毒性[38]。

2.3. AuNPs 导致三磷酸腺苷(ATP)水平的降低

ATP 是细胞承担基本功能(呼吸、增殖、分化、凋亡)的主要能量来源。完整细胞中的 ATP 水平处于稳定状态，ATP 水平的变化会影响细胞的功能，ATP 水平作为生存能力的指标，ATP 水平可以反映微生物浓度[39]。ATP 合酶是 ATP 合成需要的酶，其活性直接或间接与各种人类疾病有关，寻找这种蛋白质复合物的天然和合成抑制剂可能会产生新的先导化合物，包括新的抗菌剂[40] [41] [42]。Sivaji Sathiyaraj 等人使用 panchagavya (PG)合成的 AuNPs，对革兰氏阴性菌的抗菌活性强，对革兰氏阳性菌的抗菌活性中等，AuNPs 实现抗菌性能的其中一个过程是通过降低三磷酸腺苷(ATP)合酶活性来抑制代谢过程，导致 ATP 的耗竭[18]。Yangzhouyun Xie 等人合成的经修饰的 UsAuNPs，可导致 ATP 合成的减少并影响随后的 ATP 相关代谢，从而抑制细菌的存活[43]。有趣的是，Yuyun Zhao 等人合成的 AuPt 双金属纳米颗粒能够使细菌内的 ATP 水平升高，高 ATP 水平可能对细菌有毒，他们提出两种可能，一是 AuPt 作为替代酶可以催化 ATP 的产生，另一种可能性是 AuPt 可以抑制消耗 ATP 的蛋白质的合成，从而诱导 ATP 的积累[44]。由此可见，AuNPs 可导致细菌 ATP 水平的下降造成细菌死亡，但与 Pt 合成双金属纳米颗粒时有可能导致 ATP 水平的上升，具体机制暂不明确。

2.4. AuNPs 造成 DNA 损伤

任何生物体的 DNA 都存储有关细胞的遗传信息，DNA 作为所有生物体的遗传信息单位，是功能存在的基础，DNA 损伤可导致突变或细胞死亡[45]。AuNPs 可以通过附着在细菌 DNA 上并通过与细菌 DNA

结合来阻断 DNA 在转录过程中的解旋来抑制抑制多重耐药泌尿系病原体[46]。ROS 可以触发细胞膜破裂和 DNA 改变[47] [48]。Yulan Wang 等人研究表明 AuNPs 引起细胞内的 ROS 产生可以通过导致蛋白质聚集和 DNA 破坏，导致细菌死亡[36]。Heejeong Lee 等人发现，与未处理的细菌相比，用 AuNPs 或诺氟沙星处理的细菌显出现核凝聚的现象，并且使用 TUNEL 测定方法证实 AuNPs 诱导 DNA 片段化导致细胞凋亡样细胞死亡，有趣的是，他们表明细菌凋亡样死亡与细菌内的 ROS 无关[49]。无论是否与 ROS 有关，AuNPs 可以通过造成 DNA 损失诱导细菌死亡。

3. 回顾与展望

在本篇小型综述中，我们讨论了 AuNPs 的抗菌机制。许多研究证明 AuNPs 具有优良的抗菌性能，AuNPS 可以通过释放金离子和其自身特性杀菌，其作用机制主要归因于细胞壁损伤、细胞膜损伤包括膜通透性和膜电位改变，ROS 和氧化应激的产生、ATP 水平的降低以及 ROS 依赖或非 ROS 依赖造成的 DNA 的损伤。然而造成细菌损伤的机制也可能造成细胞的损伤，ROS 也会造成人体细胞的氧化应激，以及细菌杀伤机制并没有针对细菌的特异性，AuNPs 在一些细胞株上也表现出较强的细胞毒性，给应用造成了困难，但 AuNPs 的生物相容性与其表面积有关，调节表面积是可行的在兼顾安全性和抗菌效力的未来研究方向。

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