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Commentary

Immune-enhanced nanocomposites provide hope for drug-resistant infection treatment

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Abstract

This study proposes a multiplex antimicrobial system derived from photosynthetic bacteria and U.S. Food and Drug Administration-approved aluminum adjuvant systems. The objective is to treat drug-resistant bacterial infections and prevent their recurrence.

Keywords: Biomaterials, Immune modulation, Photothermal therapies, Implant-associated infections

Commentary

Antibiotic misuse contributes to the emergence of multidrug-resistant organisms, resulting in infections that cause over one million deaths annually [1-3]. Therefore, there is an urgent need to develop new antimicrobial methods. Traditional antibiotic therapy is often incomplete due to the emergence of drug-resistant strains, leading to relapse. Bacteria, when exposed to lethal concentrations of antimicrobials multiple times, undergo temporary dormancy, while resistance genes rapidly accumulate mutations that eventually form resistance [1,4]. To address these challenges, the development of combined and innovative photothermal therapies that can clear infections while reducing recurrence rates and protecting local tissues has gained significant attention. Photothermal therapy is highly efficient in thermokilling resistant bacteria, albeit with the risk of causing local tissue damage due to its operating temperature. In addition to photothermal therapy, host immunomodulatory therapy has emerged as a promising strategy for preventing drug-resistant bacterial infections [5-7]. This therapy utilizes host-dependent natural mechanisms to activate or enhance protective antimicrobial immunity.

To address the issues associated with most photosensitizers, such as poor permeability, insufficient targeting, and low light utilization [8], as well as slow degradation and long-term retention [9], one potential solution is the use of bacterial chlorophyll as a biosensitizer, particularly in photosynthetic bacteria. Previous studies have reported that photothermal therapy can reduce the development of resistant bacteria [10]. Therefore, our team has developed a new approach to photothermal combination immunotherapy for drug-resistant bacteria-associated infections. This approach is based on the genetically engineered bacterium *Pseudomonas natural rhododendron* (Rp), which was mixed with Al adjuvant to create Rp@Al gel. *In vitro* experiments were conducted to test the photothermal performance of Rp@Al gel, where the engineered bacteria were co-cultured with drug-resistant strains and the viability of the bacteria was assessed following photothermal therapy. Additionally, *in vivo* experiments using mouse models were carried out. The results showed that Rp@Al gel exhibited excellent photothermal performance under near-infrared laser irradiation, effectively killing drug-resistant bacteria. Furthermore, Rp@Al gel facilitated the presentation of specific antigens of methicillin-resistant Staphylococcus aureus (MRSA) by dendritic cells to helper T cells. TH1 cells mainly produce IL-4, while TH2 cells mainly produce IFNγ, and both cytokines work synergistically on memory B cells. This ultimately leads to the rapid production of a large number of specific antibodies by memory B cells upon subsequent infection, effectively controlling infection recurrence. Moreover, Rp@Al gel was found to activate dendritic cells, bridging the innate immunity and adaptive immunity to jointly combat recurrent infections. These findings highlight the potential of nanomedicine in addressing the challenges posed by drug-resistant bacteria through photothermal combined immunity [11-13].

Once resistant bacteria form biofilms, resistance increases significantly [14]. Chronic biofilm-associated infections can lead to systemic infection [15,16]. Routine antibiotics make it difficult to completely eradicate quiescent bacteria located at the center of the biofilm. In addition, high levels of glutathione (GSH) are often released and accumulated in these regions due to the large number of cell necrosis within the infected niche [17]. The rapid proliferation of bacteria leads to hypoxia within the biofilm, which may inhibit the function of immune cells [18]. Highly acidic and hydrogen peroxide-rich biofilm microenvironments affect the antimicrobial immune response of macrophages [19]. Furthermore, the infectious microenvironment often exhibits characteristics that differ from normal tissues, such as neutrophil infiltration, high proteolytic enzyme levels, elevated local temperature, and increased acidity [20,21]. During the M1-like polarization of macrophages, lactic acid accumulation occurs, resulting in "lactate-associated immunosuppression" [22,23], which inhibits the antibacterial effect of macrophages [24].

Therefore, we propose a novel non-antibiotic strategy for the eradication of bacterial biofilms. Our approach is based on the synergy of thermoamplified chemokinetic therapy driven by bionanocatalysts and innate immunomodulation. To illustrate this strategy, we present a novel "interference regulation strategy" that utilizes bovine serum albumin-iridium oxide nanoparticles (BIONPs). These nanoparticles effectively convert hydrogen peroxide into oxygen, interfering with the homeostasis of the biofilm microenvironment. Concurrently, BIONPs induce macrophages to repolarize into the pro-inflammatory M1 phenotype, promoting the engulfment of residual biofilms and preventing biofilm reconstruction [25]. In addition, we utilize GB@P, which is activated in the acidic microenvironment. This activation enhances the photothermal effect and increases the sensitivity of bacteria to heat through the penetration of hydrogen peroxide into the biofilm. Furthermore, GB@P promotes the polarization of macrophages into the pro-inflammatory M1 phenotype, leading to sustained bactericidal and biofilm eradication through innate immunomodulatory effects [26]. We also employ organic framework bionanocatalysts (MACGs) consisting of MIL-100 and CuBTC. These bionanocatalysts release glucose oxidase and activatable photothermal agents in the acidic biofilm microenvironment. The released Cu ions deplete glutathione and catalyze the cleavage of hydrogen peroxide into hydroxyl radicals (·OH), which can effectively penetrate heat-induced loose biofilms and eliminate fixed bacteria. Additionally, MACG promotes macrophage polarization, creating a continuous pro-inflammatory microenvironment that inhibits biofilm regeneration [27]. To address bacterial resistance and metabolic status associated with relapsing bacteria, we propose a metabolic interference approach that induces bacterial death. Our biofilm microenvironment-responsive copper-doped polyoxometalate cluster promotes bacterial copper apoptosis-like death through metabolic disturbances. Concurrently, it reactivates macrophage immune responses to further eliminate planktonic bacteria, achieving clearance of full-stage bacterial biofilm-associated infections [28]. Finally, we introduce a novel iron-driven Janus ion therapy anti-biofilm strategy that combines heat stress-induced iron interference with iron nutrient immune reactivation. We synthesize a biofilm microenvironment-responsive photothermal microneedle patch (FGO@MN). The catalytic products of FGO@MN, such as hydroxyl radicals (·OH), destroy bacterial heat shock proteins and induce thermosensitization of biofilms. Moreover, the iron overload in cells triggers iron death-like death, while also rejuvenating iron-trophic granulocytes surrounding the biofilm microenvironment, leading to the reactivation of anti-biofilm functions [29].

The advent of nanomedicines has provided a way to eliminate intracellular bacteria by enhancing passive/active permeability of cell membranes, increasing intramembrane antibiotic concentrations, and protecting antibiotic activity [30,31]. Vancomycin has been reported to effectively eliminate most MRSA, but some MRSAs can invade host cells, including macrophages, to avoid recognition and elimination [32,33] Intracellular bacteria can disrupt innate immune responses by interfering with the intracellular microenvironment [34]. The long-term presence of intracellular bacteria is also an important cause of infection recurrence [35,36]. A heat-responsive nanoparticle consisting of fatty acids and CaO2-vancomycin has been reported to exert a significant killing effect on intracellular bacteria [37]. Under external thermal stimulation, the shell of the nanoparticle changes from the solid phase to the liquid phase, exposing the CaO2-vancomycin core to the surrounding aqueous solution. This process releases vancomycin and produces Ca(OH)2 and oxygen, stabilizing hypoxia-inducible factor-1α (HIF-1α) to enhance the M1-like polarization of macrophages. As a result, it increases the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to the killing of intracellular bacteria. Phage-chlorin e6(Ce6)-manganese dioxide nanocomposites (PCM) can be constructed using the phage's host bacterial targeting specificity [38], ability to cross cell membranes [39], and the powerful innate immunostimulatory properties of Mn2+ [40]. With the assistance of near-infrared radiation, PCM triggers powerful ROSin the biofilm, and the presence of manganese oxide ensures that the ROS produced are not rapidly reduced by glutathione. This protection ensures the bactericidal ability of PCM against intracellular and extracellular bacteria. Additionally, PCM can promote the maturation of dendritic cells, facilitate antigen presentation, and establish an adaptive immune response [41].

Although biomaterial-based immune-enhanced antimicrobial strategies are considered promising for the treatment of implant-associated infections [42,43], the precise and orderly release of drugs cannot be fully controlled at present. This lack of control gives rise to several issues. Premature drug release hinders the attainment of effective drug concentration at the treatment site, while sudden drug release increases the risk of toxic side effects. Additionally, maintaining the effective drug concentration for an extended period proves challenging. As such, achieving precise drug release and ensuring the safety of biomaterials are pressing concerns in the development of new nano-antibacterial drugs. Future research on antimicrobial resistance will require collaborative efforts across multiple disciplines.

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