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Viewpoint

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Nanomaterials for the Treatment of Bacterial Biofilms

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ABSTRACT: Treatment of biofilm-associated infections is challenging, requiring the development of new therapeutic strategies. In this viewpoint, we discuss the use of nanoparticle-based systems as active therapeutic agents and as vehicles to transport drugs to the site of infection. These applications require understanding of the surface interactions of nanoparticles with bacteria/biofilms, an aspect that we likewise summarize.

Multidrug-resistant (MDR) bacteria cause thousands of deaths each year in the United States alone. These bacteria are commonly found in biofilms, making the resulting infections particularly challenging to cure. Biofilm formation causes persistent diseases and implant-associated infections, for example, the methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms commonly found in wound infections.[1] The eradication of biofilm is challenging because the extracellular polymeric substances (EPS) comprising the biofilm prevent the antibiotic penetration into biofilms. The EPS are composed of polysaccharides, polynucleic acids, and proteins, forming highly structured and heterogeneous networks that are resistant to penetration by small-molecule therapeutics. As a result, current methods to eradicate biofilms typically require excising of infected tissues combined with antibiotic therapy, invasive treatments that incur high medical costs.

Nanomaterials have emerged as a potential platform for diagnostic/therapeutic applications. The dimensions of nanomaterials impart unique physical and chemical properties, including multivalent interactions with biomolecular and cellular systems. Therapeutically, nanomaterials can be used as delivery vehicle to transport drugs at the site of infection or applied as active therapeutic agents using their inherent characteristics. For example, the high surface area and concomitant increase in dissolution rate of these systems is key to their use in silver-based antimicrobials, where free Ag^+ ions are the active agents.[2]

Antimicrobial properties have been demonstrated with a wide range of nanomaterials. These antimicrobial nanomaterials prevent biofilm formation, either through coating on surfaces or by interrupting biofilm growth.[3] Treating a pre-existing biofilm is, however, much more challenging. Complete eradication of biofilms requires efficient penetration and accumulation of antimicrobial agents into the biofilm network, a daunting task.

Interactions between biofilm and therapeutic are crucial in determining the efficacy of treatment. By tuning the surface capping ligands, the nanomaterial/biomolecule interfaces can be controlled using electrostatic, hydrophobic, or other noncovalent interactions. These capping agents not only serve as stabilizing agents but also provide surface functionalities that can interact multivalently with the EPS and/or the bacteria residing in the biofilm, providing transport pathways inaccessible to small-molecule therapeutics.

The ability to control the surface properties of the nanoparticles (NPs) through ligand engineering[4] can be used to provide therapeutics for both planktonic and biofilm-encapsulated bacteria. For example, we demonstrated that amphiphilic cationic gold NPs were highly efficient at killing a wide range of clinically isolated MDR bacteria at low concentrations (minimum inhibitory concentration, MIC, 8–64 nM).[5] This toxicity presumably arises from lysis of the bacteria through multivalent particle–cell interactions.[6] Significantly, resistance was not observed to these antimicrobial NPs even after 20 treatments. These particles have potential for systemic use, with substantial hemolysis occurring only at 400 nM, providing a therapeutic selectivity of up to 50-fold.

As mentioned above, treatment of biofilms requires penetration through the EPS, requiring an understanding of how materials interact with this complex matrix. The first stage of nanomaterial/biofilm interaction is through deposition, which is determined by electrostatic interaction as well as heterogeneity of charges across the biofilm surface.[7] Using fluorescence correlation spectroscopy (FCS), Peulen and Wilkinson studied the diffusion of nanoparticles within biofilms,[8] showing that the size of particles affects their mobility due to the effective pore size of biofilms.

Size is important; however, surface properties are likewise key in effecting biofilm penetration. Our studies on biofilm penetration and treatment focus once again on ligand engineering. We explored this fundamental challenge of biofilm penetration using quantum dots (QDs) functionalized with ligands with different charges and hydrophobicities.[9] We found that the anionic and neutral functionalized nanoparticles cannot penetrate into biofilms. In contrast, particles functionalized with cationic ligands showed higher penetration ability and could readily accumulate inside the biofilms. Moreover, by regulating the hydrophobicity of cationic nanoparticles, the distribution of nanoparticles within biofilms could also be modulated. For example, hydrophobic particles were observed inside the bacteria, whereas the hydrophilic analogues remained in the EPS surrounding the cells. We believe that these systematic studies will facilitate the development of nanoparticle-based antimicrobial agents for the treatment of biofilms.

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Therapeutic selectivity is very important in the development of biofilm treatments. Taking advantage of acidic biofilm microenvironments, efforts have been made on using pH-sensitive polymeric nanoparticles for delivering hydrophobic antibacterial agents into biofilms.[10] These polymeric nanoparticles are composed of cationic poly(dimethylaminoethyl methacrylate) as the outer shell for efficient binding against EPS and a hydrophobic pH-responsive moiety as the inner core to encapsulate and release antibiotics on demand. Compared to the drug alone, the polymeric vehicle showed a 2-fold increase of biofilm removal under shear force, indicating that the localized release of the therapeutic improved the antimicrobial efficiency.

The ability of cationic NPs to penetrate into biofilms makes them promising tools for therapeutic delivery. We coupled this penetration ability with self-assembly of NPs at oil−water interfaces to generate highly effective therapeutics against pathogenic biofilms. For this study we chose two naturally occurring antimicrobial oils (peppermint oil and cinnamaldehyde) and amine-functionalized cationic silica NPs.[11] Self-assembly of NPs around the mixed oil droplets resulted in nanocapsule structures (Pickering emulsions) that were further stabilized by the formation of a hydrophobic Schiff base through cinnamaldehyde−amine condensation reactions. These capsules readily penetrate biofilms due to the presence of cationic NPs, as shown by confocal microscopy. As a result of capsule penetration, the antimicrobial oils could access the interior of the biofilms, thereby enhancing their therapeutic effect. Therapeutic efficacy of the capsules was tested on several pathogenic biofilms, with therapeutic selectivity tested using fibroblast−biofilm co-culture models. These studies showed that the capsules effectively eradicated the biofilm while enhancing the growth of fibroblast cells.

In summary, nanomaterials are promising tools for delivery vehicles and as antimicrobials in their own right. Their tunability and ability to interact multivalently make them excellent candidates for targeting planktonic bacteria. Their ability to penetrate biofilms likewise makes them promising therapeutics for these particularly difficult to treat infections. There is much more to be learned on the fundamental, biological, and pharmacological features of nanoparticle−bacterial systems, however, before these systems reach their full potential as antimicrobials.

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Notes

The authors declare no competing financial interest.

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