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ANTIMICROBIAL NANOTECHNOLOGIES IN ORTHOPAEDIC IMPLANTS

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DESCRIPTION

Microbial resistance to existing antibiotics therapies is a leading cause of implant failure and adverse clinical outcomes in orthopaedic surgery. Current developments in advanced antimicrobial nanotechnologies provide several opportunities to effective remove resistant bacteria and prevent resistance from occurring through exclusive mechanisms. With tunable physicochemical properties, nanomaterials can be designed to be bactericidal, antifouling, immunomodulating, and capable of delivering antibacterial compounds to the infection region with spatiotemporal accuracy. Despite its considerable advancement, an important, but under-explored area is potential microbial resistance to nanomaterials and how this can influence the clinical use of antimicrobial nanotechnologies. This review aims to deliver a well understanding of nanomaterial-associated microbial resistance to accelerate bench-to-bedside translations of emerging nanotechnologies for active control of implant associated contagions.

Bacterial infection is one of the lethal causes of death. Amongst all, osteomyelitis is an age-associated infection with death risk scaling progressively with age. A reflective analysis of 10 615 patients with the ages ≥ 65 found that patients (between 65 and 74) with chronic osteomyelitis had a death rate of 24% and this figure is nearly double for those aged > 85. Osteomyelitis is nearly correlated to Implant Associated Infections (IAIs) which develop mainly by nosocomial pathogens attack to the implant area during orthopaedic implantation surgery. Traditional treatment of IAIs includes of a long-term (3 months) administration of either oral, intravenous or mixed antibiotics. Despite various clinical successes, over-reliance and over-use of on antibiotics have led to antibiotic resistance which significantly bounds the efficacy of antibiotics and subjects patients with IAIs to problems such as severe inflammation, amputation, and even death. Rendering to a report by Willyard, resistant bacteria is projected to cause > 700 000 deaths per year globally and this figure is expected to further upsurge due to the slow development of new antibiotics or strategies to combat bacterial resistance.

IAIs mainly results from perioperative bacterial inoculation on the implant surface, although in specific cases it can be caused by hematogenous seedings of pathogens. The main relevant bacteria in IAIs are *Staphylococcus aureus*, with others including *S. epidermidis*, *Coagulase Negative Staphylococci* (CNS), enterococci, and *Pseudomonas aeruginosa*. These pathogens are capable at adapting to everchanging environmental conditions such as light, temperature, nutrient status, and exposure to foreign substances (antibiotics, nanomaterials, host tissue, prosthetics etc.). They can change genotype as well as phenotype to regenerate homeostasis in response to environmental challenges, placing a solid foundation for antimicrobial resistance acquisition. Among these bacteria, *S. aureus* warrants the greatest concern due to its inherent virulence and ability to adapt to harsh environmental conditions. The conversion of wild-type *S. aureus* to Methicillin-Resistant *S. aureus* (MRSA) is not a rare phenomenon occurring in patients with lengthy use of antibiotics, and as a result 8.5% of such patients had experienced treatment failure post prosthetic bone or joint surgery. Mechanistic investigations have found a strong association of staphylococcal resistance to a synergistic exploit of

pathogenic stress response, self-protection and damage repair. Another pathway to acquire antimicrobial resistance is by starting a sessile bacterial community. Biofilm development is the result of the competition between bacteria and other molecules/living cells to colonize the implant surface. Once formed, living bacteria will be encapsulated by the external protective layer which activates a series of protection mechanisms and hampers the utility of aseptic treatments.

CONCLUSION

To attack antimicrobial resistance with advanced nanomaterials, a comprehensive consideration on their designs and mechanisms for building an "implant of the future" is immediately needed. Here, following a review of the current mechanistic understanding of the development of resistant strains and biofilms, we present a unique analysis of existing antimicrobial nanotechnologies focusing on their potential risks in antimicrobial resistance. Current antibacterial nanotechnologies depending on the design principles are categorized into biochemical functionalization or physical surface changes. We also provide considerations to guide future explorations of antimicrobial nanotechnology.