



Magnetic targeting of surface-modified superparamagnetic iron oxide nanoparticles yields antibacterial efficacy against biofilms of gentamicin-resistant staphylococci

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ABSTRACT

Biofilms on biomaterial implants are hard to eradicate with antibiotics due to the protection offered by the biofilm mode of growth, especially when caused by antibiotic-resistant strains. Superparamagnetic iron oxide nanoparticles (SPIONs) are widely used in various biomedical applications, such as targeted drug delivery and magnetic resonance imaging. Here, we evaluate the hypothesis that SPIONs can be effective in the treatment of biomaterial-associated infection. SPIONs can be targeted to the infection site using an external magnetic field, causing deep penetration in a biofilm and possibly effectiveness against antibiotic-resistant strains. We report that carboxyl-grafted SPIONs, magnetically concentrated in a biofilm, cause an approximately 8-fold higher percentage of dead staphylococci than does gentamicin for a gentamicin-resistant strain in a developing biofilm. Moreover, magnetically concentrated carboxyl-grafted SPIONs cause bacterial killing in an established biofilm. Thus magnetic targeting of SPIONs constitutes a promising alternative for the treatment of costly and recalcitrant biomaterial-associated infections by antibiotic-resistant strains.

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1. Introduction

The average life expectancy in the Western world is steadily increasing and is currently well over 70 years, both for men and women. With aging, the natural ability of the human body to restore function after trauma or wear is decreasing, while frequently also (oncological) intervention surgery, such as after total laryngectomy for the removal of a laryngeal tumour, yields loss of function as an unwanted side-effect. Biomaterial implants are indispensable in modern medicine for the restoration of function and allow large numbers of patients to maintain a high quality of life as they grow old. Infection of biomaterial implants or devices constitutes their major cause of failure and can develop many years after implantation [1]. Biomaterial-associated infection (BAI) can develop from perioperative bacterial contamination of implant surfaces during implantation, immediately post-surgery

during hospitalization or by haematogenous spreading of bacteria from infections elsewhere in the body [2]. In general, *Staphylococcus epidermidis* and *Staphylococcus aureus* are the most frequently isolated pathogens from infected biomaterial implant surfaces. Almost 50% of infections associated with catheters, artificial joints and heart valves are caused by *S. epidermidis* [3], whereas *S. aureus* is detected in approximately 23% of infections associated with prosthetic joints [3].

The bacteria involved in BAI often protect themselves against antibiotics and the host immune system by producing a matrix of exopolymeric substances (Fig. 1A) that embeds the organisms and is impenetrable for most antibiotics and immune cells. Metals such as silver, copper, gold, titanium and zinc have been used as antibacterial agents for centuries, but their efficacy has been surpassed by modern antibiotics and their use has diminished. Since there is growing concern that the era of antibiotics may well come to an end over the coming decades and more and more multiple-antibiotic-resistant strains are arising, alternative strategies are badly needed especially against antibiotic-resistant strains [4]. Application of metals in their nanoparticulate form is currently

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