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Selected Reading

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Local Protection for Surgical Implants

In this issue of *Chemistry & Biology*, Jose and coworkers [1] describe the covalent attachment of vancomycin to a titanium surface. The tethered antibiotic is effective against *S. aureus*, suggesting that this material has the potential to complement clinical strategies for preventing infection following implant surgery.

Implant-associated infections account for approximately 50% of the estimated two million nosocomial infections in the United States per year [2]. In orthopedic surgery, massive implants are frequently applied, and deep wound infection remains one of the most feared complications. Treatment of these infections is difficult. Revision surgery and long-term antibiotic therapy are frequently required, and an enormous burden is placed on the patient and also on health care providers, characterized by increased rates of morbidity, mortality, poor functional outcome, and prolonged hospital stays [3].

The ability of bacteria to adhere to the surface of biomaterials and the capability of many microorganisms to form biofilms on foreign body materials are crucial steps in the pathogenesis of implant-related infections [4–6]. By biofilm formation, bacteria become protected against host immune defense mechanisms and develop a marked increase in resistance toward antibiotics [4, 7–9].

With respect to the magnitude of the clinical problem, prophylaxis of deep wound infection is of major importance. In orthopedics, the rate of infection could significantly be reduced by strictly aseptic conditions, atraumatic surgical techniques, shortening of operation time, and the application of systemic antibiotic prophylaxis [10, 11]. "Bioactive, self-protecting" implants are attractive additions to these approaches and could supplement the standard methods of prophylaxis.

An interesting effort to develop these types of implants is introduced by Jose et al. [1] in this issue of *Chemistry & Biology*. The authors modified Ti-OH on the outer surface of titanium beads with 3-aminopropyltriethoxysilane. Aminoethoxyethoxyacetate linkers were interposed before vancomycin was covalently coupled to the surface, thus ensuring a proper distance from vancomycin to the implant's surface, in order to allow the antibiotic to interfere with the biosynthesis of the bacterial cell wall. The authors showed that vancomycin bonded to titanium beads was still able to bind specifically to its target, a bacterial petidoglycan ligand. Further, a significant reduction of *Staphylococcus aureus* could be shown after incubation in vitro.

At present, prophylaxis is mainly performed by local drug delivery systems. Predominantly, antibiotics are released from polymethylmethacrylate beads, various types of bone cement or collagen sponges. Their use is efficient, and high local drug levels can be achieved to protect the implant from being colonized. However, the drug carriers themselves can cause allergic and foreign body immune reactions. Moreover, some of them are not biodegradable and need to be surgically removed. Improper release kinetics of antibiotics (e.g., long-term liberation over years with suboptimal tissue levels from bone cement) may evoke the development of resistant bacterial strains.

Another method for implant protection utilizes a thin (about 10 μm thick), biodegradable, and mechanically robust poly(D,L)-lactide coating of implants that was accepted by Europe and Canada in 2005. This coating is loaded with gentamicin and is suitable to envelope stainless steel and titanium implants [12]. The antibiotic

is released with an initial burst over a limited time of 4–6 weeks, and the carrier completely dissolves within 4–6 months. Thus, high local levels of gentamicin can be achieved at the interface for a limited time.

Providing another potential treatment option, promising aspects of the presented work [1] include covalent bonding of a clinically relevant antibiotic to titanium, which is the most favored material for metallic implants in the field of orthopedics. Thus, it may be assumed that this component will suit the mechanical demands of bone surgery. As the antibiotic is tightly connected to the implant and not released into the surrounding tissue, development of vancomycin-resistant mutant bacteria is rather unlikely. Besides, long-term protection of the implant may be expected as the antibiotic resides within its microenvironment and thus might prevent bacterial adhesion and subsequent colonization.

The presented work is of clinical relevance. Hypothesizing that implant-related infection is mainly caused by incorporated bacteria during surgery, the interface of tissue and implant is the most important target for prophylaxis. Despite strictly aseptic conditions, appropriate surgical techniques, and systemic application of antibiotics, an additional local prophylaxis appears reasonable. The presented modification of titanium implants is a new approach and could supplement the present strategies.

Looking to the future, questions concerning the mechanical properties, long-term stability, and in vivo integrity of the modified surface should be answered. Considering the promising results in vitro, in vivo testing with a suitable animal model of implant-related osteomyelitis would be of great interest [13].

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