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Review

Advancements in molecular epidemiology of implant infections and future perspectives

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Abstract

Implant infection remains the major and often irreducible complication in clinical use of biomaterials, demanding new therapeutic and preventive strategies. Etio-pathogenesis of biomaterials-related infections is being more and more studied, and various virulence bacterial factors have progressively been identified, but little is still known about the weight of the distinct molecules in the context of specific peri-implant infection sites. Molecular epidemiology has become recently integrated into the research on implant infections. What distinguishes molecular epidemiology from the simple molecular biology is that the use of molecular techniques is applied to the study of the distribution and prevalence of virulence and resistance genes in collections of bacterial clinical isolates from implant infections. Here, the authors comment on the range of molecular techniques available, reviewing the various applications of molecular epidemiology to the study of implant infections and providing some experimental examples related to the field of orthopaedic implant infections. They highlight the new opportunities arising from molecular epidemiology of designing measures useful to prevent and treat implant infections. The knowledge of the relative weight of virulence factors and of their regulatory mechanisms at molecular level can open the way to new strategies also including gene therapies aimed at silencing or knocking out crucial genes responsible for the aggressive tools (adhesins, biofilm production, antibiotic resistance) of the aetiological agents of implant-related infections.

Keywords: Implant infection; Strain genotyping; *ica* genes; Adhesins; MSCRAMMs; Gene therapy

Contents

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1. Introduction on implant infections

Infectability remains the Achille's heel in the medical application of biomaterials [1–4]. Implant infection, besides being the principal cause of implant failure and an unresolved problem to the clinicians, is still an open scientific challenge to the biomaterialists.

All efforts made to reach strict sterility and asepsis standards, to minimize the possibilities of contamination during surgery, and to prevent the establishment of infection in the patients through adequate protocols of peri-operative antibiotic prophylaxis, have proved effective, but unable to completely control the occurrence of this serious phenomenon. Although relatively rare, the event of microbial infection is often cause of devastating consequences, rather frequently determines the need for implant removal and substitution, and exposes the patient to high risks of recidive.

The by far most common route of introduction of the aetiological agents subsequently colonizing prosthetic surfaces is, at least for totally internal medical devices, the contamination during the surgical procedure of implantation. However, even late haematogenous infections have been well documented [5,6], especially for those medical devices such as artificial valves, particularly exposed to the blood stream.

A first problematic aspect posed by implant infections concerns a correct and timely diagnosis. It is a common belief that implant infections represent a largely underestimated phenomenon [7–9], due to their difficult ascertainment. Frequently caused by relatively virulent microorganisms, early post-operative and haematogenous implant-related infections are likely to exhibit an acute onset of symptoms and signs of infection. Late post-operative prosthetic joint infections, developing after 3 months from the surgery, tend instead to be characterized by more deceptive symptoms, subtle signs of inflammation, chronic persistent pain and, in the case of orthopaedic prostheses, early loosening of the implant [9].

Under these circumstances, routine hospital microbiologic examination of swabs or excised tissue samples has been described to detect only a minority of the existing infections. The difficult removal and sampling of bacteria, often growing in protective biofilms tightly adhering on the biomaterials surfaces, and the pre-exposure to antibiotic treatments, able to affect viability of planktonic cells without eradicating viable sessile bacteria within the biofilms, can be thought among the factors affecting the positivity of the results. Recently proposed protocols, involving immunofluorescence microscopy or DNA amplification by polymerase chain reaction, have been reported to significantly improve the detection rate [7]. However, such promising experimental approaches are currently still limited to very few clinical settings and the diagnosis of prosthetic infections at present still largely relies on a combination of clinical, histopathologic, microbiologic, and imaging data, often lacking sensitivity and specificity [10].

If on one hand the detection of infections still needs urgent diagnostic improvements, on the other significant advancements are being observed on the front of the technologies for the identification of the pathogenic microorganisms and their finest characterization. New molecular methods are finding increasing use in molecular epidemiology, revealing their great potential in the investigations concerning opportunistic pathogens causing biomaterials-centred infections. In the following paragraphs the focus will be on the advancements of molecular epidemiology of implant-related infections, the newest molecular technologies in use and the future perspectives.

2. The aetiopathogenesis of implant infections

The aetiology of the infections related to implanted materials has some characteristic features. Firstly, as for all foreign-body reactions, the interstitial milieu that originates at the interface material–tissues are known to be a *locus minoris resistentiae*, characterized by impaired host immune defences [11]. Secondly, the material offers a support for microbial anchorage and biofilm formation [12–15], protection in superficial niches or internal pores, and, often, even nutrients that can accelerate the growth, as in the case of some metals [16], which can release ions useful to bacteria for their metabolic processes, or in that of some resorbable materials. This situation, particularly favourable to the instauration of the infection, is occasionally associated to further conditions, when the host is immuno-depressed or debilitated for an oncological pathology.

Under such circumstances even opportunistic pathogens with mild virulence can gain their way, colonizing implant surface [17–21]. The successful instauration of the infection, facilitated by the critical conditions that implant presence creates, is finally determined by the virulence potential of the microorganism.

Over the last three decades, the pathogenetic mechanisms leading to implant infection have become a main field of research. The identification of the crucial traits (i.e. biofilm, adhesins, toxins, resistance to antibiotics) that determine the capability of the microorganisms to establish on biomaterial surfaces, to elude host immuno-response, and eventually to survive to medical treatments, is of great importance [6,9,21–23]. Many investigative efforts have focused on staphylococci, and in particular on *Staphylococcus aureus* and *S. epidermidis*, two major polysaccharide–biofilm-forming agents colonizing prosthetic devices. In most cases staphylococci can establish peri-implant infection due to their ability to grow into a polysaccharide biofilm, whose formation is a two-step process [24]: first staphylococci adhere to the material surface and then accumulate into a multilayered architecture. More recently, accumulation-associated protein (AAP) protein was identified as a novel intercellular adhesion molecule mediating biofilm formation in a polysaccharide-independent manner [25]. During the primary phase of attachment,