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Leading opinion

Infection resistance of degradable *versus* non-degradable biomaterials: An assessment of the potential mechanisms

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ABSTRACT

Extended life expectancy and medical development has led to an increased reliance on biomaterial implants and devices to support or restore human anatomy and function. However, the presence of an implanted biomaterial results in an increased susceptibility to infection. Due to the severity of the potential outcomes of biomaterial-associated infection, different strategies have been employed to reduce the infection risk. Interestingly, degradable biological materials demonstrate increased resistance to bacterial infection compared to non-degradable synthetic biomaterials. Current knowledge about the specific mechanisms of how degradable biological materials are afforded increased resistance to infection is limited. Therefore, in this paper a number of hypotheses to explain the decreased infection risk associated with the use of degradable *versus* non-degradable biomaterials are evaluated and discussed with reference to the present state of knowledge.

1. Introduction

Increasing life expectancy has led to the use of different biomaterial implants and devices for the restoration and maintenance of human anatomy and function after trauma, surgery or general wear [1]. However, there are several disadvantages associated with the use of implants, including the risks of limited healing, destructive inflammation and the development of biomaterial-associated infection (BAI) [2,3]. Currently, commercial biomaterials are screened before use to minimise toxicity, inflammation and inappropriate immune reactions. However, the risk of infection associated with the use of biomaterial implants and devices is often overlooked during development, despite the fact that it is the primary cause of biomaterial implant and device failure. In addition, BAI usually shows little susceptibility to antibiotics making BAI cases difficult to treat, often requiring revision surgeries and implant removal [4].

Bacterial contamination of an implant can occur peri- and postoperatively and also many years later via haematogenous seeding from infections elsewhere in the body [1]. Bacteria possess a wide range of adhesion molecules which target a vast array of surface chemistries and adsorbed proteins aiding their adhesion to a biomaterial surface or surrounding tissue yielding contamination of the surgical site [5,6]. Upon adhesion, the bacterial phenotype changes, leading to the formation of a biofilm: an organized community of adhering bacteria embedded in a matrix of extracellular polymeric substances (EPS) [7]. Bacteria in this mode of growth demonstrate an increased resistance to antimicrobials and effective removal by the immune system [8–10].

The presence of an implanted material alone increases the risk of infection dramatically, as first illustrated by Elek and Conen in 1957. It was demonstrated that 10^4 times fewer bacteria were required to infect human volunteers receiving a suture compared to those without [11]. This feature of decreased infection resistance has been attributed to the compromising of the immune system by the presence of "non-self" material which leads to the development of a foreign body reaction. A foreign body reaction is a characteristic immune response to material in the body identified to be xenogenic and involves the recruitment of phagocytic cells [12]. Depending on the material present, the foreign body reaction can lead to chronic inflammation, frustrated phagocytosis, granulation tissue development, formation of multinucleated foreign body giant cells, fibrous capsule development and the release of reactive oxygen species. It has been suggested that the host reaction to a foreign material may reduce the effectiveness of the immune system, generating a

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refractory period in which bacteria are not cleared effectively, leading to increased infection risk [12–15].

The consequences of a BAI are significant and include increased hospitalization times, treatment costs, the requirement for implant removal and tissue debridement, morbidity and in worst cases even death [16–19]. Due to the severity of the potential outcomes of BAI, different strategies have been used in clinical applications to reduce infection risk. For example, chlorhexidine-releasing vascular catheters have been employed to reduce blood stream infections [20] and antibiotic-loaded bone cements and antibiotic-coated arthroplasties are applied in orthopaedic surgeries [21]. The use of antimicrobials associated with implants may reduce infection risk, but moreover may stimulate the development of bacterial resistance. This is especially true, when these drugs are used and eluted for prolonged periods of time in concentrations below clinical efficacy. Therefore non-adhesive coatings [22], preventing initial bacterial adhesion, and coatings with contact-killing activity [23,24] are under development that may provide long-lasting functionality, without the drawbacks of current antimicrobial strategies.

Another clinically effective strategy to reduce infection risk is, where appropriate, to use degradable biomaterials. For example, hernia repair grafts composed of an a-cellular collagen scaffold from human cadaveric, porcine or bovine sources, show improved resistance to bacterial infection compared to non-biological grafts [25–27]. The benefits of using degradable biological grafts to decrease infection risk have been reported in a number of clinical and pre-clinical *in vivo* studies [28–33]. Animal studies comparing biological meshes with synthetic meshes found biological materials to be more resistant to *Staphylococcus aureus* [13,25,27]. Also in clinical trials, biological materials have been shown to possess higher bacterial clearance rates in patients with either a contaminated wound or a history of infection. For instance, the results of a 5-year follow-up study suggested that in infected or potentially contaminated fields where infection resistance of an implant is required, placement of degradable, biological meshes is preferred over non-degradable biomaterials [30]. Therefore, degradable meshes of biological origin are often recommended for the treatment of abdominal wall hernias in high infection risk scenarios indicated by co-morbidity factors (smoking, Chronic Obstructive Pulmonary Disease (COPD), obesity, an immune compromised state, etc.) [34]. Additionally, these degradable implants show a reduction in growth restriction [35], pain [36], implant migration [37], requirement for secondary revision and removal surgeries [38]. However, the mechanisms by which degradable materials are afforded this increased resistance to infection have yet to be established. To date, a number of hypotheses have been proposed to explain the reduced risk of infection of degradable *versus* non-degradable biomaterials, these will be critically discussed in this article.

2. Current hypotheses of infection resistance of degradable biomaterials

2.1. Increased vascularisation

Increased vascularisation has been suggested to be a reason for the higher infection resistance associated with the use of degradable materials [39,40]. Enhanced vascularisation may aid resistance by facilitating immune cell infiltration into damaged and infected host tissue [41]. The vascularisation hypothesis is based on observations such as that made by Disa et al. that degradable meshes cause increased angiogenesis and decreased infection risk [42]. It is unclear, however, whether there is a causal relationship between neovascularisation and the so called "inherent" infection resistance of degradable grafts. To date this link can only be regarded as circumstantial and must be interpreted with great care, because of the complexity of immune response between implantation and outcome of healing and bacterial contamination. The processes of tissue healing, including neovascularisation, and host clearance of contaminating microorganisms are driven by the immune system, which in turn is affected by material choice [43,44]. Neovascularisation is controlled by the production of cytokines and recruitment of cells to the site of healing. These same processes influence and are in turn influenced by other aspects of the immune response. For example, vascular endothelial growth factor is an important protein in the development of angiogenesis [45]. However, this same protein is also chemo-tactic for macrophages and increases vascular permeability [46]. Thus the presence of cytokines involved in promoting vascularisation may have direct implications on the host response to pathogens and this link may be more complicated than vascularisation alone influencing infection risk.

2.2. Reduction of the local immunological deficit

For many years, the "immunological deficit" associated with the presence of a foreign material has been linked to decreased infection resistance [11], though the nature of this feature has yet to be defined. The underlying principle is that the presence of a foreign material skews the immune responses away from the normal competency to remove pathogens. The responses to foreign materials include inflammation, necrosis, immune cell recruitment, differentiation and the release of numerous signalling molecules to cause an immune response relevant to the non-self material. However, to date, there is no consensus on which specific immune responses simultaneously promote tissue healing and effective pathogen removal. A clear point in case, is the cytokine IL-12 which promotes an inflammatory response by stimulating the differentiation of naïve T cells into TH1 cells. In the literature, both the presence of IL-12 releasing coatings and the blocking of IL-12 by anti-IL-12p40 monoclonal antibodies have been shown to reduce BAI risk [47,48]. Therefore, even on a single cytokine level there is controversy as to what is the desirable immune response. In addition to the specifics of immune responses, there are differing opinions as to how some of the broader outcomes of the immunological cascade affect infection risk. The lack of knowledge about the immune response to BAI and the outcome of the host response is a clear area for further research, both for degradable and non-degradable implant materials alike.

Traditional, non-degradable meshes have been shown to induce increased inflammatory interleukin (IL)-1, tumour necrosis factor (TNF) and immune cell recruiting chemokines and simultaneously decreased anti-inflammatory (IL-10 and IL-1 receptor antagonist) cytokine activity compared with treatment in the absence of an implant [49,50]. Such immune responses to implanted non-degradable materials lead to a higher influx of inflammatory cells when compared with repair without an implant [49]. Together, these features may prevent the immune response from being able to effectively target and clear bacteria. In contrast, the use of degradable materials may decrease the immunological deficit via two mechanisms. Firstly, degradable biomaterials are readily broken down and may not frustrate the immune system to the same extent as non-degradable materials, thus permitting immune responses to develop targeted to contaminating pathogens rather than to the material itself [51]. There are a number of examples which support this hypothesis of lower immunogenicity. The use of degradable implants leads to a significant reduction in the recruitment of inflammatory cells when compared with non-degradable implants [30,52,53]. In addition, degradable materials have been shown to avoid the formation of multinucleated foreign body giant cells, a key sign of a frustrated immune reaction and the foreign body reaction, when compared with non-degradable equivalents [40]. Furthermore, xenogenic degradable meshes have been shown to stimulate the release of IL-10, an anti-inflammatory, suppressive cytokine, whilst non-degradable prolene stimulated inflammatory signals such as TNF-α and interferon gamma (IFN-γ) in a murine model [54]. These features suggest that degradable meshes have a lower immunogenicity than their non-degradable equivalents which may subsequently permit a specific anti-bacterial immune response to develop contributing to a decreased infection risk. Whether this decreased immunogenicity is due to the degradable nature, the biological origin of the mesh materials or a combination of both has yet to be clarified.

In addition to lowering immunogenicity, the full degradation of an implant material may also restore the immune system to full efficacy. In a study by Daghighi et al., it was observed that amongst degradable materials, the degree of infection correlated to the extent of degradation *in vivo* [13]. Over a 28 day study, infection persisted in animals with non-degradable or incompletely degraded implants; whilst in contrast, infection was no longer present in animals after the material had completely degraded. The persistence of infection around degraded materials until complete degradation suggests that the presence of any amount of biomaterial, regardless of type, may prevent the immune response from effectively eradicating the infection. This supports the hypothesis that the elimination of foreign material is an effective method to prevent infection.

Analogous to the prevention of infection associated with the complete degradation of implants, success of therapies in case of infected non-degradable materials seems to only be achieved by revision surgery and implant removal. For instance, several clinical studies [18,19] have shown that antibiotic therapy is unsuccessful before foreign body removal, e.g. in case of coronary stent infections [55] and catheter-related urinary tract infections [18]. According to a study of coronary stent infections, only early sub-acute infections (occurring less than 10 days after implantation) were amenable to antibiotics therapy, while in the cases of late infections (occurring more than 10 days after implantation) a surgical intervention was necessary to relieve sub-chronic symptoms, combining foreign body removal and antibiotic therapy [55,56]. These cases illustrate that antibiotics alone are often ineffective to fully resolve the biomaterial associated infection and fail to treat

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