Host response against biomaterials: the role in the pathogenesis of biomaterial-associated infections
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Chapter 9

Summary
Biomaterial-associated infections (BAI) are a major problem in modern medicine. The majority of BAI, 40 to 75%, is caused by the relatively avirulent Coagulase Negative Staphylococci (CoNS), particularly *Staphylococcus epidermidis*.

The pathogenesis of BAI is poorly understood. The initial step in the pathogenesis of BAI is considered to be the adherence of bacteria onto the biomedical device. During the last decades various strategies have been employed in the prevention of BAI, such as the use of strict protocols for preoperative skin preparation and postoperative wound care to reduce the risk for contamination of the wound and biomaterial and the use of systemic peri-operative prophylaxis of antibiotics. Additionally, regarding bacterial adherence as an essential step in the pathogenesis of BAI, the use of biomaterials with the ability to reduce bacterial adherence appeared to be a very attractive preventive approach. Therefore, surface-modified biomaterials and biomaterials impregnated/coated with antiseptic agents or antimicrobials have been developed. Although promising results regarding inhibition of bacterial adherence and duration of antibacterial activity of such novel biomaterials are often found in vitro, the use of such biomaterials did not always result in a reduced infection rate in vivo. This suggests that there are other factors, such as alterations in the host defense mechanisms due to an implanted biomaterial, which may be important in the pathogenesis of BAI. Therefore, the aim of this thesis is to obtain insight into the role of the host response against biomaterials in the pathogenesis of biomaterial-associated infections (BAI; chapter 1). Especially the role of the various cytokines involved was studied. Insight in the role of cytokines may lead to immunomodulating strategies to prevent and treat BAI.

In chapter 2 the antibacterial activity over time of two clinically used hydrocephalus shunts soaked in solutions of various antibiotics and antibiotic combinations is studied. One of these materials, polyvinylpyrrolidone-grafted Silicon Elastomer (SEpvp) was surface modified to make the surface more hydrophobic. The grafting of SE with the hydrogel polyvinylpyrrolidone make the surface more hydrophobic. It is assumed that on hydrophobic surfaces fewer bacteria will adhere. Indeed, the experiments described in this chapter showed that on SEpvp fewer bacteria adhered and that SEpvp absorbs more antibiotic than the unmodified, Silicon Elastomer (SE). In chapter 3 we found an incompatibility reaction around the novel surface-modified hydrocephalus shunt SEpvp. In the presence of bacteria or their components abscesses developed around SEpvp, subcutaneously implanted in rabbit or mice. Around the unmodified SE no abscess formation was seen, even when challenged with very high bacterial inocula. We concluded that the combined presence of a biomaterial and bacteria enhances the inflammatory tissue response resulting in abscess formation and persistent infection. Thus, although fewer bacteria adhered onto SEpvp in vitro, this novel subcutaneously implanted material is more prone to infection. Therefore, biocompatibility testing of new catheters should include experiments in which the inflammatory effects of the combination of catheter and bacteria or bacterial components are tested. In chapter 4 we
sought to determine whether specific changes in local cytokine production were associated with the enhanced susceptibility to infection of SEpvp. We found sustained levels of IL-1β in the peri-catheter tissue of SEpvp. In addition we showed that implantation of SEpvp was associated with a delay in foreign body response, characterized by a delay in formation of giant cells and a delay in encapsulation of SEpvp. In chapter 6 we studied the role of IL-1β in the pathogenesis of biomaterial-associated infections by assessing the susceptibility of IL-1 Receptor Type I gene-deficient (IL-1R-/-) mice to infection associated with SEpvp implanted subcutaneously in mice. We demonstrated that IL-1R-/- mice had no abscess formation and were less susceptible to persistent *S. epidermidis* infection associated with SEpvp catheters than wild type mice. The foreign body reaction around SEpvp was delayed in wild type mice but not in IL-1R-/- mice. These data suggest that IL-1 play a detrimental role in this experimental model for BAI. Thus, local inhibition of IL-1 activity may be of benefit to the host as an adjunctive therapy for infections associated with biomaterials. In chapter 5 we described a novel process which may be pivotal in the pathogenesis of BAI. We demonstrated that *S. epidermidis* was able to persist in pericatheter macrophages. This persistence of *S. epidermidis* in pericatheter macrophages was found around 4 out of 4 commonly used biomaterials. Apparently, the local host defense is compromised due to the presence of the implanted biomaterials, resulting in macrophage deactivation and subsequent deficient intracellular killing. Speculating that reversal of macrophage deactivation in the vicinity of an implanted biomaterial, may increase the antimicrobial efficacy of the immune system, we tested whether subcutaneous administration of interferon (IFN)-γ could reduce the susceptibility to infection in a mouse model of biomaterial-associated *S. epidermidis* infection. IFN-γ has many biological activities, including induction of MHC class II proteins on phagocytic cells, activation of mononuclear phagocytes, and regulation of the humoral immune response. In chapter 7 we describe the results of these experiment. Mice treated with scheduled IFN-γ injections were less susceptible to a BAI. IFN-γ may therefore be beneficial in the prevention of BAI.

In chapter 8 this thesis is discussed. We concluded that due to the combined presence of a biomaterial and bacteria, an inflammatory response is induced which is favorable to the survival of the relatively non-pathogenic *S. epidermidis*. Not the surface of a biomaterial, but the surrounding tissue, especially the intracellular environment of a macrophage seems to be an important niche for these bacteria to persist. Rather than inhibiting adherence through surface modification or by developing biomaterials coated with antimicrobials, immunomodulating the local host inflammatory response may be more effective in preventing BAI.