Göteborg, 2018

ON THE PATHOGENESIS OF INFECTIONS ASSOCIATED WITH PERCUTANEOUS OSSEOINTEGRATED ORTHOPAEDIC IMPLANTS

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, fredagen den 14 december, 2018, klockan 13.00 av

Magdalena N Zaborowska

Fakultetsopponent:

Professor Artur Schmidtchen,

Lund University, Division of Dermatology and Venerology, Department of Clinical Sciences, Lund, Sweden

Avhandlingen baseras på följande delarbeten

I. Zaborowska M, Welch K, Brånemark R, Khalilpour P, Engqvist H, Thomsen P, Trobos M. Bacteria-material surface interactions: methodological development for the assessment of implant surface induced antibacterial effects. *Journal of biomedical materials research. Part B, Applied biomaterials*, 2015; 103(1): 179-187.

II. Zaborowska M*, Tillander J*, Brånemark R, Hagberg L, Thomsen P, Trobos M. Biofilm formation and antimicrobial susceptibility of staphylococci and enterococci from osteomyelitis associated with percutaneous orthopaedic implants. *Journal of biomedical materials research. Part B, Applied biomaterials*, 2017; 105B(8): 2630-2640.
** Equal contribution.*

III. Zaborowska M, Vazirisani F, Shah FA, Omar O. Ekström K, Trobos M, Thomsen P. Extracellular vesicles from *S. epidermidis* and *S. aureus* isolated from bone-anchored prostheses induce cytolysis and proinflammatory cytokine secretion. *In manuscript.*

IV. Zaborowska M*, Taulé Flores C*, Vazirisani F, Thomsen P, Trobos M. Role of extracellular vesicles from *Staphylococcus epidermidis* on antibiotic tolerance, planktonic growth, and biofilm formation under antimicrobial selective pressure. *In manuscript.*
** Equal contribution.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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On the pathogenesis of infections associated with percutaneous osseointegrated orthopaedic implants

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Abstract

Orthopaedic implants enable the restitution of locomotor function and improve the quality of life of many people. However, biomaterial-associated infection may occur due to the propensity of microorganisms to adhere and colonize implant surfaces. The objective was to gain knowledge on the pathogenesis of infections associated with percutaneous osseointegrated implants for lower limb amputation prostheses. The aims were to design *in vitro* methods for the evaluation of antimicrobial surface properties, evaluate a novel method for biofilm-susceptibility testing and characterising virulence factors in bacterial isolates from patients with implant-associated osteomyelitis, and to investigate extracellular vesicle (EV)-host cell and EV-bacterial cell interactions.

Results demonstrated that several methods, tailored to the specific surface modification and antimicrobial mode of action, should be applied to provide complementary information when evaluating the prophylactic and treatment effects of antimicrobial surfaces on planktonic and biofilm bacteria. The majority of clinical isolates of *Staphylococcus* spp. and *Enterococcus* spp. causing osteomyelitis were biofilm producers that required higher antimicrobial concentrations compared with non-producers. The biofilm susceptibility testing method may be useful to guide antimicrobial treatment decisions in orthopaedic implant-associated infection. All staphylococcal strains were able to produce EVs *in vitro.* A significantly higher level of cytotoxicity was induced in THP-1 monocytes by EVs compared with unstimulated controls. THP-1 cells internalised EVs and secreted proinflammatory cytokines to a greater degree than controls. Sub-inhibitory concentrations of gentamycin increased secretion of EVs and their protein content in *S. epidermidis*. EVs may play a role as survival factors by modulating cell growth and adherence to surfaces.

In conclusion, isolates from implant-associated infection reveal multiple virulence traits relevant for understanding and treating these infections. This thesis proposes EVs as a novel pathogenic mechanism of biomaterial-associated infection, requiring further research focus.

Keywords: osseointegration, amputation prosthesis, implant-associated infection, biofilm, staphylococci, extracellular vesicles, host defence, cytokines, cell death

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