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Studies on *Staphylococcus epidermidis* biofilm formation and the bacterial interaction with the human cathelicidin antimicrobial peptide LL-37

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ABSTRACT

The long-term use of central venous catheters for delivering nutrients and drugs in preterm neonates has been related to nosocomial infections. The majority of late-onset sepsis in very preterm infants (<28 gestational weeks) are caused by Gram positive bacteria. Coagulase-negative staphylococci (CoNS) are responsible for almost the half of these cases. *Staphylococcus epidermidis* is the most prevalent bacteria identified from CoNS bacteraemia and biofilm production is found to be the main determinant of persistent infection.

The major host defense peptide LL-37 is the only cathelicidin antimicrobial peptide that exists in humans. The peptide is broadly distributed in the human body and possesses several additional functions related to host defense. As a cathionic peptide, it interacts with the negatively charged bacterial surface. LL-37 is shown to inhibit biofilm formation and regulates biofilm-associated gene expression in *Pseudomonas aeruginosa in vitro.*

In *Paper I*, we showed that *S. epidermidis* strains obtained from bloodstream infection in preterm infants had different characteristics than the skin strains isolated from healthy term neonates. The blood isolates were equipped with an invasive genetic element IS256 and showed higher antimicrobial resistance compared with the skin isolates. However, vancomycin resistance was not detected among any of the strains. We also observed short and long filament-like structures on the cell surface of *S. epidermidis*. These filaments were involved in the attachment to the catheter surface and also in cell to cell attachment and/or communication.

Our in vitro studies in *Paper II* and *Paper III*, revealed that physiological LL-37 peptide concentrations, below those that kill or inhibit growth of the free-floating bacteria, inhibited *S. epidermidis* attachment and biofilm formation on abiotic surfaces. In *Paper III*, we observed that the peptide regulates genes involved in the biofilm formation.

In *Paper IV*, we found that the circulating serum level of hCAP18/LL-37 was similar in preterm and term neonates at birth and both the inactive protein and the active peptide were detectable independent of the gestational time. We observed positive correlation between maternal and infant peptide concentration. This may indicate that the peptide passes over early during pregnancy.

In summary, our work revealed that *S. epidermidis* strains that cause bloodstream infection in preterm infants are more virulent compared with skin strains in term neonates. Physiological concentration of the human cathionic peptide LL-37 had inhibitory effect on *S. epidermidis* biofilm formation by regulating biofilm genes. The similar LL-37 peptide concentration in preterm and term infants' blood might suggest that these neonate's vulnerability is not connected to the lower antimicrobial peptide level at birth.

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