[O73] GLOBAL CHANGES IN STAPHYLOCOCCUS AUREUS GENE EXPRESSION DURING HUMAN PROSTHETIC JOINT INFECTION

Yijuan Xu[1], Raluca Georgiana Maltesen[2], Lone Heimann Larsen[2], Henrik Carl Schonheyder[3], Per Halkjær Nielsen[4], Jeppe Lund Nielsen[5], **Trine Rolighed Thomsen**[5], Kåre Lehmann Nielsen[4]

[1]Danish Technological Institute, Aarhus, Denmark
[2]Aalborg University Hospital, Aalborg, Denmark
[3]Aalborg University Hospital, Department of Clinical Microbiology, Aalborg, Denmark
[4]Dep. of Chemistry and Bioscience, Aalborg University, Aalborg, Denmark
[5]Department of Chemistry and Bioscience, Aalborg University, Medical Biotechnology, Danish Technological Institute, Aarhus, Denmark

Aim: The aim of this study was to gain insight into the ***in vivo*** expression of virulence and metabolic genes of ***Staphylococcus aureus*** in a prosthetic joint infection in a human subject.

Method: Deep RNA sequencing (RNA-seq) was used for transcriptome profile of joint fluid obtained from a patient undergoing surgery due to acute ***S. aureus*** prosthetic joint infection. The ***S. aureus*** gene expression in the infection was compared with exponential culture of a ***S. aureus*** isolate obtained from the same sample using EdgeR. In addition, the genome of the isolate was sequenced on Miseq, assembled in CLC genomics workbench and annotated by MaGe. Moreover, using nuclear magnetic resonance (NMR) spectroscopy we analysed the metabolites in the joint fluid and in the culture supernatants to determine the biochemical composition of the environments.

Results: Antibiotic susceptibility testing by disk diffusion (EUCAST) demonstrated that the strain was susceptible to β-lactams (penicillin and cefoxitin) and macrolides (erythromycin and roxitromycin). This was indirectly confirmed by the annotated genome, because of absence of known resistant genes. The patient showed no signs of improvement during 2-days treatment with antibiotics (different β-lactams and gentamicin) prior to the surgery. The RNA-seq data indicated that the strategy employed by ***S. aureus*** to survive and proliferate in the host during antibiotic treatment involved overexpression of various enzymes related to cell-wall synthesis and multidrug efflux pumps. Interestingly, these efflux pumps are only known to be related to fluoroquinolone resistance. Many of the genes encoding virulence factors were upregulated, including toxins and superantigen-like proteins, hemolysins, and immune evasion proteins. A number of chaperones and stress related genes were overexpressed indicating a stress response. Furthermore, the RNA-seq data provided clues of the potential major nutrient sources for the pathogen ***in vivo***. Several amino acid degradation pathways were highly upregulated, e.g. arginine, histidine. Additional carbon sources included N-acetylneuraminate and purine/pyrimidine deoxyribonucleosides as indicated by the upregulation of the genes involved in the degradation pathways of these compounds and higher concentration of these substances in the joint fluid compared to culture supernatants.

Conclusions: Our results show that the gene expression pattern of ***S. aureus in vivo*** is vastly different from that of an ***in vitro*** grown exponential culture, indicating that the pathogen adapts to host environmental conditions by altering gene expression. Finally our study emphasizes the importance of ***in vivo*** study in elucidating pathogenesis of ***S. aureus*** in prosthetic joint infections.