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Analysis of epidermicin NI01-induced changes in the proteome of S. aureus NCTC 11965 using label-free quantitative proteomics

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Background: Epidermicin NI01 is a promising unmodified bacteriocin. Its low toxicity, nano molar activity range and broad spectrum of activity makes it an excellent candidate for future antibiotic development. While the structure and physicochemical properties of epidermicin NI01 is well defined its exact mode of action remains elusive, although previous studies conducted support membrane damaging activity. However, to drive further development and rational design, molecular mechanisms underpinning the antibacterial action must be elucidated. Observing the cellular response of susceptible bacteria to epidermicin NI01 induced stress using label free quantitative proteomics could help uncover pathways and systems that are effected.

Material/methods: To measure the cellular response of *Staphylococcus aureus* strain NCTC 11956 to epidermicin NI01, two flasks of bacteria were grown to mid log phase in Muller Hinton broth. At this point 0.5x minimum inhibitory concentration of epidermicin NI01 was introduced to one flask and samples were incubated for 15 hours. The proteins were than harvested using a commercial kit and whole cell extracts were digested using filter assisted sample preparation (FASP). Tandem mass spectrophotometry analysis was performed using the orbitrap LC-MS system. Peptide identification and label free quantification was carried out using PEAKS 8 software suit. Functional annotation was carried out using DAVID Bioinformatics Resources.

Results: Label free quantification results have shown differential regulation of 35 proteins. Of these, all downregulated proteins were ribosomal proteins that included 50S (RplJ, RplL and RplO) and 30S (RpsG) subunits. Expression of some proteins involved in pyruvate pathway was also significantly altered. The results indicate that the edition of 0.5x MIC epidermicin NI01 induces a stringent response-like reaction from the *S. aureus* strain NCTC 11956.

Conclusions: Down regulation of ribosomal proteins is a hallmark of stringent response and upregulation of pyruvate metabolism is also observed. This is most likely caused by leakage of some

vital resources from the bacterial that trigger the stringent response due to some loss of membrane integrity. This study further consolidates data indicating membrane active nature of epidermicin NI01.