Differences and similarities on metabolic response to pH by commensal and pathogenic *Staphylococcus epidermidis* strains

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Staphylococcus epidermidis is the main human skin commensal, however, when the host is immunocompromized and there is a skin barrier break, this bacterium can convert into a life-threatening pathogen associated to medical devices-related infections. *S. epidermidis* population structure is composed of two genetic lineages (clonal complex 2 (CC2) and non-CC2) that co-exist in the human skin. CC2 strains are more frequently found causing disease, but the basis of this increased pathogenicity is still poorly understood. Improved knowledge of *S. epidermidis* pathogenicity mechanisms is needed to be able to design more effective prevention and treatment strategies.

To address this issue we compared the adjustments of the metabolic and proteomic processes performed by CC2 and non-CC2 strains when facing pH stimulus that mimic skin (pH=5.5) and blood (pH=7.4) - a key contrasting environmental factor during commensal-to-pathogen conversion. Proteomics and metabolomics of cellular extracts recurred to nanoscale liquid chromatography-tandem mass spectrometry (nano LC-MS/MS) and 1H NMR, respectively.

We observed that both strains shared similar metabolic adaptations to the low skin pHs, such as an increase in glycerolipid metabolism and a decrease in metabolites involved in the two-component regulatory system SaeRS. On the other hand, they showed distinctive and specific responses to the two pHs tested. **At skin pH** CC2 strain promoted menaquinone biosynthesis and peptidoglycan-related pathways while non-CC2 strain, increased polyphosphate metabolism, betaine and folate biosynthesis. **At blood pH** CC2 strain showed a higher abundance of proteins that manage heme toxicity and adhesion while non-CC2 strain altered his carbohydrate-active transport system, butonate, arginine and proline metabolism.

Our results showed that CC2 and non-CC2 strains resort to distinct metabolic and cellular processes to cope with skin and blood pH. Contact of CC2 strain with blood pH induced metabolic pathways that allow survival in blood and can promote adhesion to medical-devices. Data gathered suggest that acidification of the infection site and inhibition of heme detoxification and adhesion might be effective treatment strategies against *S. epidermidis* infections.

Funding: ONEIDA project (LISBOA-01-0145-FEDER-016417) co-funded by FEEI from "Programa Operacional Regional Lisboa 2020" and by national funds from FCT. Project LISBOA-01-0145-FEDER-007660 (MOSTMICRO) funded by FEDER funds through COMPETE2020 - POCI and by FCT. Transnational Cooperation Portugal/France –

Pessoa Program/2019 "Identification of putative bacterial targets for the development of precision antimicrobials against pathogenic *S. epidermidis* – a strategy to prevent medical device associated infections", FCT/Campusfrance. The NMR data were acquired at CERMAX, ITQB-NOVA, Oeiras, Portugal, with equipment funded by FCT, project AAC 01/SAICT/2016.; PD/BD/150980/2021.