The Small Colony Variant Of Listeria Monocytogenes Is More Tolerant To Antibiotics And Grows Better Within Caco-2 Epithelial Cells Than The Wild Type - DTU Orbit (08/11/2017)

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Introduction: Small Colony Variants (SCV) of bacteria are a slow growing phenotype with a pinpoint colony morphology and several specific characteristics. In several pathogens they have been linked to recurrent and chronic infections. SCV of *Listeria monocytogenes* can be generated when exposed to sublethal concentration of triclosan, and in this study, we characterized their tolerance to antibiotics and ability to invade and survive in host cells. Results: Complementation assays showed that SCV E18 phenotype is caused by a mutation in the heme biosynthesis pathway. Although no difference in MIC, the SCV E18 survived significantly better than the wild type N53-1 (one and three $\log_{10}$ higher CFU/ml) when exposed to super-MIC concentrations of most tested antibiotics, indicating a persister-like phenotype of the SCV. While SCV E18 displayed sensitivity towards oxygen, it was significantly more tolerant of 20mM H_2O_2 as compared to the wild type, with 6.3 $\log_{10}$ CFU/ml and 3.7 $\log_{10}$ CFU/ml, respectively. The SCV E18 had lower survival rate in unactivated macrophages, however, it was able to survive and multiply to almost 100-fold higher CFU/ml than the wild type in CaCo-2 epithelial cells. Conclusions: This study is the first to demonstrate that the persister-like SCV phenotype of *L. monocytogenes* potentially could complicate treatment by causing an increase in tolerance towards most of the clinically relevant antibiotics, while also enabling the bacteria to persist in the protected intracellular environment.

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