Streptococcus mitis and S. oralis mutate an ‘essential’ gene upon exposure to daptomycin

Daptomycin (DAP) is a lipopeptide antibiotic with bactericidal activity against Gram-positive pathogens. Its addition into clinicians’ antibiotic repertoire was an important step in combating increasing numbers of multi-drug resistant (MDR) infectious agents. DAP has been shown to have potent activity against vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA). However, resistance to DAP has emerged over the last 20 years. This resistance is normally a step-wise process involving multiple genes working together. Recently, studies on the viridans group streptococci (VGS) and their response to DAP have demonstrated that rapid mechanisms of resistance can develop in these opportunistic pathogens. In this study, we used whole genome sequencing and comparative genomics to identify potential polymorphisms associated with the resistant phenotype in S. mitis and S. oralis. Briefly, we identified a mutation in a single gene (cdsA) within these VGS that conferred resistance to DAP. To date, mutations in this gene have not been seen, as cdsA is considered to be essential for bacterial growth. cdsA encodes the enzyme phosphatidate cytidylyltransferase (CdsA), which is responsible for the conversion of phosphatidic acid (PA) to CDP-diacylglycerol (CDP-DAG). CDP-DAG is the common precursor for the synthesis of all major phospholipids found in bacterial membranes. Using lipidomics, we confirm that these cdsA mutations result in a loss-of-function phenotype, as demonstrated by the accumulation of PA in the membranes of S. mitis and S. oralis and the depletion of the lipids phosphatidylglycerol and cardiolipin. Taken together, this research provides critical insight into the mechanisms of resistance to the clinically relevant antibiotic DAP and provides evidence that S. mitis and S. oralis share a unique physiology that allows them to survive CdsA loss-of-function mutations.