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Microbiology Congress 2018: The msaABCR operon is involved in persister formation in Staphylococcus aureus - Shanti Pandey - University of Southern Mississippi

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Chronic staphylococcal infections are primarily caused by the persister cells; a phenotypic variant that shows extreme tolerance to antibiotics resulting in treatment failure. While this phenomenon has posed a great threat in public health, mechanism underlying their formation in Staphylococcus aureus remains largely unknown. Mounting evidences of causal link between persister cells and recalcitrant infections underscore the great urgency to unravel the mechanism by which these cells are formed and survived. We characterized msaABCR operon that regulates virulence, biofilm development and antibiotic resistance in S. aureus.

Transcriptome of the operon deletion mutant shows differential expression of genes involved in various metabolic pathways including down-regulation of more than 10 genes involved in oxidative stress that led us to hypothesize that the operon play role in persister formation against antibiotics as well as oxidative stress leading to intracellular persister formation. In this study, we examined the persister cell formation in wild type S. aureus (USA300 LAC), isogenic msaABCR deletion mutant and complemented mutant strains against clinically relevant bactericidal antibiotics Rifampicin, Vancomycin, Daptomycin, Gentamicin and Linezolid. The persister ratio was measured at different time points after adding antibiotics.

Our result shows that Î” msaABCR generates significantly less number of persister cells relative to the wild type strain in most of the antibiotics tested while the complement restores the phenotype suggesting a vital role of msaABCR operon in development of persister cells. Likewise, growth of Î” msaABCR was abolished by 25 mM H2O2 while wild type and complementation strains could grow as comparable to the unstressed cells. Chromatin immunoprecipitation (ChIP) assay revealed that MsaB protein directly binds the promoter region of OsmC/Ohr family protein (SAUSA300_0786) that is involved in the oxidative stress.

Furthermore, significantly down-regulated transcript of SAUSA300_0786 in Î” msaABCR suggests MsaB as an activator of this protein. These results suggest that msaABCR operon is involved in oxidative-stress-defense mechanism possibly via regulation of OsmC/Ohr family protein facilitating intracellular persister formation and recurrent infections. In addition, the MsaB protein also binds the FumC; a gene of tricarboxylic acid (TCA) cycle, deletion of which forms higher number of persister cells.

Collectively, these results suggest that msaABCR operon of S. aureus regulates persister formation against antibiotics and oxidative stress. Further, we plan in vivo study for understanding this mechanism underlying intracellular persister development and consequently overcome treatment failures of staphylococcal infections. Background Persister cells comprise a phenotypic variant that shows extreme antibiotic tolerance resulting in treatment failures of bacterial infections. While this phenomenon has posed a great threat in public health, mechanisms underlying their formation in Staphylococcus aureus remain largely unknown. Increasing evidences of the presence of persister cells in recalcitrant infections underscores the great urgency to unravel the mechanism by which these cells develop. Previously, we characterized msaABCR operon that plays roles in regulation of virulence, biofilm development and antibiotic resistance.

We also characterized the function of MsaB protein and showed that MsaB is a putative transcription factor that binds target DNA in response to nutrients availability. Results In this study, we compared the number of persister cell in wild type, msaABCR deletion mutant and the complemented strain in two backgrounds USA300 LAC and Mu50. Herein, we report that msaABCR deletion mutant forms significantly less number of persister cells relative to wild type after challenge with various antibiotics in planktonic and biofilm growth conditions.

Complementation of the msaABCR operon restored wild type phenotype. Combined antibiotic therapy along with msaABCR deletion significantly improves the killing kinetics of stationary phase and biofilm S. aureus cells. Transcriptomics analysis showed that msaABCR regulates several metabolic genes, transcription factors, transporters and enzymes that may play role in persister cells formation, which we seek to define in the future. Conclusions This study presented a new regulator, msaABCR operon, that is involved in the persister cells formation, which is a poorly understood in S. aureus. Indeed, we showed that msaABCR deletion significantly reduces the persister cells formation in all growth phases tested. Although, we have not yet defined the mechanism, we have shown that msaABCR regulates several metabolic, transporters, and extracellular proteases genes that have been previously linked with persister cells formation in other bacterial systems. Taken together, this study showed that inactivation of the msaABCR operon enhances the effectiveness of antibiotics for the treatment of S. aureus infections, especially in context of persister cells.

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