J Infect Dis. 2015 Apr 15;211(8):1317-25.
doi: 10.1093/infdis/jiu602. Epub 2014 Oct 31.

A liaR deletion restores susceptibility to daptomycin and antimicrobial peptides in multidrug-resistant Enterococcus faecalis.

Jinnethe Reyes, Diana Panesso, Truc T. Tran, Nagendra N. Mishra, Melissa R. Cruz, Jose M. Munita, Kavindra V. Singh, Michael R. Yeaman, Barbara E. Murray, Yousif Shamoo, Danielle Garsin, Arnold S. Bayer and Cesar A. Arias

Abstract

Daptomycin is a lipopeptide antibiotic that is used clinically against many gram-positive bacterial pathogens and is considered a key frontline bactericidal antibiotic to treat multidrug-resistant enterococci. Emergence of daptomycin resistance during therapy of serious enterococcal infections is a major clinical issue. In this work, we show that deletion of the gene encoding the response regulator, LiaR (a member of the LiaFSR system that controls cell envelope homeostasis), from daptomycin-resistant Enterococcus faecalis not only reversed resistance to 2 clinically available cell membrane-targeting antimicrobials (daptomycin and telavancin), but also resulted in hypersusceptibility to these antibiotics and to a variety of antimicrobial peptides of diverse origin and with different mechanisms of action. The changes in susceptibility to these antibiotics and antimicrobial peptides correlated with in vivo attenuation in a Caenorhabditis elegans model. Mechanistically, deletion of liaR altered the localization of cardiolipin microdomains in the cell membrane. Our findings suggest that LiaR is a master regulator of the enterococcal cell membrane response to diverse antimicrobial agents and peptides; as such, LiaR represents a novel target to restore the activity of clinically useful antimicrobials against these organisms and, potentially, increase susceptibility to endogenous antimicrobial peptides.