Targeting Both Host and Bacteria to Overcome Vancomycin Resistance in *Enterococcus faecalis*

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Biography

Kimberly Kline is a professor at University of Geneva, Switzerland. Before that, she was a Professor of Microbiology at Nanyang Technological University in Singapore, and a Principal Investigator at the Singapore Centre for Environmental Life Sciences Engineering. Prior to coming to Singapore, Kimberly received an MPH in Biostatistics and Epidemiology and PhD in Microbiology and Immunology from Northwestern University. Kimberly completed postdoctoral training at Washington University in St. Louis and at the Karolinska Institute in Stockholm Sweden.

Kimberly has received multiple awards for her contributions to the field of microbiology, including a NIH K99 Career Development Award in 2011, the Singapore National Research Foundation Fellowship in 2011, the ICAAC Young Investigator Award from the American Society of Microbiology in 2014, and the Nanyang Education Award in 2017.

Abstract

Among Enterococci, intrinsic and acquired resistance to antibiotics such as β-lactams and vancomycin critically limit treatment options for infection with these opportunistic pathogens. We have recently shown that Enterococus faecalis exists as both an extracellular pathogen and also replicates within a variety of mammalian cells, including macrophages, further complicates treatment of infections caused by this opportunistic pathogen. Antimicrobials that enhance the host immune response are emerging as alternative approaches, with the added advantage of overcoming bacterial resistance. Here, we investigate the antibiotic and immunological activity of an FDA-approved anticancer agent in vitro and in vivo against vancomycin resistant Enterococcus faecalis (VRE). In vitro, this drug is a potent antibiotic against Gram-positive bacteria through induction of reactive oxygen species and DNA damage. At sub-inhibitory concentrations, this drug synergizes with vancomycin and lowers the vancomycin concentration required to kill VRE by over 140-fold. This synergy is specific to vancomycin-resistant, but not susceptible, strains because vancomycin renders the resistant strains more permeable to this drug and thus drug-mediated DNA damage. In a murine wound infection model, treatment with this drug effectively reduced VRE bacterial numbers by 120-fold and with further reductions when combined with vancomycin. Wounds treated with this drug had significantly more macrophages and pro-inflammatory cytokines compared to untreated wounds. In addition, this drug augmented intracellular bacterial killing by both murine and human macrophages by upregulating the expression of lysosomal hydrolases. These results show that this drug is a potent antibiotic against Gram-positive bacteria, sensitizes VRE to vancomycin, enhances macrophage recruitment and intracellular bactericidal activity, and represent a promising dual bacterium- and host-targeted therapeutic for overcoming vancomycin resistance.