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Towards rapid phenotypic antibiotic susceptibility testing through RNA detection

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Rapid antibiotic administration remains our most effective weapon against bacterial pathogens but the emergence of antibiotic resistance poses serious challenges. Current culture-based susceptibility determination is too slow for early evidence-based antibiotic selection, while newer genotypic methods have limited ability to predict phenotypic antibiotic resistance. RNA detection offers a “semi-phenotypic” assay with the potential to identify antibiotic susceptibility more rapidly, agnostic to the genetic basis for resistance. Susceptible bacteria enact different transcriptional programs than resistant ones within minutes of antibiotic exposure, independent of resistance mechanism. We report RNA-Seq analysis of the key drug-resistant pathogens *Acinetobacter baumannii* and *Klebsiella pneumoniae* treated with three key antibiotics from distinct classes: Ciprofloxacin, gentamicin and meropenem. These studies reveal transcripts whose expression levels clearly distinguish susceptible from resistant organisms within minutes of drug exposure. We validate these transcriptional signatures for multiple antibiotic classes against clinical isolates, including a “test set” of multidrug-resistant strains from the US Centers for Disease Control using a simple, rapid commercial RNA hybridization assay (NanoString) to robustly distinguish susceptible and resistant clinical isolates within hours. Susceptibility metric derived from these transcriptional assays correctly grouped isolates in 148 of 151 antibiotic susceptibility tests (98% accuracy); 2 of the 3 incorrectly grouped isolates were within one dilution of the breakpoint MIC. We have previously shown proof-of-concept that this 8-hour assay may be applied to a positive blood culture with minimal sample processing. In principle, this rapid phenotypic assay for antibiotic resistance can be extended to any pathogen-antibiotic pair, without foreknowledge of resistance mechanism.

Biography

Roby Paul Bhattacharyya has completed his MD and PhD from the University of California, San Francisco in 2007, trained in Internal Medicine and Infectious Diseases at Massachusetts General Hospital. He is currently an Assistant in Medicine in the MGH Division of Infectious Diseases, Instructor at Harvard Medical School and a Researcher at the Broad Institute of MIT and Harvard. His research interests focus on both basic and applied aspects of antibiotic resistance in bacteria.

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