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Countering bacterial antibiotic resistance on Earth and space

Abstract:

Uropathogenic Escherichia coli (UPEC) causes urinary tract infections, e.g., cystitis, which are treated by gentamicin. The protein ss, encoded by the rpoS gene, controls E. coli general resistance. We discovered that rpoS deletion renders UPEC more sensitive to Gm and other bactericidal antibiotics (BAs) e.g., norfloxacin, and proteomic analysis suggested a weakened antioxidant defense (OD) as the reason. Reactive oxygen species (ROS) detectors (psfiA gene reporter/appropriate chemicals) revealed that BAs caused greater oxidative stress (OS) in the mutant; anaerobic conditions (which prevent ROS formation) or co-treatment with an antioxidant decreased the drugs lethality. E. coli strains missing antioxidant proteins (SodA/SodB; KatE/SodA; Zwf/Gnd;TalA) were also more sensitive to these antibiotics. Use of a microfluidic device indicated that the results applied to single cells. Treating UPEC infection of mice bladder corroborated these findings in vivo. Normal metabolism generates ROS, and the results showed that its insufficient quenching increases BA lethality. BAs kill by well-established mechanisms, e. g.., inhibition of protein synthesis, but bacteria have become resistant to these. Our findings show that mitigating bacterial OD can restore BA effectiveness, and using bioinformatic approaches we have identified small molecule that can be co-administered along with BAs to attain this. In microgravity (MG) of space flights, astronauts often suffer from cystitis, and as MG is known to alter bacterial gene regulation, it was unclear whether the above findings would be relevant in treating astronauts. The "EcAMSat" Stanford-NASA mission showed, however, that antagonizing OD has the same beneficial effect in combating UPEC as on Earth. EcAMSat employed a free-flying "nanosatellite" equipped with a highly sophisticated microfluidic system for autonomous determination of UPEC sensitivity to Gm in space flight and its telemetric transmission in real time to Earth. Bacterial multidrug resistance (MDR), such as the one regulated by the emrRAB operon and the EmrR protein is an additional problem for controlling bacterial infections. Its activation is due to alteration in the EmrR protein conformation, which too can be prevented by small molecules and bioinformatic approaches that we have pursued.

Biography

A. C. Matin was a Pakistani-American microbiologist, immunologist, academician and researcher. He was a professor of microbiology and immunology at Stanford University School of Medicine. Matin published over 100 research papers plus several reviews and has many patents registered in his name. His research was focused on bio-molecular engineering, cellular resistance and virulence, drug discovery, biology of microgravity, bioremediation, stress promoters, stress sensing, and biotechnology. He made pioneering research contributions in biology and physiology of mixotrophy, starvation responses at the cellular and genetic levels, bacterial multidrug and biofilm resistance, role of G proteins in starvation and motility, discovery of an imageable cancer prodrug, specific drug targeting and the development of heritable contrast agent for molecular resonance imaging. Matin's work on antibiotic resis**tance along with his work as a** principal investigator on E. coli AntiMicrobial Satellite (EcAMSat) system resulted in NASA sending E. coli to space for astronaut health protection in 2017. He was the recipient of NASA honor award for the ECAMSAT Project. Matin was the editor-in-chief of Open Access Journal of Applied Sciences.