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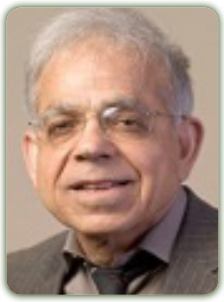

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Role of bacterial antioxidant defense in their resistance to bactericidal antibiotics

Sigma S (σ^s) controls the synthesis of resistance proteins in stationary pathogenic bacteria like *Escherichia coli*. Deletion of the *rpoS* gene rendered *E. coli* more sensitive to Bactericidal Antibiotics (BAs): Gentamicin, norfloxacin and ampicillin. Proteomic analysis implicated a weakened Antioxidant Defense (AD). Use of the *psfiA* genetic reporter, 3-(p-hydroxyphenyl) fluorescein (HPF) dye and Amplex Red showed that BAs generated more Oxidative Stress (OS) in the mutant. Co-administration of the antioxidant N-Acetyl Cysteine (NAC) and treatment under anaerobic conditions decreased drug lethality of the mutant further indicating AD involvement. The greater OS in this strain results from impaired capacity to quench endogenous ROS, e.g., respiration- linked electron leakage. Infection by UPEC in mice showed that AD was important for UPEC antibiotic resistance also *in vivo*. Disruption of AD by eliminating quencher proteins or those of pentose phosphate pathway (which provides NADPH for quenching oxygen radicals) also generated greater OS and killing by BAs. Thus, BAs kill stationary-phase bacteria also by generating OS and targeting AD can therefore enhance their efficacy. Using bioinformatics, small molecule compounds were identified towards this end, and initial results have given promising results. In space flights, astronauts often suffer from UPEC infection. The EcAMSat mission, using a highly sophisticated microfluidic system showed that UPEC missing σ^s had increased sensitivity to gentamicin also in space. We have also developed method for determining resistance at single cell level. Together, these results promise to provide powerful means to combat bacterial antibiotic resistance.

Biography

A C Matin has obtained his PhD from University of California. He served as a Group Leader at State University of Groningen, The Netherlands before joining Stanford, where he has been full Professor for several years. He has served on several professional panels and Editorial Boards and is recipient of many awards. He is elected as Fellow of American Academy of Microbiology.

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