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Role of bacterial antioxidant defense in their resistance to bactericidal antibiotics

Statement of the problem: Bacterial antibiotic resistance is a world-wide public health problem requiring and new approaches. Background: Sigma S (σs) controls the synthesis of proteins that contribute to the resistance of bacteria like uropathogenic *Escherichia coli* (UPEC) in the stationary phase of growth, where bacteria are most virulent; σs is encoded by the *rpoS* gene. Methodology: Colony forming unit formation was used to determine antibiotic sensitivity; a novel microfluidic device determined sensitivity at single-cell level. Results: Lack of *rpoS* increased UPEC sensitivity to bactericidal antibiotics: gentamicin (Gm), ampicillin and norfloxacin. Gm will be discussed to illustrate the findings with the three antibiotics. Global proteomic analysis implicated weakened antioxidant defense. Use of the p*sfiA* genetic reporter, 3-(p-hydroxyphenyl) fluorescein (HPF) dye, and Amplex Red showed that Gm generated more oxidative stress in the mutant. Cell elongation can compromise the results of HPF, but the antibiotic treatment did not affect the dimensions of stationary phase bacteria. The antioxidant, N-acetyl cysteine (NAC), & anaerobiosis decreased drug lethality. Thus, greater oxidative stress caused by insufficient quenching of endogenous ROS and/or respiration-linked electron leakage contributed to the increased sensitivity of the mutant; this was confirmed also *in vivo*. Eliminating of quencher proteins, SodA/SodB and KatE/SodA, or the pentose phosphate pathway proteins, Zwf/Gnd and TalA, (source of NADPH required by the quenchers), also generated greater oxidative stress and killing by Gm. The results were confirmed at single-cell level, as well as under microgravity during space flight where astronaut immune response is compromised. Conclusion and Significance: Besides their established mode of action, bactericidal antibiotics also kill bacteria by oxidative stress. Targeting the antioxidant defense will therefore enhance their efficacy. Bioinformatic approaches have identified small molecules that inhibit these proteins and are under study.

Recent Publications

1. J-H Wang, R Singh, M Benoit, M Keyhan, M Sylvester, M Hsieh, A Tathireddy, Y-J Hsieh, AC Matin. 2014. Sigma S-dependent antioxidant defense protects stationary phase *Escherichia coli* against the bactericidal antibiotic gentamicin. Antimicrob. Agents Chemother. 58(10): 5964-5975
2. AC Matin, J-H Wang, Mimi Keyhan, Rachna Singh, Michael Benoit, Macarena P. Parra, Michael R. Padgen, Antonio J. Ricco,* Matthew Chin, Charlie R. Friedericks, Tori N. Chinn, Aaron Cohen, Michael B. Henschke, Timothy V. Snyder, Matthew P. Lera, Shannon S. Ross, Christina M. Mayberry, Sungshin Choi, Diana T. Wu, Ming X. Tan, Travis D. Boone, Christopher C. Beasley, and Stevan M. Spremo. Payload hardware and experimental protocol for testing the effect of space microgravity on the resistance to gentamicin of stationary-phase uropathogenic *Escherichia coli* and its ss-deficient mutant. Life Sciences in Space Research 15: 1-10 (2017)

3. Fengjiao Lyu; Ming Pan; Sunita Patil; Jing-Hung Wang; A. C Matin; Jason R Andrews; Sindy K.Y. Tang. 2018. Phenotyping antibiotic resistance with single-cell resolution for the detection of heteroresistance. Sensors & Actuators: B. Chemical 270 (2018) 396–40.

Biography

A.C. Matin got his PhD from University of California in Microbiology (1969). He is serving as the Chair of MS senate task force on postdoctoral affairs (2009-present), Member of MS senate steering committee (2008-present) & Senator of Medical School senate (2006-present). He is a Fellow of the American Academy of Microbiology. He got 16 Honors and Awards which are Star Award in Environmental Protection Agency (1991-1997), Review Committee Member in Accreditation Board for Engineering and Technology (1992) and Foundation for Microbiology Lecturer in American Society for Microbiology (1991-1993). He has authored about 37 Publications that include review articles. His Community & International Work involved in Bacterial antibiotic resistance in space flight, Stanford University; NASA Ames and Nuclear waste remediation.

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