

Mechanisms of induction of antibiotic resistance reversion through epigenetic modification of bacterial DNA caused by iodine-containing nano-molecular complex

Oleg N. Reva^a, Ilya S. Korotetskiy,^b Sergey V. Shvidko^b, Sergey V. Shilov^b, Ardak B. Jumagazyeva^b, Sabina T. Kenesheva^b, Aleksandr I. Ilin,^b

^aCenter for Bioinformatics and Computational Biology (CBCB); Department of Biochemistry, Genetics and Microbiology; University of Pretoria, Pretoria, South Africa.

^bScientific Center for Anti-Infectious Drugs (SCAID), Almaty, Kazakhstan.

Abstract:

Wide distribution of antibiotic resistant infections is a global challenge to public health. Pre-treatment of drug resistant bacteria with newly developed iodine-containing complex FS-1 makes them sensitive to regular antibiotics. This phenomenon was demonstrated in vitro and in clinical trials on multidrug resistant *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Escherichia coli* and *Acinetobacter baumannii*. Possible mechanisms of drug resistance reversion were studied experimentally and by deep DNA and RNA sequencing using PacBio and IonTorrent technologies on two reference strains – MRSA *S. aureus* ATCC BAA-39TM and ESBL *E. coli* ATCC BAA-196TM. In both cases, a stable reversion to antibiotic sensitive phenotype was achieved associated with alterations in gene expression patterns reflecting a general oxidative stress and deregulation of drug resistance mechanisms. The latter effect correlated with observed abnormalities in epigenetic modifications of bacterial chromosomes compared to control conditions. Epigenetic patterning of sequenced chromosomes was performed using the SMRT base-call kinetics analysis in PacBio reads. The most dramatic changes were observed in the level of methylation of chromosomal architecture imparting sequences (AIMS) orchestrating the DNA replication and reparation in bacteria. Moreover, a significant increase in number of modified, putatively oxidized nucleotides was observed. It was shown with a statistical reliability that the abnormal modifications of nucleotides within bodies of genes encoding for ncRNA in *S. aureus* do correlate with the observed alterations in the expression of these top level regulatory elements that deregulate the general gene expression in the affected bacteria. Discovered mechanisms of drug resistance reversion provide us with new approaches to overcome drug resistance problem.

Biography

Prof. Oleg Reva is Full Professor in the Centre for Bioinformatics and Computational Biology, Department of Biochemistry, Genetics and Microbiology at the University of Pretoria. He received his PhD degree in microbiology in the Institute of Microbiology and Virology, Kyiv, Ukraine. His current field of research is bioinformatics, bacterial genomics and next generation sequencing. He is an author of more than 100 publications in this field of research.