Prem Lakshmanane, J Bacteriol Parasitol 2014, 5:4
http://dx.doi.org/10.4172/2155-9597.S1.006

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Congress on
Bacteriology & Infectious Diseases
November 17-19, 2014 DoubleTree by Hilton Hotel Chicago-North Shore, USA

Towards anti-virulence drugs targeting disulfide bond-forming enzyme DsbA

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Current bactericidal antibiotics are losing their effectiveness against the rapidly growing drug resistant 'superbugs'. Novel strategies are therefore urgently needed to combat multi-drug resistant bacterial infection and to prolong the lifespan of existing antibiotics. The disulfide bond-forming enzyme DsbA is a master regulator of bacterial virulence and pathogenesis. DsbA has been identified as an attractive anti-virulence molecular target because it is not essential for survival of pathogenic bacteria, but its disruption attenuates virulence in a number of clinically relevant bacteria. DsbA enzymes are diverse that either partner with integral membrane protein DsbB or VKOR to catalyze disulfide bond formation. Structural analyses of a library of 15 well-characterized DsbA proteins from various pathogenic bacteria suggest four sub-classes (DsbAIa, Ib, IIa and IIb) on the basis of surface features. DsbAIa sub-class comprises enteric bacterial DsbAs that characteristically have a large groove on the catalytic surface. DsbAIb subclass covers a wide range of DsbAs from Gram-negative bacteria that has small, less conserved, surface exposed pockets on the catalytic surface. Both DsbAIa and Ib members also have a large non-catalytic protein interaction surface. In contrast, surface surrounding the catalytic site of DsbAs from Gram-positive bacteria, including mycobacteria (DsbA II) are charged and have relatively shallow groove. We provide information on druggability of DsbA enzymes in the context of available binding peptides, and evolutionary conservation across bacterial DsbAs.

Biography

Prem Lakshmanane earned his PhD in structural biology and biological chemistry from the Weizmann Institute of Science in 2005. He pursued his postdoctoral research at the Sanford-Burnham Medical Research Institute. He is currently a senior research fellow at the University of Queensland. His research interests are approaches to combat drug resistant bacteria and to prevent the spread of drug-resistant plasmids.

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