Novel strategies to tackle antimicrobial resistance

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Abstract

Multidrug resistant (MDR) pathogens are among the top threats to global public health. Five bacteria called ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) are of particular concern, responsible for a third of hospital associated infection. These bacteria have evolved to resist any conventional antibiotics. The pace of emerging drug resistance in these pathogens is faster than the speed of discovery of new antibiotic drugs.

Overcoming antimicrobial resistance is not a simple task. The problem lies in that the development of resistance in bacteria is not an anomaly, but a natural process where evolutionary selection intervenes. Whenever bacteria are under the pressure of lethal agents, their resistance will emerge inevitably and spontaneously. Therefore, we need totally different approaches from the mechanisms of past antibiotics. Many efforts are being made to overcome these problems. These include repurposing of old drugs, anti-virulence approach, inhibition of efflux pumps, discovery of adjuvants and development of antibody-antibiotic conjugates, to name a few.

In this tutorial talk, I will review and discuss the approaches made in our laboratory for the last 5 years. First of our approaches is to target metabolic pathways. We studied the mannitol pathways in Staphylococcus aureus, and demonstrated that it was a potential antibacterial target, inhibition of which gave S. aureus a quandary of whether it has to give up its important defense molecule or it is forced to wait for implosion. Second is the anti-virulence approach via inhibition of a bacterial two-component signal transduction system. S. aureus has a few master signal transduction systems that regulate a majority of its virulence factor production. Inhibition of one or few of them led to the shutdown of virulence factors, making the bug less harmful and more vulnerable while this does not result in direct killing of S. aureus, therefore, slowing down the resistance selection. Third, we discovered a drug influx system and its activation mechanism. This gave us a chance to enhance the effect of an old antibiotic drug. Activation of the drug influx could overcome the efflux and modification of the drug molecule. The enhanced reuse of old drugs is an attractive option that has not only scientific implication but also a big societal and economic impact because the reuse of old drugs does not require the expensive cost in obtaining the approval of new drugs from the authorities, and old drugs have been already understood well.

The results from these studies provide an insight into how to fight antimicrobial resistance, and we believe that there are still options that we can use to avert the catastrophic post-antibiotic era.

Keywords: *antimicrobial resistance, mannitol metabolism, two component system, drug transporter*

References

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Biography

Dr Seung Seo Lee obtained his BSc and MSc in chemistry from Seoul National University. He then worked in the pharmaceutical industry before starting his doctoral study in chemistry at University of British Columbia in Vancouver, Canada. After postdoctoral studies at University of Cambridge and University of Oxford, he was appointed as a lecturer in Chemical Biology at University of Southampton. His research interest is antimicrobial resistance, biosynthesis and biocatalysts.