Plenary Lectures

PL.1

Parnas Lecture

Beyond the role in plasmid maintenance – a regulatory function of *Staphylococcus aureus* toxin-antitoxin system PemIK$_{Sa}$

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Toxin-antitoxin (TA) systems are broadly distributed throughout the domain of *Bacteria*. Until recently, TA systems were considered to play only an ancillary role in bacterial physiology by maintaining the stability of certain plasmids. However, multiple recent findings strongly suggest that the major role and the true importance of TA systems lies in global coordination of stress response. If these assumptions are confirmed, the TA systems may emerge as one of the most versatile and widespread regulatory systems known, contributing broadly to the evolutionary success of bacteria. Potential exploitation of such crucial factors in future therapeutic, industrial and agricultural applications seems almost innumerable.

Our recent work constitutes one of the most detailed available evidence demonstrating the ability of a TA system to differentially regulate gene expression in bacteria [1]. We identified and characterized a novel TA system (PemIKSa) located on Staphylococcus aureus plasmid pCH91. The toxin (PemKSa) is a sequence-specific endoribonuclease recognizing the tetrad sequence U↓AUU. The antitoxin (PemISa) inhibits toxin activity through physical interaction. We demonstrated that alike many previously characterized TA systems, PemIKSa is responsible for stable plasmid maintenance. However, the major significance of our study is that it provided data suggesting that PemIKSa is capable of differentially affecting the translation of large pools of genes thereby regulating staphylococcal virulence. Such global regulation mediated by TA systems has been proposed previously, but our work provided first convincing, comprehensive experimental evidence in favour of this hypothesis. One of the basic properties of an efficient regulatory machinery is its ability to efficiently switch between active and inactive states. Prior to our study the potential of reversible activation of TA systems remained unknown. We proposed a common switching mechanism based on antitoxin transcript resistance to toxin cleavage and provided experimental evidence in favour of such regulation. In conclusion, our study clarified several important and previously unresolved issues regarding the regulatory role of TA systems in bacteria, bringing us closer to understanding these most interesting global regulatory switches.

Reference:

1. Bukowski M, Lyzen R, Helbin WM, Bonar E, Szalewska-Palasz A, Wegrzyn G, Dubin G, Dubin A, Wladyka B (2013) A regulatory role for Staphylococcus aureus toxin-antitoxin system PemIKSa. *Nature Communications* **4**: 2012. doi:10.1038/ncomms3012.

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