SUPERFAST EVOLUTION OF BACTERIAL RESISTANCE TO BETA-LACTAM ANTIBIOTICS MEDIATED BY BACTERIAL DNA RECOMBINATION

By

LE ZHANG

Institute for Biomedical Materials & Devices

Faculty of Science

Supervisors:

Prof. Dayong Jin, Prof. Elizabeth Harry, Prof. Antoine van Oijen,

Dr. Yuen Yee Cheng, and Dr. Qian Peter Su

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Certificate of Original Authorship

I, Le Zhang declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the IBMD, Faculty of Science at the University of Technology Sydney. This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literatures used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

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List of Publications

Research papers:

- [1] Jin D*, Xi P*, Baoming Wang, **Zhang L**, Enderlein J, van Oijen AM. Nanoparticles for super-resolution microscopy and single-molecule tracking. Nature Method. 2018, 15: 415-423.

- [2] Tingting Chen, Anna B. Liu, Shili Sun, Nadim J. Ajami, Matthew C. Ross, Hong Wang, **Le Zhang**, Kenneth Reuhl, Koichi Kobayashi, Janet C. Onishi, Liping Zhao, Chung S. Yang*. Green Tea Polyphenols Modify the Gut Microbiome in db/db Mice as Co-Abundance Groups Correlating with the Blood Glucose Lowering Effect. Molecular nutrition & food research. 2019, 63: 1801064.

- [3] **Le Zhang**, Qian Peter Su, Zhichao Kang, Yuen Yee Cheng, Yan Liao, Nural Cokcetin, Amy L. Bottomley, Qiongfang Li, Iain Duggin, Andrew Robinson, Elizabeth J. Harry, Antoine v. Oijen, Dayong Jin*. Superfast bacterial evolution of resistance to β-lactam antibiotics mediated by bacterial DNA recombinases. Science. 2020. (Submitted).

Abstract

The emergence of antibiotic resistance is a global problem. Many studies show that sub-lethal concentration of antibiotic exposure or transit exposure to antibiotics can induce the formation of persistence or tolerance; whereas, cyclic exposure (usually 8-17 days) of antibiotics promotes the accumulation of bacterial adaptive mutations in persisters towards the subsequent evolution of resistance. However, the antibiotics induce mutagenesis that damage bacterial DNA has been poorly understood. Notably, the induction of SOS response has always been believed to aid bacterial propagation defense against antibiotic lethality, which requires the activation of SOS-promoting *recA*. A recent study implicated the essential role of RecA in the evolution of resistance to fluoroquinolones antibiotics, but it is unclear whether this is a conserved mechanism of resistance in response to different antibiotic classes.

RecA has been considered as a drug target to suppress the induction of SOS response towards the evolution of resistance caused by the broad-spectrum fluoroquinolone antibiotics. Here, we report that single exposure of β-lactam antibiotics can trigger a superfast evolution of resistance in *recA* deletion *E. coli* strain, independent to the SOS response. This type of single exposure causes gene mutations on an uncharacterized gene *pinR*, and its encoded protein may be involved in DNA recombination. Moreover, single or intermittent treatment of β-lactam antibiotics fails to induce the resistance in the *pinR* deletion *E. coli* strain. This work highlights the antagonistic role among DNA recombinases in the emergence of antibiotic resistance, and demonstrates that loss of *recA* increases the rate of resistance to β-lactam antibiotics, but PinR is likely to be a novel drug target.

Key words: Antibiotic tolerance, heritable resistance, RecA, *pinR*, *ampC*,

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