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Alanine enhances aminoglycosides-induced ROS production by metabolic regulation

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Metabolite-enabled killing of antibiotic-resistant pathogens by antibiotics is an attractive strategy to manage antibiotic resistance. Our previous study demonstrated that alanine or/and glucose increased the killing efficacy of kanamycin on antibiotic-resistant bacteria, whose action is through up-regulating TCA cycle, increasing proton motive force and enhancing antibiotic uptake. Despite the fact that alanine altered several metabolic pathways, other mechanisms could be potentially involved in alanine-mediated kanamycin killing of bacteria which remain to be explored. In the present study, we adopted proteomic approach to analyze the proteome changes induced by exogenous alanine. Our results revealed that the expression of three outer membrane proteins was altered and the deletion of nagE and fadL decreased the intracellular kanamycin concentration, implying their possible roles in mediating kanamycin transport. More importantly, the integrated analysis of proteomic and metabolomic data pointed out that alanine metabolism could connect to riboflavin metabolism that provides the source for reactive oxygen species (ROS) production. Functional studies confirmed that alanine treatment together with kanamycin could promote ROS production that in turn potentiates the killing of antibiotic-resistant bacteria. Further investigation showed that alanine repressed the transcription of antioxidant-encoding genes, and alanine metabolism to riboflavin metabolism connected with riboflavin metabolism through TCA cycle, glucogenesis pathway and pentose phosphate pathway. Our results suggest a novel mechanism by which alanine facilitates kanamycin killing of antibiotic-resistant bacteria via promoting ROS production.

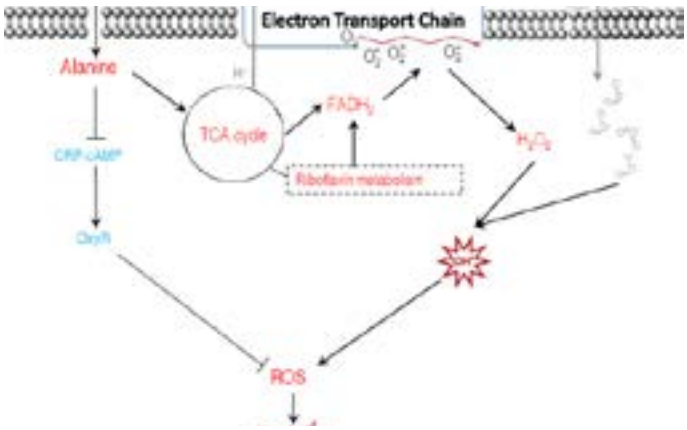

Figure: Proposed model for the dual roles of alanine in facilitating kanamycin to kill antibiotic-resistant bacteria

Recent Publications:

1. Jin-zhou Ye, Xiang-min Lin, Zhi-xue Cheng, Yu-bin Su, Wan-xin Li, Far-man Ali, Jun Zheng and Bo Peng (2018) Identification and efficacy of glycine, serine and threonine metabolism in potentiating kanamycin-mediated killing of Edwardsiella piscicida. Journal of Proteomics 183:34-44.

2. Dan-feng Zhang, Jin-zhou Ye, Hong-hou Dai, Xiang-min Lin, Hui Li and Xuan-xian Peng (2018) Identification of ethanol tolerant outer membrane proteome reveals OmpC-dependent mechanism in a manner of EnvZ/OmpR regulation in Escherichia coli. Journal of Proteomics 179:92-99.

3. Su Yu-Bin, Peng Bo, Li Hui, Cheng Zhi-Xue, Zhang Tian-Tuo, Zhu Jia-Xin, Li Dan, Li Min-Yi,Ye Jin-Zhou, Du Chao-Chao, Zhang Song, Zhao Xian-Liang, Yang Man-Jun and Peng Xuan-Xian (2018) Pyruvate cycle increases aminoglycoside efficacy and provides respiratory energy in bacteria. Proceedings of the National Academy of Sciences of the United States of America 115(7):E1578-E158.

4. Ye Jin-Zhou, Su Yu-Bin, Lin Xiang-Min, Lai Shi-Shi, Li Wan-Xin, Ali Farman, Zheng Jun and Peng Bo (2018) Alanine enhances aminoglycosides-induced ROS production as revealed by proteomic analysis. Frontiers in Microbiology 9(29):1-14.

5. Peng Bo ,Ye Jin-zhou, Han Yi, Zeng Li, Zhang Jian-ying and Li Hui (2016) Identification of polyvalent protective immunogens from outer membrane proteins in Vibrio parahaemolyticus to protect fish against bacterial infection. Fish & Shellfish Immunology 54:204-210.

Biography

Ye Jinzhou is passionate about metabolic regulation of bacterial resistance. During his PhD and Postdoctoral periods, he devoted himself to studying the metabolic regulation mechanism in the process from tolerant to resistant.

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