15th International Conference on

Metabolomics and Systems Biologys

August 29-30, 2019 | Vienna, Austria

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Alanine exerts immunomodulatory functions by promoting phagocytosis but limiting tissue injury

Statement of the Problem: Many infectious pathogens are susceptible to killing by antibiotics; however, mechanisms exist whereby susceptible pathogens as well as commensal bacteria can acquire resistance to antibiotics, especially after long-term, high-dose, or otherwise inappropriate exposure to one or more growth-inhibiting or cytotoxic drugs. This is the rational explanation for the recent surge in appearance of multidrug-resistant (MDR) bacterial strains, especially in the hospital environment, leading to increased human mortality. Therefore, new drugs and/or approaches are needed for treating such infections in the clinic. One possible approach would be to enhance the innate immune response of the infected host, recruiting endogenous host defense mechanisms to kill bacterial pathogens in a relatively risk-free manner.

Methodology & Theoretical Orientation: A systems biological approach was used to examine the host-bacterium interaction with the goal of identifying agents that could enhance the innate response to pathogens but limit tissue injury.

Findings: High levels of L-alanine promote phagocytosis of clinically-relevant pathogens. And more importantly, the downstream catabolite, palmitic acid could attenuate the tissue injury by excessive immune response through downregulating pyroptosis.

Conclusion & Significance: Host clearance of multidrug-resistant microbes is strongly associated with metabolic states, and that specific metabolic profiles are correlating with certain host defense strategy. Our study proposed a novel approach to identify metabolic modulator through investigation of metabolomics, by which crucial modulators can be used for therapeutic purpose..

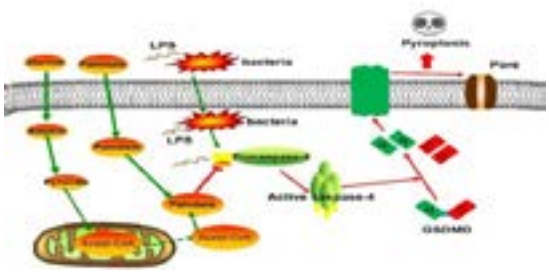

Figure: Proposed model of alanine in attenuating pyroptosis. Alanine or palmitate outcompete LPS on the binding of caspase-4, thus attenuating the downstream activation of GSDMD

Recent Publications:

1. Su Y B, Peng B, Li H, Cheng Z X, Zhang T T, Zhu J X, Li D, Li M Y, Ye J Z, Du C C, Zhang S, Zhao X L, Yang M J and Peng X X (2018) Pyruvate cycle increases aminoglycoside efficacy and provides respiratory energy in bacteria. Proc Natl Acad Sci USA 115(7):E1578-E1587.
2. Ye J Z, Su Y B, Lin X M, Lai S S, Li W X, Ali F, Zheng J and Peng B (2018) Alanine enhances aminoglycosides-induced ROS production as revealed by proteomic analysis. Front Microbiol 9(29).
3. Ye J Z, Lin X M, Cheng Z X, Su Y B, Li W X, Ali F, Zheng J and Peng B (2018) Identification and efficacy of glycine serine and threonine metabolism in potentiating kanamycin-mediated killing of Edwardsiella piscicida. J Proteomics 183:34-44.
4. Cheng Z X, Gong Q Y, Wang Z, Chen Z G, Ye J Z, Li J, Wang J, Yang M J, Ling X P and Peng B (2017) Edwardsiella tarda tunes tricarboxylic acid cycle to evade complement-mediated killing. Front Immunol 8:1706
5. Peng B, Su Y B, Li H, Han Y, Guo C, Tian Y M and Peng X X (2015) Exogenous alanine or/and glucose plus kanamycin kills antibiotic-resistant bacteria. Cell Metab 21(2):249-261.

Biography

Bo Peng has his expertise in metabolic regulation of antibiotic resistance. His research focuses on the elucidation of the metabolic features antibiotic-resistant bacteria. He proposed that antibiotic-resistant bacteria have their metabolomes, naming antibiotic-resistance metabolome (ARM).

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