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NaCl promotes antibiotic resistance by reducing redox states in *Vibrio* alginolyticus

The development of antibiotic resistance in *Vibrio alginolyticus represents* a threat to human health and fish farming. Environmental NaCl regulation of bacterial physiology is well documented, but whether the regulation contributes to antibiotic resistance remains unknown. To explore this, we compared minimum inhibitory concentration (MIC) of *V. alginolyticus* cultured in different media with 0.5% to 10% NaCl, and found that the MIC increased as the NaCl concentration increased, especially for aminoglycoside antibiotics. Consistent with this finding, internal NaCl also increased, while intracellular gentamicin level decreased. GC-MS-based metabolomics showed different distributions of pyruvate cycle intermediates among 0.5%, 4% and 10% NaCl. Differential activity of enzymes in the pyruvate cycle and altered expression of Na(+)-NQR led to a reducing redox state, characterized by decreased levels of NADH, proton motive force (PMF) and ATP. Meanwhile, NaCl negatively regulated PMF as a consequence of the reducing redox state. These together are responsible for the decreased intracellular gentamicin level with the increased external level of NaCl. Our study reveals a previously unknown redox state-dependent mechanism regulated by NaCl in *V. alginolyticus* that impacts antibiotic resistance.

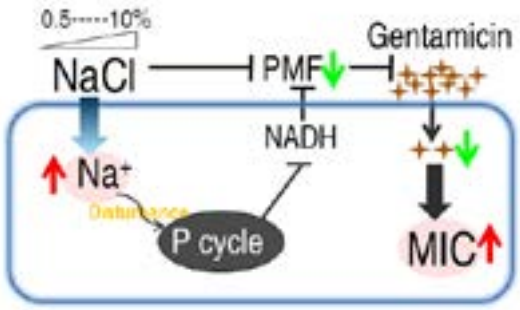

Figure: V. alginolyticus resistance to aminoglycoside antibiotics is affected by NaCl concentration through a redox state-dependent mechanism. It proceeds by affecting the activity of the P cycle enzymes to reduce NADH generation. This occurs when the external NaCl impacts membrane potential to regulate PMF production directly, thereby leading to a reduction in antibiotic uptake and elevation in bacterial MIC

Recent Publications:

1. Peng B, Su YB, Li H, Han Y, Guo C, Tian YM, Peng XX*. (2015) Exogenous alanine and/or glucose plus kanamycin kills antibiotic-resistant bacteria. Cell Metab. 21(2):249-261.
2. Su YB, Peng B, Li H, Cheng ZX, Zhang TT, Zhu JX, Li D, Li MY, Ye JZ, Du CC, Zhang S, Zhao XL, Yang MJ, Peng XX*. (2018) Pyruvate cycle increases aminoglycoside efficacy and provides respiratory energy in bacteria. PNAS 115 (7) E1578-E1587.
3. Yang J, Zeng ZH, Yang MJ, Cheng ZX, Peng XX, Li H*. (2018) NaCl promotes antibiotic resistance through reducing redox states in *Vibrio alginolyticus*. Environmental Microbiology, 20(11):4022-4036
4. Yang MJ, Cheng ZX, Jiang M, Zeng ZH, Peng B, Peng XX, Li H*. (2018) Boosted TCA cycle enhances survival of zebrafish to *Vibrio alginolyticus* infection. Virulence 9(1):634-644
5. Li H, Huang X#, Zeng Z, Peng XX, Peng B*. (2016) Identification of the interactome between fish plasma proteins and *Edwardsiella tarda* reveals tissue-specific strategies against bacterial infection. Int J Biochem Cell Biol. 78:260-267

Biography

Hui Li is a Professor, School of Life Sciences, Sun Yat-Sen University, China. She received her Ph.D. from Sichuan University, China and studied at Sun Yat-sen University,China as a postdoctoral fellow. Her research focuses on functional metabolomics for antibiotic resistance, which have recently been published in Cell Metabolism and PNAS.

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