

The Human/Bacterial Arms Race for Iron

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Transferrin maintains free human serum ferric ion concentration at 10^{-24} M. Pathogenic bacteria compete against this thermodynamic limit through clever coordination chemistry to obtain iron from their human host. It is difficult to overestimate the significance of iron as a limiting nutrient in microbial growth: enhancement of pathogenicity of 4 to 7 **orders of magnitude** are seen when iron is supplemented. Powerful and selective iron chelators (siderophores) are produced and secreted in response to iron deficiency. These are taken up by membrane transporters.

Spectacular advances have taken place in recent years in understanding the recognition and transport processes involved in siderophore-mediated iron acquisition. In the last few years siderocalin, a protein of the human innate immune system has been found to interrupt siderophore mediated iron transport of pathogenic bacteria.¹ Pathogens such as *Bacillus anthracis* (anthrax) produce “stealth” siderophores that are designed to evade this protein.² The production of different types of siderophores correlates with the different life cycles of *B. anthracis*. This seems part of a general pattern in which the more pathogenic type or stage of a bacterium correlates with the production of a stealth siderophore. Furthermore, there is recent evidence of a human siderophore,³ which will be discussed.

Iron and Bacterial Infections

- 1600's: To treat the Earl of Gloucester's gouged out eyes: "I'll fetch some flax and whites of eggs to apply to his bleeding face"
- 1850's: A. Trousseau, a Parisian Professor of Clinical Medicine warns his students against administrating an iron preparation to TB patients



¹ D. Goetz, M. Holms, N. Borregaard, M. Bluhm, K. Raymond and R. Strong, “The Neutrophil Lipocalin NGAL is a Bacteriostatic Agent that Interferes with Siderophore-Mediated Iron Acquisition.” *Mol. Cell* **2002**, *10*, 1033-1043.

² A. Zawadzka, R. Abergel, R. Nichiporuk, U. Andersen and K. Raymond, “Siderophore-mediated iron acquisition systems in *Bacillus cereus*: identification of receptors for anthrax virulence-associated petrobactin,” *Biochemistry* **2009**, *48*, 3645–3657.

³ G. Bao, M. Clifton, T. Hoette, K. Mori, S. Deng, A. Qiu, M. Viltard, D. Williams, N. Paragas, T. Leete, R. Kulkarni, X. Li, B. Lee, A. Kalandadze, A. Ratner, J. Pizarro, K. Schmidt-Ott, D. Landry, K. Raymond, R. Strong and Jonathan Barasch, “Iron traffics in circulation bound to a siderocalin (Ngal)–catechol complex,” *Nature Chemical Biology*, **2010**, *6*, 602-609.