Metal-related antimicrobials

Historically, some unpleasantly hazardous metals have been used to treat infections, such as mercury for syphilis, arsenic and antimony for Leishmania. In agriculture, copper sulphate in Bordeaux mixture is an effective fungicide for treating vines, and hospital trusts have replaced steel fixtures and fittings with copper ones, since copper surfaces (unlike those containing iron) are antimicrobial barriers. A range of products contain metal chelants such as Ethylene Diamine Tetra Acetic acid (EDTA) with preservative, antimicrobial action. A well-known shampoo, which generates multiple billions of dollars of revenue each year, contains Zinc Pyrithione (ZPT) which interferes with the iron handling circuitry of fungi through an intricate sequence of biochemical interactions which also involve copper[1]. ZPT treats dandruff which is triggered by the fungal microflora of the scalp. But there is a much longer history of using metals to fight microbes, because immune systems have evolved to exploit metals to combat infections. This is emerging as a new sub-discipline called nutritional immunity[2].

Iron often limits life, from restricting primary productivity in the oceans to a most prevalent human dietary deficiency, anaemia[3,4]. Microbial pathogens fight to obtain this valuable element from hosts, often releasing iron scavenging siderophores. This has triggered an evolutionary arms race fought on a battle ground of iron, with hosts producing defensive siderocalins to bind siderophores, in turn selecting for stealth siderophores which the siderocalins fail to recognise, combatted by stealth siderocalins from adapted hosts and so on. Host immune cells such as macrophages engulf microbes whereupon a specialised protein, Natural Resistance Associated with Macrophage Protein 1 (NRAMP1), helps to kill the entrapped invader. Some years after its discovery, NRAMP1 was found to pump vital metals such as iron from the microbe-containing compartment, presumably to starve it of essential elements. The compartment subsequently fills with a toxic dose of copper. Calprotectin is liberated from other immune cell types, classes of neutrophils, to scavenge zinc and manganese, starving microbes of these essential elements[9].

As details of the cell biology of metals are uncovered, it becomes possible to tailor more precise antimicrobial treatments by design, not just stumbled upon empirically or by evolution. Metals, and by implication chelants, ionophores, and agents that interfere with the metal-handling systems of microbes and hosts, are increasingly recognized among the promising candidates for new antimicrobials[5]. A BBSRC NIBB event in November 2015 highlighted advances in understanding metal-handling systems of microbes and hosts, and explored why metals are a microbial “Achilles heel”, and encourage innovation at this academia-business interface. This event brought together multiple research communities and revealed opportunities to collaborate, for example to tackle the scourge of antimicrobial resistance.

1. *Antimicrob. Agents Chemother*. (2011) 55, 5753–5760.
2. *Nature Rev. Micro.* (2012) 10, 525- 537.
3. *Nature Geoscience* (2013) 6, 701–710.
4. *Nature* (1999) 397, 694-697.
5. *Nature* (2015) 521 402.

OUTCOME: The workshop highlighted multiple opportunities arising from increased communication between the diverse communities exploiting and developing metal related antimicrobials, investigating the cell biology of metals and nutritional immunity. Robert Poole, University of Sheffield, edited a dedicated volume of *Advances in Microbial Physiology* “Microbiology of Metal ions” https://www.elsevier.com/books/microbiology-of-metal-ions/author/978-0-12-812386-7

Metals

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