Metal-related antimicrobials: targeting the Achilles heel of bad bugs

A BBSRC Metals in Biology NIBB scoping workshop highlighted advances in the understanding of metal-handling systems of microbes and hosts, with the aim of improving collaboration to tackle antimicrobial resistance.

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There is a long history of using metals to fight microbes[1]. Historically, some unpleasantly hazardous metals have been used to treat infections, such as mercury for syphilis, as well as arsenic and antimony for Leishmania. In agriculture, copper sulphate in Bordeaux mixture — identified in the 1880s — is an effective fungicide for treating diseased vines. More recently, steel fixtures and fittings in hospitals have been replaced with copper ones, since copper surfaces (unlike those containing iron) are antimicrobial barriers.

A range of products with antimicrobial properties currently on the market contain metal chelants such as ethylene diamine tetra acetic acid (EDTA). A well-known anti-dandruff shampoo, which generates multiple billions of dollars of revenue each year, contains zinc pyrithione (ZPT). This compound treats dandruff that is triggered by the fungal microflora of the scalp by interfering with the iron-handling circuitry of fungi through an intricate sequence of biochemical interactions (which also involve copper)[2].

Metals can act as antimicrobials because broadly speaking, host immune systems have evolved to exploit metal availability to combat infections. Hosts protect against infection through the sequestration of nutrient metals (that are essential to microbes – a concept called nutritional immunity[3] – that has garnered renewed attention in recent years**.** In turn Microbial pathogens fight to obtain valuable elements such as iron from hosts, often releasing iron-scavenging siderophores.

This triggers an evolutionary arms race fought on a battle ground of iron, with hosts producing defensive siderocalins to bind microbial siderophores, the microbes in turn selecting for stealth siderophores that are not recognised by siderocalins, combatted by stealth siderophores or enterochelin-like molecules released from adapted hosts.

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. Neurophils release calprotectin to scavenge zinc and manganese, starving microbes of these essential elements.

As details of the cell biology of metal availability 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[4].

At the BBSRC Metals in Biology NIBB scoping workshop we highlighted new knowledge of microbe and host metal- handling systems and explored why metal availability is the microbial Achilles heel. This event brought together multiple research communities to encourage innovation at this academia-business interface. and revealed opportunities to collaborate to help tackle the scourge of antimicrobial resistance.

1. *The Physicochemical Basis of Therapy (1979*) 385-442
2. *Antimicrob. Agents Chemother*. (2011) 55, 5753-5760
3. *Nature Rev. Micro.* (2012) 10, 525-537
4. *Nature* (2015) 521, 402

OUTCOME: The workshop highlighted 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,* volume 70 'Microbiology of Metal ions'
https://www.elsevier.com/books/microbiology-of-metal-ions/author/978-0-12-812386-7

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