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Introduction: Metals in Biology

*METALS AT THE HOST-PATHOGEN INTERFACE**

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This seventh Metals in Biology Thematic Series deals with the metal-based interactions of mammalian hosts with pathogens. Both pathogens and hosts have complex regulatory systems for metal homeostasis. Understanding these provides strategies for fighting pathogens, either by excluding essential metals from the microbes, by delivery of excess metals to cause toxicity, or by complexing metals in microorganisms. Intervention is possible by delivery of complexing reagents or by targeting the microbial regulatory apparatus.

This, the seventh in the Metals in Biology Thematic Series (1–6), is focused on metals in host-pathogen interactions. In the way of a general introduction, it is important to reiterate that biochemistry is not just about proteins, lipids, carbohydrates, and nucleic acids. One estimate is that 40% of the proteins crystallized to date have a metal bound somewhere thought to be relevant to function (7). In the world of micronutrient biochemistry, it has long been known that Na, K, Mg, Ca, V, Cr, Mn, Fe, Co, Cu, Zn, Se, and Mo are critical to mammals (although a role for Cr in glucose tolerance is still unclear). Toxicologists have known since the time of ancient Greece (8) that metals can be toxic (*e.g.* Pb), and a list of potentially toxic metals would include As, Be, Cd, Cr, Pb, Hg, Ni, Fe, Cu, Mg, Mn, Mo, Se, Al, Bi, Ga, Au, Li, Pt, Sb, Ba, In, Ag, Te, Th, Se, Ti, U, and V (9). Of course, the reader will note that some of these are also essential. The fact is that, as all toxicologists know, the dose makes the poison (8), and chemicals, including metals, can be both beneficial and toxic, depending upon the dose, as well as the form they are in. For instance, the free levels of metals such as Fe and Cu are kept extremely low in cells.

This Thematic Series deals with how metals are involved in disease, from a number of aspects, both detrimental and beneficial to the host. Thus, both mammals and pathogens are utilizing metals in this war between them at the host-pathogen interface. The practical goal is to understand these interactions and manipulate them to the benefit of the hosts, *i.e.* animals and humans. Accordingly, eight Minireviews are included, dealing with aspects of this conflict with pathogens.

The first Minireview, by Garcia-Santamarina and Thiele (10), deals with Cu and fungal pathogenesis. Fungi have enzymes they use in Cu transport and homeostasis. However, mammalian hosts have the ability to mount antifungal responses through the accumulation of toxic Cu within the phagolysosomes of their innate immune cells and to limit Cu in other infectious niches such as the brain. The authors propose that chemical modulation of fungal Cu homeostasis is a possible strategy in treating infection.

The second Minireview in the Thematic Series also deals with Cu, as well as Zn, in the context of innate immune defense against bacterial pathogens. Djoko *et al.* (11) discuss the toxicity of Cu and Zn to bacteria. As in the first Minireview with fungi (10), attenuation of bacterial metal detoxification systems reduces the infectivity of a number of bacteria, and many of the involved biochemical systems are now understood in some detail.

The third Minireview, by Darwin (12), also deals with aspects of Cu and a specific bacterium, *Mycobacterium tuberculosis*. Transporters and regulatory proteins in the organism have been characterized and are reviewed. As in the first two Minireviews in the Thematic Series, there is potential for metal-based intervention in an infectious disease.

Our fourth Minireview, by Koh and Henderson, also deals with Cu and infection (13). Siderophores have long been known in microorganisms, mainly characterized by Fe binding. However, multiple Cu-binding siderophores have been characterized in pathogenic *Escherichia coli*. These siderophores are protective, in general, acting as Cu scavengers, and can act as a countermeasure against superoxide-based host defenses.

The fifth Minireview in the Series, by Schmidt (14), deals with another transition metal, Fe. The protein hepcidin was originally characterized for its antimicrobial activity. Hepcidin, which plays a critical role in Fe homeostasis, is up-regulated by Fe, by inflammation, and by infection with pathogens. Some of the mechanisms of regulation of hepcidin expression are discussed. Hepcidin is accepted to be a master regulator of vertebrate Fe metabolism and homeostasis, and expression allows for sufficient concentrations of Fe to be made available for the host but leads to sequestration of this metal from infectious pathogens.

The sixth article in the Series, by Wessling-Resnick (15), discusses Fe and Mn during the course of infection. Nramp1, Nramp2, and other Fe and Mn (and Zn) transporters function in infected mammalian hosts to protect them. The overall strategy is one of nutritional warfare, that of starving the invading pathogen of essential elements.

The seventh Minireview in this Series, by Zackular *et al.* (16), continues the concept of nutritional deprivation of pathogens as a host strategy. S100 proteins are secreted proteins, highly

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regulated. During infection, they act to sequester Zn and Cu ions, as well as Mn. Thus, these proteins can be involved in pro-inflammatory and anti-inflammatory responses.

Our eighth and final Minireview, by Wareham *et al.* (17) involves a different perspective, that of antimicrobial agents that act by releasing carbon monoxide to complex metals and kill microorganisms. The CO is contained in metal clusters that target microbes and then release the CO. Not only are microbial hemoproteins targets, but so are bacterial NO synthases, heme oxygenases, and other enzymes.

In summary, we see a wide variety of metal-based interactions between pathogens and their hosts. In some cases the host strategy is to deplete a metal in the pathogen, whereas in others it is to overload it with a toxic level. The considerable importance of metal to the outcome of the host-pathogen interaction underscores the potential value of manipulating these systems in an effort to develop new intervention strategies for the treatment of infectious diseases.

We hope that you will enjoy reading these Minireviews and learn some new things about this field. The next Metals in Biology Thematic Series will feature Fe(II)/α-ketoglutarate-dependent dioxygenases and is scheduled to be published later this year.

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