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Competition for Metals among Microbes and Their Host

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Abstract

Both microorganisms and their eukaryotic hosts must acquire and compete for metal ions, often from scarce environmental sources, for their metabolism. Since metal ions can also be toxic, their cellular levels must be precisely regulated. The battle over these nutrients may affect the balance between microbe and host, impacting inflammatory responses and determining the outcome of this relationship during colonization and disease. This chapter examines aspects of the thrust and parry among bacteria residing in a host, and between bacteria and their host over metals.

Introduction

Microbial metabolism requires the acquisition of numerous metals from environmental sources. Many microbes reside within a niche, such as the mammalian respiratory or urinary tracts, where these nutrients are available in extremely limited quantities. To be successful in such a niche where many species coexist, microbes must thus compete with one another to obtain required metals. Microbes that reside within a host face an additional challenge; namely, they must compete for these nutrients with their host, which may require the same metals for its metabolism. The most thoroughly studied of these biological battles over metals involves the acquisition of iron (Fe), although there is a growing appreciation over the struggle for manganese (Mn), zinc (Zn), and copper (Cu) among microbes and their hosts. Bacteria, for example, utilize iron for electron transport, amino acid synthesis, DNA synthesis, and protection from superoxide radicals. Under aerobic conditions, iron is primarily in the ferric [Fe (III)] oxidation state and readily forms insoluble complexes. Sequestration of scarce quantities of soluble iron is a prototypical protective response against invading bacteria, mediated by the Fe-binding proteins transferrin and lactoferrin and the storage protein ferritin. In contrast to Zn supplementation, which can

be protective, nutritional supplementation with iron and Fe overload states is associated with an increased risk for certain bacterial infections. Additionally, in response to infection, the host increases production of hepcidin peptide hormone, which acts to block Fe uptake from the gut and the release of Fe stores, thereby restricting Fe levels in the bloodstream (Ganz 2009). To acquire iron within the host and counteract Fe binding by the host, bacteria must develop ways of scrounging iron directly from host sources or secrete siderophores that bind ferric iron with greater affinity. Growth limitation through the sequestration of essential elements or nutrients has been termed "nutritional immunity" and is now known to extend beyond Fe deprivation to other metals, including zinc and manganese (Hood and Skaar 2012).

Cooperation and Competition among Bacteria for Metals

The scavenging of scarce amounts of ferric iron may provide an advantage to siderophore-expressers by depleting the availability of this limiting, required nutrient for competitors. Siderophore production may also be an altruistic or cooperative trait, where the cost of production for the individual is outweighed by the benefit to the group when other individuals can take up the siderophore-iron complex (Griffin et al. 2004). The fitness impact of siderophore-mediated cooperation on microbial ecology has been examined in detail using pyoverdin secreted by *Pseudomonas aeruginosa* (Buckling et al. 2007). These *in vitro* studies demonstrate that among closely related populations (kin selection), cooperative utilization of a close relative's siderophore is indeed favored. The *in vivo* relevance of these observations was subsequently shown in a wax moth larvae infection model, where a combination of pyoverdin-cooperating *P. aeruginosa* strains were more virulent compared to other combinations (Buckling et al. 2007).

In turn, microbes that are noncooperating cheats ("cheaters") avoid the energetic cost of siderophore production but are able to obtain iron by taking up siderophores made by their neighbors. Buckling et al. (2007) predict that cheats would be especially more fit under greater Fe-limiting conditions. *Neisseria gonorrhoeae*, for instance, produces no known siderophores but depends on host-derived, Fe-binding proteins, including transferrin and lactoferrin, for its iron (Strange et al. 2011). In addition, the gonococcus has been shown to acquire its iron from siderophores produced by other bacteria (termed "xenosiderophores"), such as the common catecholate class of siderophores. In this study, xenosiderophore-mediated growth was shown to be dependent on the *fbpABC* operon encoding the same ABC transport system that enables the gonococcus to transport iron into the cell from host Fe-binding sources. An additional strategy for microbes to conserve the energy required for Fe uptake is to cease production of siderophores when these are no longer needed. In fact, studies from the *P. aeruginosa* wax moth larvae infection model demonstrate

that cheaters which no longer produce pyoverdin arise *de novo* under conditions where they have a selective advantage. The full extent of competitive and cooperative interactions involving Fe acquisition in extensive and heterogeneous microbial communities, such as within the mammalian gut, are likely to be complex and have yet to be fully explored.

Microbial competition for zinc *in vivo* has recently been demonstrated for the gut microbe *Campylobacter jejuni*. Expression of a high-affinity ABC transporter for Zn uptake was required for Campylobacter survival in chicken intestines in the presence of a normal microbiota, but not when chickens were reared under germ-free conditions with a more restricted microbiota. Differences in survival correlated with the presence of numerous Zn-binding proteins in the intestines of conventional chicks compared to the number in limited-microbiota chicks. This study concluded that the microbiota stimulates the production of host Zn-binding enzymes, which restrict the growth of bacteria that lack high-affinity Zn transporters (Gielda and DiRita 2012).

Bacterial Infection Induces Metal Ion-Sequestering Components of Innate Immunity

Host–pathogen interactions often begin with colonization of mucosal surfaces. These relationships are highly specific, as certain microbial species are found only in particular microenvironments. We previously reported the use of transcriptional microarrays to screen host genes whose expression in the murine nasal mucosa was affected by colonization with the Gram-positive bacterium *Streptococcus pneumoniae* (Nelson et al. 2005). In this study, the most upregulated gene in response to colonization was lipocalin 2 (Lcn2, also known as siderocalin or neutrophil gelatinase-associated lipocalin, NGAL), whose expression was increased up to 65-fold during colonization as measured using qRT-PCR. Western analysis showed that Lcn2 was secreted into airway surface fluid in colonized animals. Immunohistochemical analysis localized Lcn2 expression primarily to Bowman's glands, which secrete Lcn2 into the nasal lumen where it bathes the colonized mucosa. Similar results were observed during colonization with the Gram-negative bacterium *Haemophilus influenzae*, suggesting that Lcn2 secretion is a general response to infection of the airways that may have a role in determining the establishment or maintenance of mucosal colonization (Nelson et al. 2005). Indeed, Lcn2 is induced by broad innate immune signals, including TLR4 stimulation and IL-1β (Chan et al. 2009).

Lcn2 contributes to antimicrobial defense by sequestration of a subset of microbial siderophores (Correnti and Strong 2012). Lcn2 specifically binds siderophores, such as the catecholate enterobactin (Ent), with an affinity similar to the *Escherichia coli* Ent receptor FepA; thus, it is able to compete with bacteria for Ent binding. Lcn2 is able to bind both ferric and aferric Ent, thereby depleting Ent from the microenvironment and inhibiting bacterial uptake

of Ent-bound iron (Abergel et al. 2008). As a result, Lcn2 is bacteriostatic. Bacterial growth can be restored by the addition of excess iron or Ent. In a murine sepsis model, serum Lcn2 is protective against an *E. coli* strain that requires Ent to obtain iron (Flo et al. 2004). Accordingly, Lcn2-deficient mice ($Lcn2^{-/-}$), which are otherwise healthy, succumb more readily to invasive *E. coli* infection. Conversely, co-injection of *E. coli* and a siderophore to which Lcn2 cannot bind is sufficient to cause lethal infection in $Lcn2^{+/+}$ mice.

As neither *S. pneumoniae* nor *H. influenzae* are known to produce or utilize siderophores, successful colonizers of the nasal passages appear to have evolved siderophore-independent mechanisms, such as the binding and utilization of host sources including heme, transferrin, and lactoferrin, to acquire essential iron and to evade the inhibitory effects of Lcn2. The Fe-sequestering effects of Lcn2 are likely an effective defense against Ent-dependent species in the mammalian respiratory tract. Indeed, high levels of Lcn2 correlate with increased survival of patients with Gram-negative bacterial pneumonia (Warszawska et al. 2013). In contrast, Lcn2 appears to be less of a determining factor in the composition of the gut flora where the Ent-expressing members of the Enterobacteriaceae family are abundant.

As is the case for ferric iron, the host also sequesters other metals required for microbial physiology during infection. To acquire zinc and manganese from the host reservoir, many bacterial species must express dedicated transport systems to compete for these metals. Virulence is often reduced when mutants of these Mn or Zn transporters are studied. Zinc is bound and sequestered from microbes when bound by albumin, 2-macroglobulin, and transferrin (Foote and Delves 1984; Moutafchiev et al. 1998). Additionally, the Zn status of the host affects immune functions (Knoell and Liu 2010; Nairz et al. 2010), and serum Zn levels are reduced upon infection or exposure to LPS, an effect that restricts availability of the metal to invasive microbes (Weinberg 1972; Liuzzi et al. 2005). Manganese is bound by apoferritin, lactoferrin, and transferrin (Macara et al. 1973; Lönnerdal et al. 1985; Davidsson et al. 1989; Critchfield and Keen 1992; Aschner and Gannon 1994; Moutafchiev et al. 1998). The extracellular protein calprotectin (a heterodimer of S100A8/S100A9 or calgranulin A and B), a major product of neutrophils that migrate to sites of inflammation, binds manganese and possibly zinc (Kehl-Fie and Skaar 2010). Abscesses formed in response to *Staphylococcus aureus* infection are devoid of manganese. However, in mice lacking calprotectin, these are replete with manganese and have an increased bacterial burden, suggesting that calprotectin-mediated Mn chelation protects against disease (Corbin et al. 2008). It has also been postulated that other S100 proteins contribute to antimicrobial activity by restricting the bioavailability of other metals. At the other end of the spectrum, zinc may be toxic and levels elevated during inflammation. It has been proposed that zinc, like copper, accumulates in phagosomes and may contribute to host defense against intracellular pathogens (Botella et al. 2012). Within the phagocytic cell, NRAMP1 modulates microbial access to iron,

manganese, and possibly zinc within vesicles. Thus, intracellular organisms must deal with cellular mechanisms that restrict survival through modulations of local metal concentrations. The scope of the battle with the host over levels of metals for microbial communities and interactions among the microflora *in vivo* has not yet been fully explored.

The Battle between Microbes and Host over Metals Affects Inflammatory Responses

A number of cell culture studies have shown siderophore-dependent effects (Bierer and Nathan 1990; Coffman et al. 1990; Autenrieth et al. 1991, 1995; Britigan et al. 1994, 1997, 2000; Hileti et al. 1995; Tanji et al. 2001; Lee et al. 2005; Paauw et al. 2009). Many, but not all, of these effects are due to Fe sequestration, and together these reports indicate that both Fe deficiency and excess affects immune function. For example, in cultured human respiratory epithelial cells, treatment with aferric Ent produces a dose-dependent increase in proinflammatory signals, such as secretion of the chemokine IL-8, which promotes an influx of neutrophils (Nelson et al. 2007). Similar effects on pro-inflammatory signaling have been attributed to the microbial siderophore deferrioxamine, where the effect of Fe chelation was ascribed to the activation of p38 and extracellular signal-regulated kinase pathways (Choi et al. 2004). Furthermore, siderophores are potent activators of hypoxia inducible factor-1 (HIF-1), a global transcriptional regulator that enhances myeloid function and cytokine release (Peyssonnaux et al. 2005). However, the contribution of HIF-1 to siderophore-triggered inflammation during infection is unknown.

Through its interaction with Ent, Lcn2 can act as a signaling molecule. Two potential receptors for Lcn2 have been identified: megalin and 24p3R (Devireddy et al. 2005; Hvidberg et al. 2005). Megalin is expressed in kidney tubules and mediates uptake of siderophore-bound complexes with iron through endocytosis (Bao et al. 2010a). 24p3R is widely expressed in tissues, including the lung, as well as in lymphoid and myeloid cells. Although 24p3R has been shown to internalize Lcn2 alone or Lcn2 bound to a siderophore and to modulate Fe homeostasis and apoptosis, these findings are controversial (Correnti et al. 2012). In respiratory epithelial cells, Lcn2 is internalized and potentiates the cytokine release triggered by aferric Ent. In contrast, ferric Ent (Fe-Ent) does not elicit significant IL-8 release. Thus, aferric Ent may be a proinflammatory signal for respiratory epithelial cells, permitting detection of microbial communities that have disturbed local Fe homeostasis. Lcn2 expression by the host amplifies this signal. This may be a mechanism for the mucosa to respond to metabolic signals (i.e., the depletion of ferric iron) of expanding microbial communities (i.e., the expression of increasing amounts of siderophores).

Perhaps due to the actions of Lcn2, successful pathogens do not typically depend solely on Ent for iron and have evolved to use alternative siderophores that do not bind to Lcn2, allowing iron to be acquired even in its presence. An example in which the relative contribution of different Fe-scavenging systems has been studied *in vivo* is the Gram-negative member of the Enterobacteriaceae family, *Klebsiella pneumoniae*. *K. pneumoniae* is an opportunistic pathogen capable of colonizing multiple mucosal surfaces, including the nasopharynx, urinary tract, and large intestine of humans; it is also a common cause of bacterial pneumonia, urinary tract infection, and sepsis (Bachman et al. 2011). Isolates of *K. pneumoniae* invariably produce Ent, and a subset produces additional siderophores, including yersiniabactin (Ybt), aerobactin, and salmochelin. Salmochelin is glycosylated Ent (Gly-Ent) encoded by the *iroA* locus in some isolates of *K. pneumoniae, Salmonella enteric*, and *E. coli* (Fischbach et al. 2006). This cluster encodes the Ent glycosylase IroB that blocks Lcn2 binding, IroC for export, IroN for import, IroE for linearization, and IroD to degrade Gly-Ent and release iron. Transformation of *E. coli* with the *iroA* locus is sufficient to allow for lethal infection in $Lcn2^{+/+}$ mice. Conversely, disruption of either the *iroC* exporter or *iroB* glycoslyase attenuates virulence in a mouse model of systemic *Salmonella* infection (Crouch et al. 2008).

To study each potential effect of Lcn2, Lcn2-deficient mice and *K. pneumoniae* mutants predicted to be susceptible to Lcn2-mediated Fe sequestration (*iroA ybtS* mutant) or inflammation (*iroA* mutant) or to not interact with Lcn2 (*entB* mutant) were compared in a *K. pneumoniae* colonization model (Bachman et al. 2009). During murine nasal colonization, the *iroA ybtS* double mutant was inhibited: *iroA, entB,* and *ybtS* mutants were not, and this inhibition was Lcn2 dependent. Therefore, either Gly-Ent or Ybt are sufficient to protect against Lcn2-mediated growth inhibition. However, colonization with the *iroA* mutant induced an increased influx of neutrophils compared to the *entB* mutant and this enhanced neutrophil response to Ent-producing *K. pneumoniae* was Lcn2 dependent. These findings indicate that Lcn2 has both proinflammatory and Fe-sequestering effects along the respiratory mucosa in response to bacterial Ent and may serve as a sensor of microbial Fe metabolism to modulate the host's response appropriately.

Metal Ion Acquisition As a Determining Factor in the Pathologic Features of Infection

To determine whether *K. pneumoniae* must produce Lcn2-resistant siderophores to cause disease, siderophore production was examined in clinical isolates ($n = 129$) from respiratory, urine, blood, and stool samples through genotyping and liquid chromatography mass spectrometry (Bachman et al. 2011). Three categories of *K. pneumoniae* isolates were identified: Ent(+) (81%), Ent(+) Ybt(+) (17%), and Ent(+) Gly-Ent(+) with or without Ybt (2%). The

expression of aerobactin was rare among clinical isolates of *K. pneumoniae*. Ent(+) Ybt(+) strains were significantly overrepresented among respiratory tract isolates ($p = 0.0068$). In *ex vivo* growth assays, Gly-Ent but not Ybt allowed evasion of Lcn2 in human serum, whereas siderophores were dispensable for growth in human urine. In a murine pneumonia model, an Ent(+) strain was an opportunistic pathogen that was completely inhibited by Lcn2 but caused severe, disseminated disease in $Lcn2^{-/-}$ mice. In contrast, an Ent(+) Ybt(+) strain was a frank respiratory pathogen, causing pneumonia despite Lcn2. However, Lcn2 retained partial protection against disseminated disease. Ybt, therefore, is a virulence factor that promotes lower respiratory tract infections through evasion of Lcn2 (Bachman et al. 2011) and leads to worsened survival from pneumonia (Lawlor et al. 2007). In addition to its role in Fe acquisition, Chaturvedi et al. (2012) report that Ybt secreted by uropathogenic *E. coli* facilitates bacterial infection by binding to copper and sequestering Cu(II). The removal of Cu(II) prevents catecholate-mediated reduction to the more toxic form Cu(I), which is able to generate reactive oxygen species and inactivate intracellular iron-sulfur clusters in bacteria.

The siderophores Ent, Gly-Ent, and Ybt are not functionally equivalent and differ in their abilities to promote growth in the upper respiratory tract, lungs, and serum. To understand how Lcn2 exploits functional differences between siderophores, isogenic mutants of an Ent(+) Gly-Ent(+) Ybt(+) *K. pneumoniae* strain were inoculated into $Lcn2^{+/+}$ and $Lcn2^{-/-}$ mice, and the pattern of pneumonia was examined (Bachman et al. 2012). Lcn2 effectively protected against the *iroA ybtS* mutant [Ent(+) Gly-Ent(–) Ybt(–)]. $Lcn2^{+/+}$ mice had small foci of pneumonia, whereas $Lcn2^{-/-}$ mice had many bacteria in the perivascular space. The *entB* mutant [Ent(–) Ybt(+) Gly-Ent(–)] caused moderate bronchopneumonia but did not invade the perivascular space that accumulated transferrin during infection. Accordingly, transferrin or serum blocked Ybt-dependent growth *in vitro,* a result that contrasts with experimental systems using other pathogens and growth conditions (Fetherston et al. 2010). Wild-type *K. pneumoniae* and its *iroA* mutant, which both produce Ent and Ybt, had a mixed phenotype, causing a moderate bronchopneumonia in $Lcn2^{+/+}$ mice and perivascular overgrowth in $Lcn2^{-/-}$ mice. These findings demonstrated that Ent promotes growth around blood vessels that are rich in the Fe-binding protein transferrin, but Ybt does not. Together, transferrin and Lcn2 protect these spaces in the lungs against all types of *K. pneumoniae* tested. Therefore, the way in which iron is acquired can be a determining factor as to where an organism is able to grow and cause disease.

Siderophores are also required for pulmonary infection by *Bordetella pertussis, Burkholderiea cenocepacia, Legionella pneumophila,* and *Yersinia pestis*, and several of these pathogens express multiple siderophores (Brickman et al. 2008; Allard et al. 2009; Fetherston et al. 2010). In the case of *Y. pestis,* which has a complex life cycle with stages of infection involving different tissues, the inability to produce Ybt also affected inflammation in the lungs and,

in this instance, shifted an intranasal infection route from a pneumonic to a systemic disease (Fetherston et al. 2010; Lee-Lewis and Anderson 2010). In addition, a *Y. pestis* Ybt mutant was completely avirulent by a subcutaneous route (bubonic plague), although a mutant defective in the Ybt system was fully virulent by an intravenous route (septicemic plague) (Fetherston et al. 2010). This indicates that the Ybt system is not essential for Fe acquisition (or non-iron effects) after *Y. pestis* enters the bloodstream. Ferrous transporters are another example of systems required for Fe acquisition in some host environments but not others. Again, *Y. pestis* provides an example: a *Y. pestis* strain with mutations in two ferrous transporters experienced a significant loss of virulence in a bubonic plague model but was fully virulent in a pneumonic plague model (Fetherston et al. 2012). The same pattern holds true for a strain with mutations in the two known Mn transporters, thus demonstrating that Mn transport mechanisms affect virulence in some host environments but not others (Fetherston et al. 2012). Again, these studies illustrate that the way in which essential metals are obtained can be a determining factor in the tissue tropism for infecting agents.

A recent study also demonstrated the importance of evasion of the Fe-dependent inhibitory effects of Lcn2 in the outcome of bacterial competition and in determining the composition of the microflora (Deriu et al. 2013). The non-pathogenic "probiotic" bacterium *E. coli* strain Nissle, which is equipped with multiple redundant Fe uptake systems, outcompetes *Salmonella* Typhimurium in a mouse model of acute colitis and chronic persistent infection. The success of *E. coli* strain Nissle is dependent on its ability to acquire iron in the gut, since mutants deficient in Fe uptake colonize the intestine but no longer reduce *S*. Typhimurium colonization. *S*. Typhimurium, however, is able to overcome the inhibitory effect of *E. coli* strain Nissle in $Lcn2^{-/-}$ mice. Deriu et al. (2013) concluded that Fe availability impacts *S*. Typhimurium growth and that in this example the beneficial action of probiotic bacteria is mediated by a reduction in intestinal colonization by pathogens like *S*. Typhimurium through competition for this limiting nutrient. Since many Ent-expressing members of the Enterobacteriaceae family normally reside in the gut lumen, a further implication is that inflammation increases the relative role of Lcn2 in modulating the flora in this environment. Interestingly, Nissle resembles uropathogenic *E. coli* strains. Genomic and metabolomic studies suggest that this subset of *E. coli* is generally more fit to colonize the Fe-limited environment of the bladder because of the expression and activity of additional siderophore systems (Henderson et al. 2009).

Detrimental Effects of Metals on Microbial Interactions

Despite the requirement for metals for normal microbial and host physiology, they may be extremely toxic when present in excessive amounts or under

certain environmental conditions. It appears that some organisms may take advantage of this situation and use the toxicity of certain metals for their own competitive success. For example, hydrogen peroxide is produced by *S. pneumoniae* as a byproduct of the activity of pyruvate oxidase (SpxB) under conditions of aerobic growth. Coculture with *S. pneumoniae* leads to a rapid decrease in viable counts of other bacterial species (Pericone et al. 2003). The addition of purified catalase or use of an *spxB* mutant prevents killing of other common inhabitants of the upper respiratory tract (including *H. influenzae, Moraxella catarrhalis*, and *Neisseria meningitidis*) in coculture experiments, suggesting that hydrogen peroxide may be responsible for this bactericidal activity. Production of hydrogen peroxide by *S. pneumoniae* has also been shown to have cytotoxic effects on human epithelial cells in culture and host tissue in animal models of pneumococcal disease. These antimicrobial and cytotoxic effects are thought to occur mainly through DNA damage from hydroxyl radicals ($OH^{\bullet}$) produced via the Fenton reaction: $H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-}$. Accordingly, the amount of ferrous iron (Fe^{2+}) available to associate with DNA is believed to be a rate-limiting factor in Fenton-reaction killing. At millimolar concentrations of hydrogen peroxide generated by the pneumococcus, killing is thought to involve inactivation of housekeeping enzymes, perhaps through oxidation of active site thiols. The remarkable ability of *S. pneumoniae* to avoid Fenton chemistry and escape lethal damage at the high concentrations of hydrogen peroxide it generates when grown aerobically allows it to outcompete species vying for the same niche (Pericone et al. 2000). There is now clinical and experimental evidence for this effect. As is the case for the pneumococcus, nasal colonization by *S. aureus* is a major predisposing factor for subsequent infection. Recent reports of increased *S. aureus* colonization and disease among children receiving pneumococcal vaccine implicate *S. pneumoniae* as an important competitor for the same niche (Bogaert et al. 2004). Studies in a mouse model showed that expression of catalase by *S. aureus* contributes to the survival of this pathogen in the presence of *S. pneumoniae* during nasal cocolonization (Park et al. 2008). Therefore, iron can mediate interspecies competition by enabling the toxic effects of reactive oxygen molecules produced by one bacterium on its neighbor.

Most antibiotics are derived from the natural products employed by microbes to target other microbes. Although antibiotics act primarily on a number of essential targets of microbial physiology, there is experimental evidence, albeit controversial, that a common effect of antibiotic stress is an increase in levels of reactive oxygen species which triggers damage through the Fenton reaction (Kohanski et al. 2007; Liu and Imlay 2013). There is also a growing appreciation for how microorganisms manipulate the type and amount of potentially toxic metal ions to survive oxidative stress. *E. coli*, for example, can adapt to increased levels of hydrogen peroxide through the exchange of metals (Sobota and Imlay 2011). This mechanism involves Mn import and Fe depletion, converting a key enzyme in the pentose-phosphate pathway from Fenton

chemistry susceptible to resistance. However, replacing iron with the wrong metal can also be disastrous. Gallium, a metal structurally similar to iron but unable to perform its redox chemistry, disrupts *P. aeruginosa* Fe metabolism and protects mice from lethal pneumonia (Kaneko et al. 2007). Excess zinc may also be toxic to bacteria. Zinc(II) concentrations are elevated in response to inflammation, and dietary supplementation with zinc has been associated with a decreased incidence of pneumonia in children (Brooks et al. 2005). For the leading bacterial cause of acute respiratory infection, *S. pneumoniae*, Mn(II) is an essential metal, but extracellular Zn(II) inhibits the acquisition of Mn(II) by competing for binding to the solute binding protein PsaA (McDevitt et al. 2011). Although the affinity of PsaA for Zn(II) is far lower, Zn(II)-PsaA is more thermally stable than Mn(II)-PsaA. This suggests that Zn(II) may bind the permease irreversibly inducing Mn(II) starvation. Binding of Zn(II) does not lead to its transport and it does not substitute the organism's requirement for Mn(II). The superoxide dismutase of the pneumococcus contains Mn(II), and the loss of this micronutrient leaves the organism more sensitive to oxidative killing by neutrophils. These observations suggest that host levels of Zn(II) and metal ion competition maybe an important mechanism for innate defense of host mucosal surfaces.

Conclusion and Future Research Directions

The competition that microbes face for essential metals is severe and multifaceted. Microbes compete among themselves, compete with their hosts, and even exploit host competition factors to inhibit growth of their rivals. Metals themselves compete for binding to microbial proteins and if microbes successfully accumulate substantial metal concentrations, they risk lethal toxicity. Although our understanding of microbial competition for metals is substantial, important questions remain unanswered: What are the pathologic effects of microbial metal theft by pathogens on their hosts? How does competition for metals influence microbiome dynamics and how do metal-based changes in our microbiome affect our health? We have clues to these questions regarding iron, but Mn, Zn, and Cu metabolism appear to be crucial to microbial fitness as well. By unraveling the intricacies of microbial competition for metals, we may discover novel therapeutic approaches to protect us from these microbial pathogens.

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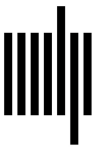

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