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Note on nutritional immunity

Bacteria, like mammals, require transition metals, such as manganese, iron, cobalt, nickel, copper and zinc, as vital cofactors for numerous enzymes and other proteins. Similarly, at high concentrations, these metals can be toxic to both mammals and bacteria. This creates an interesting dynamic between hosts and their resident bacteria as both strive to meet their requirements and maintain homeostasis. Host metal homeostasis can be disrupted by bacterial pathogens and so the host employs various mechanisms to sequester metals, thus limiting their availability to bacteria, in a process termed "nutritional immunity". Equally, bacteria have evolved strategies to counteract host metal sequestration and toxicity (used as a host defence strategy), and this dynamic struggle can influence the outcome of bacterial pathogenesis.

Bacteria and transition metals

Iron is probably the best-known transition metal that is required by bacterial pathogens for essential processes. Dietary iron is considered to be absorbed with low efficiency and thus the majority is available to the intestinal microbiota, which helps shape composition and may influence susceptibility to infection (Jaeggi et al., 2015). Likewise, zinc deficiency/low intestinal zinc is associated with dysbiosis of the gut microbiota (Lopez and Skaar, 2018) or may stress pathogens and induce the expression of virulence factors (Bolick et al., 2014), which can be reversed by dietary zinc supplementation (Medeiros et al., 2013). Alternatively, high dietary zinc can reduce the expression of a key virulence factor by enteropathogenic *E. coli* (Xue et al., 2015), and this process may help explain some of the gut health benefits derived from zinc-containing compounds. However, excess zinc may induce gut microbial dysbiosis and affect susceptibility to infection (Lopez and Skaar, 2018), implying that there is an optimum range for zinc availability in the gastrointestinal tract. Currently, less is known about the roles of manganese, cobalt, nickel, and copper acquisition in bacterial pathogenesis but it is established that these transition metals are essential cofactors for virulence factor expression by various pathogens (Palmer and Skaar, 2016) and it can be assumed that their availability in the intestine can influence the microbiome and host health.

Host defence strategies

Following pathogen recognition by the immune system, immune mediators (e.g. interleukin-6) promote iron accumulation by phagocytic cells, while neutrophils block bacterial iron acquisition by preventing availability (lactoferrin) and uptake (lipocalin-2) (Lopez and Skaar, 2018). Generally, transferrin has been shown to inhibit microbial growth by binding iron in blood and tissue, while lactoferrin performs a similar role at mucosal surfaces. Calprotectin is also released by neutrophils and helps bind the transition metals. There is a significant decrease in the serum concentrations of the transition metals (e.g. iron and zinc) post-infection as the host's uptake and sequestration mechanisms are activated as part of the acute phase response (Palmer and Skaar, 2016).

Conclusions and implications

Attempting to deprive microbes of vital transition metals is a key defence strategy employed by the host during infection. These protective mechanisms are largely coordinated by the immune system. Moreover, host status and the availability of these metals within the intestine, and their interaction, may affect microbial populations, the incidence of dysbiosis, and thus gut and host health/disease susceptibility, which makes the appropriate supply of these essential metals to the host an important consideration.

References

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