

Inorganic Battlegrounds in Infectious Disease: Zinc and Iron Chemistry of Malaria parasite

Janet Wolford, Matt Kidd, James E. Penner-Hahn and Thomas V. O'Halloran
Northwestern University and University of Michigan

Living organisms concentrate many transition metal ions to precise levels. An extensive array of cellular proteins appear to maintain 'quotas' for each metal within a narrow range. The ensemble of metal concentrations then is referred to as the metallome of the cell. As the nature of metallome is revealed for each type of cell, we are finding that a general pattern of metal ion utilization is highly conserved across evolution. We are also find cases where specialized cells exhibit unique transition metal signatures that are consistent with specific functions. The malaria causing parasite, *Plasmodium falciparum*, shows several interesting patterns in its utilization of metal ions. In one stage of infection, it must cope with the high concentration of iron released as it digests its primary source of amino acid precursors: i.e. the hemoglobin molecules of erythrocyte host. While the parasite is known to compartmentalize the host's iron in hemazoin crystals, its ability to concentrate zinc to a level several fold higher than that of the uninfected red blood cell is less well understood (rbc). Eluding detection from the immune system, *P. falciparum* hides in the erythrocyte where it asexually replicates to as much as 32N before leaving the host cell. The parasite devours the cell's hemoglobin and restructures its host to receive extraerythrocytic nutrients and to expel toxins. Using zinc detection methods like ICP-MS and fluorescent zinc-specific probes, we have found that total zinc concentration of an infected red blood cell more than doubles as the parasite replicates, and "free" zinc localizes to a compartment surrounding the parasite. With X-ray fluorescent nanoprobe in Sector 2 of the APS at Argonne National Labs, we have, for the first time, determined the spatial organization of "total" zinc in an infected erythrocyte and found that the localized zinc concentration can reach over 50-times the concentration of a normal erythrocyte. Apparently the rapidly proliferating organisms must acquire and compartmentalize significant amounts of zinc to populate a number of parasite metalloenzymes such as those required for transcription and translation. The specialized zinc metabolism of the malarial parasite may present a potential therapeutic target.