

On the abundance of zinc in the evolutionarily old protein domains

A recent paper in PNAS (1) analyzed the evolution of metalloproteins and confirmed our earlier observation on the abundance of Zn-binding proteins among the most widespread—and evolutionarily oldest—protein folds (2). Because that observation seemed to contradict the extremely low ($<10^{-12}$ M) estimates of Zn levels in the primeval anoxic ocean (3), we had suggested that the first cells developed in continental Zn-rich environments (2, 4). Specifically, we proposed that hydrothermal precipitates of zinc sulfide (ZnS), similar to those seen at modern deep sea vents, catalyzed abiogenic photosynthesis of organic compounds under the solar light (2, 4). This led to the release of Zn ions, yielding a Zn-rich milieu. In the course of evolution, cells have maintained the initial metal homeostasis and preserved high levels of Zn in the cytoplasm (2).

The study by Dupont et al. (1) offers two alternative explanations to reconcile the abundance of ancient, ubiquitous Zn-binding protein domains with the extremely low Zn levels in the anoxic ocean. First, they suggest cambialism (i.e., “using a different metal in what are modern day Zn metalloenzymes”); these metals were supposedly replaced by Zn when its levels started to rise with the oxygenation of the ocean (1). However, the increase in the ocean Zn content is said to have occurred 0.8–0.5 Gy ago (1) (i.e., long after the separation of the major phylogenetic lineages). Thus, the cambialism hypothesis implies the unlikely scenario where the incorporation of Zn into the plethora of ubiquitous enzymes, which are now unambiguously Zn-dependent, took place independently in multiple lineages. The specific suggestion of Dupont et al. (1) that modern Zn fingers initially bound cobalt does not sound credible. Cobalt-dependent enzymes, with few exceptions, rely on vitamin B₁₂ as the cobalt-binding cofactor, because amino acid residues are poor ligands for Co (3). The concentration of Co in the ancient

ocean (estimated at 10^{-9} M) (3) was too low to allow its direct recruitment by amino acid ligands of the first life forms.

Second, Dupont et al. (1) state that “while the concentration of uncomplexed Zn was likely very low, aqueous Zn-S species were certainly present and microbial Zn acquisition might have proceeded through a ligand production and scavenging strategy similar to that employed for Fe acquisition in the modern world”. The abundance of aqueous ZnS species in the anoxic ocean is unlikely, because it contained $>10^{-6}$ M Fe²⁺ (3); therefore, Zn could be present only as a minor impurity in the aqueous FeS clusters (5). Besides, the efficient metal-scavenging machinery of modern bacteria, as argued elsewhere (2), must have been absent at the stage of the first cells.

Finally, the cambialism and scavenging explanations contradict each other; if the first cells were able to efficiently scavenge and accumulate Zn ions, there would be no reason to substitute Zn for other metals in the course of evolution. In summary, we believe that emergence of the first cells in terrestrial metal-enriched habitats still provides the most plausible explanation for the abundance of Zn in the evolutionarily old protein folds.

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