

Panning for precious metals: mechanics of a transition metal transporter

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The Nramp (natural resistance associated macrophage protein) family, found in all kingdoms of life, is an important class of transporters for transition metal homeostasis. Two mammalian Nramp paralogs are required for the dietary uptake and endosomal recycling of non-heme iron, as well as in the innate immune response to intracellular pathogens. We have determined structures of a bacterial Nramp homolog. Using these structures, and other results from computational approaches and biochemical and cell-based functional assays, we arrive at a working model for the conformational change mechanism and metal selectivity of Nramps [1-2]. Our results explain how Nramps specifically discriminate against the highly abundant divalent metals calcium and magnesium, and yet at the same time remain promiscuous in their ability to transport other divalent metals including the toxic metal cadmium. We also describe the molecular mechanism for disease-causing missense mutations in mammalian Nramps.

[1] Bozzi, A.T., Bane L.B., Weihofen, W.A., et al. (2016) *Structure* 24, 2102-2114.

[2] Bozzi, A.T., Bane L.B. et al. (2016) *Proc Natl Acad Sci U S A.* 113, 10310-10315.

Keywords: [MntH](#); [Nramp transition metal transporter](#); [molecular dynamics](#)