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On the mechanisms underpinning biological nickel isotope fractionation

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Background: Microbes use nickel (Ni) as a cofactor in several vital proteins, including key enzymes in methanogenesis and anaerobic carbon cycling. Ni proteins are also used to manage oxidative stress, metabolize hydogen, and access urea as a nitrogen source. Recent work suggests that marine microbes bind and preferentially take up isotopically-light Ni (^{58}Ni), with the expression of this effect dependent on community composition and/or function[1]. In contrast, laboratory cultures show preference for isotopically-heavy Ni (^{60}Ni)[2]. This presentation will consider whether such discrepancies can be explained, in part, by Ni^{2+} binding to different amino acid ligands and differential expression of Ni proteins.

Materials and Methods: We employed a machine learning model to predict metal binding sites (e.g. coordination number and amino acid ligand identity) in proteomes of marine phototrophs, including the diatom *Thalassiosira* and the cyanobacterium *Synechococcus*. Protein sequences were retrieved from the UniProt database and analyzed using the machine learning program M-Ionic[3]. Benchtop experiments were then conducted to assess Ni isotope fractionation during complexation by different amino acid ligands including histidine, cysteine, glutamate and a Ni-binding peptide. Free and complexed Ni was separated via equilibrium Donnan dialysis following Selden et al. (2024)[4] and measured via multicollector inductively coupled plasma mass spectrometry (MC-ICP-MS).

Results and Discussion: The machine learning analysis of the *Thalassiosira* and *Synechococcus* proteomes revealed that Ni binding to proteins is dominated by complexation to the nitrogen ligands of histidine and sulfhydryl ligands of cysteine. Laboratory experiments showed Ni^{2+} binding to histidine favored light ^{58}Ni ($^{60/58}D_{complex\text{-}free}$ = -0.12 ±0.08‰) while ligation to cysteine favored the heavy ^{60}Ni ($^{60/58}D_{complex\text{-}free}$ = +1.27 ±0.19‰). Glutamate (oxygen ligands) preferentially bound ^{60}Ni as observed for copper[3] ($^{60/58}D_{complex\text{-}free}$ = +0.14). These results can explain the Ni isotope effects observed in a more complex peptide (3 S and 1 N; $^{60/58}D_{complex\text{-}free}$ = +0.74 ±0.04‰). In the context of the varied Ni-binding structures observed across multiple clades, these results suggest that binding by structurally distinct proteins may explain variability in Ni isotopes observed across multiple environments.

[1]Lemaitre et al. 2022. *EPSL.*
[2]Wang et al. Preprint. https://doi.org/10.21203/rs.3.rs-2207343/v1.
[3]Shenoy et al. (2024). *Bioinformatics.*
[4]Selden et al. (2024). *Scientific Reports.*