UNDERSTANDING COPPER FLUXES IN CANCEROUS CELLS USING NATURAL COPPER ISOTOPIC COMPOSITIONS IN A MODEL ORGANISM

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Abstract

Copper (Cu) is an essential cofactor in several proteins and is transported from blood to organs by Cu-proteins. In cancer, Cu concentration increases in tumor cells. Balter et al. (PNAS 2015) have shown that liver cancer tumors are enriched in heavy Cu isotopes compared to healthy patients liver tissue. However, the reason for this difference remains unknown. We proposed that this differential isotopic composition could be due to differences in Cu transport between tumors and healthy cells. To test this hypothesis, we have used the model yeast Saccharomyces cerevisiae in which Cu enters cells through both high-(CTR1, CTR3) and low-affinity importers after its enzymatic reduction by FRE proteins. These three activities are the three potential sources for isotopic fractionation in the system. To understand the impact of Cu import on Cu isotopic composition, we have monitored the evolution of both Cu concentration and isotopic composition as a function of time in two strains with different uptake systems: a wild type strain (WT) with both high- and low-affinity transporters and a strain lacking high-affinity importers (MPY17). Both WT and MPY17 show a preferential uptake of the lighter Cu isotope compared to the culture media with similar fractionation: Δ65Cu=-1 and -0.8, respectively. Hence, the observed fractionation is not due to the activity of high-affinity importers. The impact of the reductase activity was tested using strain SKY34 which has a low reductase activity. In this strain, the Δ65Cu remains stable ca. 0. This absence of fractionation may be due to the low availability of Cu(I) as a consequence of SKY34 low reductase activity. In fact, if Cu is exclusively provided to the cell as Cu(I), the Δ65Cu=-1. These results clearly demonstrate that the origin of the fractionation in yeast is linked to the activity of low-affinity transporters.

Keywords: Yeast model, Cancer, Cu transporters, high, low, affinity, Reductase, Cu, importers

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