Zinc isotope study of neurotoxic peptide aggregation

FRANCK POITRASSON[1*], LAURENT SABATER[2], MANUEL HENRY[1], ELENA ATRIAN-BLASCO[2], JEROEN E. SONKE[1], JÉRÔME VIERS[1], CHRISTELLE HUREAU[2].

[1]Géosciences Environnement Toulouse, CNRS-UPS-IRD-CNES, 14, avenue E. Belin, 31400 Toulouse, France. (*Franck.Poitrasson@get.omp.eu)

[2]Laboratoire de Chimie de Coordination, CNRS, 205, route de Narbonne, 31400 Toulouse, France.

Mice brains affected by the Alzheimer disease (AD) yield a heavier Zn isotopic signature relative to healthy subjects [1]. Although interesting, bulk organ analyses make it difficult to understand the exact molecular mechanism responsible for such Zn isotope dynamics.

We therefore investigated this isotopic effect at the molecular scale to understand the biochemical reactions at play. Amyloid Beta (Aβ) peptide aggregation is a key process leading to plaques typical of brains affected by AD. Transition metal ions such as Zn are known to be involved in this aggregation process, but the chemical reactions involved remain obscure [2].

We conducted aggregation experiments of $A\beta_{40}$ and its simplified form $A\beta_{28}$ in the presence of Zn. Incubations were performed for 20h to 24h under agitation at pH 7.3, 37°C in the presence of Thioflavin-T to monitor the aggregation progress by fluorescence. Experiments were ran using different Aβ/Zn ratios and various dissolved amino-acids (AA) having different functional groups (N, O, S) to examine the effect of Zn exchange between aggregated Aβ and the ambient solution on δ^{66}Zn. Zinc concentration analysis by ICP-MS performed after sample centrifugation and mineralization revealed contrasted partitionning of Zn between the aggregated peptides and the supernatant depending on the nature of the peptide, Aβ/Zn ratio and AA added. Subsequent Zn purification and isotopic analyses by MC-ICP-MS revealed Δ^{66}Zn fractionation between peptide and supernatant ranging from nil to ~0.6‰. These elemental and isotopic results were reproducible and correlated for certain AA. This suggests that the Zn elemental and isotopic partitioning reflect changes of the functional groups of Aβ depending on experimental conditions, in agreement with spectroscopic inferences [2]. Overall, the direction of isotopic fractionation towards heavy Zn upon Aβ agregation agrees with that observed in mice brain affected by AD [1].

[1] F. Moynier et al. (2017) Geophys. Perspect. Lett., 3: 142-150.

[2] B. Aliès et al. (2016) Inorg. Chem. , 55: 10499-10509.