An isotope metallomic perspective on aging

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With more than 1 billion elderly people expected in 2040 in the world, aging has become a significant research subject over the past few years. Characterized by the decline of vital biological functions, it comes with several impairments ranging from loss of mobility to more profound problems like the development of neurodegenerative diseases and cancers. To date, despite all the theories developed to account for these progressive deteriorations, our knowledge of the mechanisms involved in aging is still far from complete and limited by the complexity of their interactions. More recently, chemical and isotopic changes have been observed during aging offering new perspectives to better constrain this process. However, the role of these chemical variations remains unclear.

To address this problem and provide a more comprehensive view of the process, we analyzed the concentrations of ~20 chemical elements and the Cu-Zn isotopic compositions in C57BL/6-mice organs (e.g. liver, brain, kidney) and worms (*C. elegans*) of different ages. Based on principal component analyses we show that mice organs are chemically distinct from each other and are affected by specific chemical changes through time. Using isotopic mixings we demonstrate that ~25% of the Cu and Zn initially present in liver is remobilized into brain over time highlighting an important chemical dyshomeostasis during aging.

Supported by correlations observed with proteomic and metabolic parameters, we show that these chemical variations are more relevant in terms of biomarkers of the cumulated metabolic activity rather than of the chronological age.

Using genetically modified worms, we then demonstrate that mutants with improved lifespan (i.e. daf-2 (e1370)) are affected by reverse or less important chemical shifts compared to wild type worms. These results represent a real technological breakthrough and suggest that targeting these age-induced chemical changes could appear as an opportunity to develop innovative therapeutic treatments aiming at enhancing healthy lifespan.