

Zinc enhances albumin's protective role against Parkinson's disease

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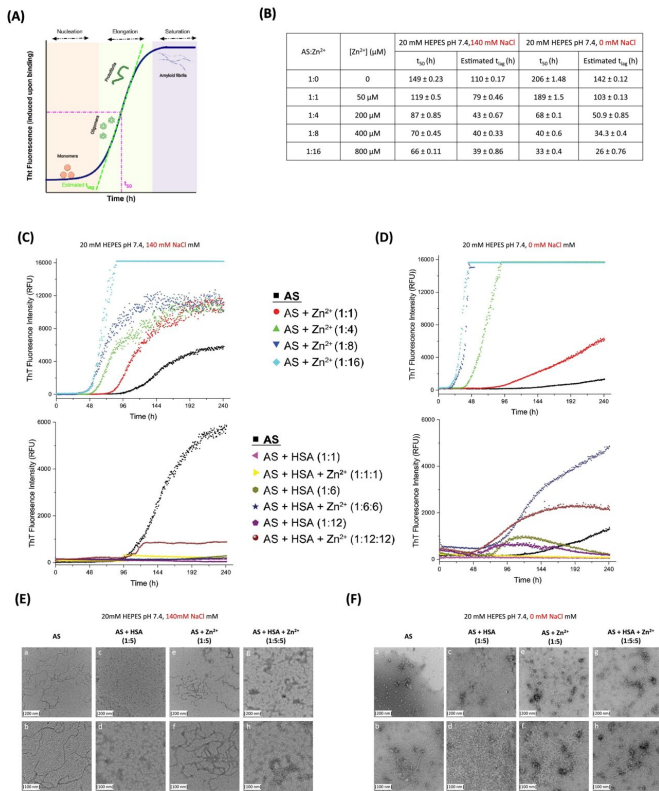


Fig. 1. Fibrillization kinetics of AS under pH 7.4, low and high ionic strength in the presence and absence of Zn²⁺ and/or defatted human serum albumin (DE-HSA). (A) The nucleation dependent polymerization reaction of amyloid fibril formation causes a sigmoidal growth curve with nucleation, elongation, and saturation phases. (B) Table highlighting the estimated t₅₀ and t_{lag} parameters for two experimental conditions setup. (C) AS fibrillization in the presence of increasing amount of Zn²⁺ (AS:Zn²⁺, 1:1, 1:4, 1:8, 1:16 M ratio) and increasing amount of HSA and/or Zn²⁺ under high-ionic strength (140 mM NaCl) and (D) under low-ionic strength (0 mM NaCl). (E) TEM images of fibrils formation of (a, b) AS (WT); (c, d) AS in the presence of HSA (1:5); (e, f) AS in the presence of Zn²⁺ (1:5); (g, h) AS in the presence of HSA and Zn²⁺ (1:5) under high-ionic strength and (F) under low-ionic (Scale bar: upper row 200 nm and lower row 100 nm). Credit: *International Journal of Biological Macromolecules* (2022). DOI: 10.1016/j.ijbiomac.2022.10.066

Revealing zinc's interaction with a critical transport protein underscores the need to study biological pathways under physiologically relevant conditions.

Heavy metals in the body have long been thought to induce the aggregation of disease-linked proteins, but a KAUST study shows this is not always the case.

It turns out that [zinc](#) ions tune the ability of human serum albumin (HSA), an abundant transport [protein](#) in the body, to better prevent α -synuclein from aggregating, a process directly linked to Parkinson's disease.

The finding should "open new avenues for preventive treatments," says Samah Al-Harhi, a Ph.D. student who won a best poster award at the International Symposium on Frontiers in Molecular Science for the work.

The unexpected role for zinc discovered by Al-Harhi only became evident after she and her mentor, [Pawel Jarek](#), studied the metal's effects on HSA, the main carrier of zinc in [blood plasma](#) and spinal fluid, under physiologically relevant conditions.

In unrealistically massive quantities, zinc tends to accelerate the aggregation of α -synuclein, a neuronal protein implicated in Parkinson's disease. This is what other scientists had shown in the past. But, under the types of biologically plausible experimental conditions considered by Al-Harhi, the metal actually interacts with HSA to cause the opposite effect.

Using a state-of-the-art imaging technique known as proton-less [nuclear magnetic resonance spectroscopy](#), Al-Harhi and colleagues showed that zinc binding alters the chaperone function of HSA, a multifunctional molecule that plays a role in blocking α -synuclein accretion. In particular, zinc

ions biased HSA toward stronger interactions with the aggregation-prone fragments of α -synuclein, a change that blunts fibril formation and slows down the toxic process of protein deposition that can lead to neurodegeneration.

Provided by King Abdullah University of Science and Technology

The results dovetail with another recent report from Al-Harhi and Jaremko on the complex interplay between [fatty acids](#), zinc ions and HSA. That report also required careful consideration of human physiology and experimental conditions to show how a particular fatty acid, one used regularly to treat diabetes, can help stabilize HSA function to address metabolic irregularities.

Together, the papers from Al-Harhi and Jaremko underscore the need to think about biological complexity when investigating intricate molecular pathways. "These medically relevant biomolecules cannot be studied in isolation if we want to discover medically relevant findings that can be of any future therapeutic use," Al-Harhi says.

"Biology is not so simple as the laboratory flask. This," she says, "is the driving force and motivation of my studies."

The recent papers are published in the *International Journal of Biological Macromolecules* and *Frontiers in Chemistry*.

More information: Samah Al-Harhi et al, Zinc ions prevent α -synuclein aggregation by enhancing chaperone function of human serum albumin, *International Journal of Biological Macromolecules* (2022). [DOI: 10.1016/j.ijbiomac.2022.10.066](https://doi.org/10.1016/j.ijbiomac.2022.10.066)

Samah Al-Harhi et al, Lipoic Acid Restores Binding of Zinc Ions to Human Serum Albumin, *Frontiers in Chemistry* (2022). [DOI: 10.3389/fchem.2022.942585](https://doi.org/10.3389/fchem.2022.942585)

Samah Al-Harhi et al, Towards the functional high-resolution coordination chemistry of blood plasma human serum albumin, *Journal of Inorganic Biochemistry* (2019). [DOI: 10.1016/j.jinorgbio.2019.110716](https://doi.org/10.1016/j.jinorgbio.2019.110716)

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