The S100B Alarmin Is a Dual-Function Chaperone Suppressing Amyloid-β Oligomerization through Combined Zinc Chelation and Inhibition of Protein Aggregation

Cristóvão JS, Figueira AJ, Carapeto AP, Rodrigues MS, Cardoso I, and Gomes CM

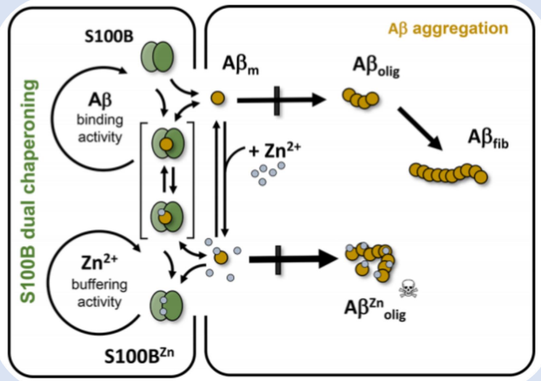
R&D UNIT: BioISI

CONTACT: fc47773@alunos.fc.ul.pt

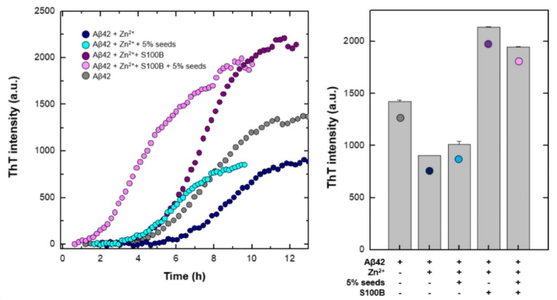
ACS Chem. Neurosci. **2020**, *11*(17), 2753

Here we demonstrate that **S100B protective functions** converge, making this protein a dual-function chaperone capable of suppressing the formation of toxic Aβ oligomers through both chelation of zinc and inhibition of protein aggregation.

Amyloid beta (Aβ) aggregation and imbalance of metal ions are major hallmarks of Alzheimer's disease (AD). Indeed, amyloid plaques of AD patients are enriched in zinc and Aβ42, and AD related-cognitive decline is dependent on extracellular zinc concentration. In vitro, zinc induces the formation of Aβ42 oligomers that delay the formation of amyloid fibers at the expense of increased cellular toxicity. Recent findings have uncovered **neuroprotective functions for S100B as a suppressor of Aβ aggregation and toxicity and in the regulation of zinc homeostasis in neurons.**



Effect of S100B over Aβ42 aggregation in the presence of Zn^{2+}

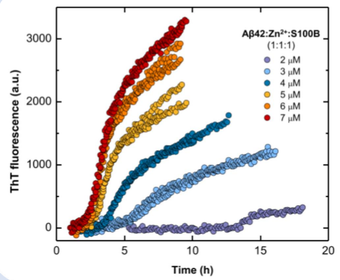


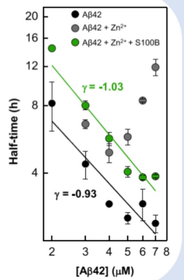
ThT Aβ42 kinetic experiments (seeded and non seeded) reveals that zinc **reduces the amounts of fibrils formed**, as well as **delays** aggregation.

S100B, **reestablishes normal amounts of ThT positive fibrils** and increases the **flux towards on-pathways species**.

Kinetic traces of ThT-monitored aggregation of Aβ42 (2 μM, gray) in the presence of equimolar Zn^{2+} (dark blue) and with 5% seeds (light blue), equimolar Zn^{2+} and S100B (violet) and with 5% seeds (pink) Averaged traces, n = 3. ThT-intensity at the end point of kinetic traces in different conditions (n = 3).

S100B restores Aβ42 aggregation mechanism with zinc

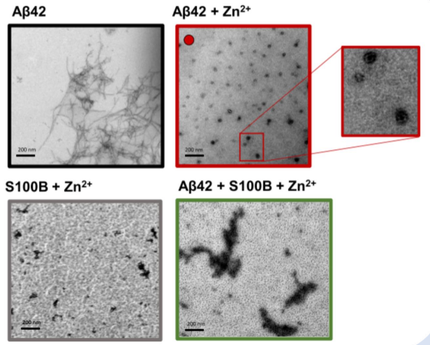


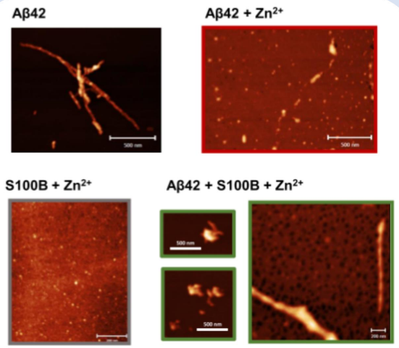


Scaling exponent (γ) are indicative of dominant mechanisms on amyloidogenic proteins. In the presence of zinc, Aβ42 dominant mechanism is lost, **but is recovered when 1:1:1 S100B is added.**

Effect of S100B on the mechanism of Aβ42 aggregation in the presence of Zn2+. Kinetic trace of ThT-monitored aggregation of Aβ42 with equimolar Zn2+ and S100B (left). Log−log plot of the half-time (t1/2) of the Aβ42 aggregation reaction as a function of the initial Aβ42 monomer concentration (black), with Zn2+ (gray) and Zn2+ and S100B (green). The slope of the trend lines is the scaling exponent (γ) (right).

S100B effect on the morphology of Aβ42 end-point species

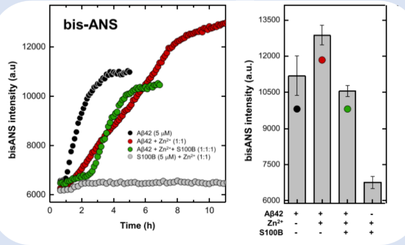




Representative transmission electron microscopy (left) and atomic force microscopy (right) images of end point species observed under different conditions.

Bio-imaging tools reveals morphological diversity between amyloid beta fibrils and spherical zinc-induced oligomers, which **are absence in the presence of zinc and S100B (1:1).**

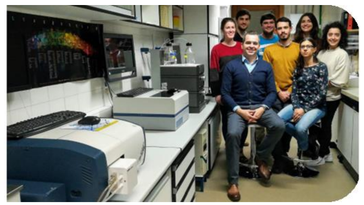
Bis-ANS kinetic traces of Aβ42 with zinc and S100B



Bis-ANS kinetics shows high **hydrophobic content of zinc mediated oligomer**s, which is diminished in the presence of S100B.

Conclusion

In this work we showed that S100B **prevents the formation of zinc-promoted toxic oligomers**, through it´s **chelation,** reinforcing the S100B protective role against Aβ42 mediated toxicity.



Acknowledgments: PTDC/BIA-BQM/29963/2017; UIDB/04046/2020; POCI01-0145-FEDER-007274; FCT/MCTES (PTDC/NEU-NMC/2138/2014 ; Bial 343/14; COST Action TD1304 343; PhD fellowship SFRH/BD/101171/2014 (to JSC)