Inhibition of Aβ42 oligomers relevant in Alzheimer's disease by a chaperone multimer

P30006

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Protein aggregation is central in Alzheimer´s disease (AD) in which aggregation of Aβ and tau occurs. While extracellular space is the primary site for Aβ aggregation, tau is promptly secreted to nearby cells. Therefore, extracellular proteostasis is key to define molecular events in AD brain. Our recent work established proteins of the S100 family as anti-aggregation chaperones. S100 proteins are Ca^{2+}-binding proteins with intra/extracellular roles which are neuronally abundant and secreted as alarmins. We showed that S100 proteins colocalize with aggregates in AD mice brains, and that S100B inhibits the aggregation and toxicity of Aβ42 and tau (Previously published in: Cristóvão 2018 *Sci Adv*; Moreira 2021 *Nat Comm*). S100B occurs predominantly as homodimers but also exists as tetramers (Previously published in: Hagmeyer 2019 *Front Neurosci*), whose chaperone activity we here investigated. Using ThT-monitored Aβ42 aggregation kinetics, we discovered that tetrameric S100B, unlike the dimer, effectively inhibits Aβ42 aggregation even in the absence of Ca^{2+} binding, at sub/equimolar ratios. Structural analysis revealed a secondary Ca^{2+} independent binding site for-med through tetramerization, which facilitates the binding of monomeric and fibrillar Aβ42, as suggested by molecular docking calculations, CD and electron microscopy. Additionally, our investigation explored the impact of S100 multimers on the generation of neurotoxic Aβ42 oligomers (AβO). Mechanistic analysis revealed that dimeric and tetrameric S100B preferentially inhibit Aβ42surfacecatalysed nucleation, reducing AβO formation by 90%. Overall, our findings highlight S100B multimers as versatile inhibitors of Aβ42 oligomerization and aggregation. Ongoing research on brain related S100 proteins reveals a network of chaperones with multiple client interactions, mitigating protein aggregation and toxicity.

Acknowledgements: Funded by the EU (TWIN2PIPSA, GA101079147) and FCT Portugal (BD/06393/2021 to AJF and UID/MULTI/04046/2020 to BioISI).