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S100B inhibits the formation of Aβ42 fibrils and intermediate oligomers implicated in Alzheimer´s disease

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Alzheimer's disease (AD) neurodegeneration involves aggregation of the amyloid beta-42 peptide (Aβ42) into transient oligomers and fibrils, whose emergence is regulated by a limited set of extracellular chaperones. Among these is S100B, a homodimeric protein that is up-regulated in AD and which acts as a Ca2+-activated Aβ42 amyloid suppressor. Nonetheless, S100B occurs in the human brain also as a homotetramer (Ostendorp T et al., 2007 EMBO J.), whose AD-linked neuroprotective functions remain uncharacterized.

Here we present recent research in which we establish and compare the Aβ42 anti-aggregation and anti-oligomerization activities of both S100B multimers. Using thioflavin-T monitored Aβ42 aggregation kinetics, we discovered that unlike the dimer, tetrameric S100B inhibits Aβ42 aggregation even in the absence of Ca2+ binding, while operating at sub/equimolar ratios. Next, we used computational predictors of aggregation-prone regions to map surfaces within tetrameric S100B amenable to interact with Aβ42. We found a secondary Ca^{2+}-independent cleft that facilitates binding to both Aβ42 monomers and fibrils, as corroborated by circular dichroism, electron microscopy and docking calculations (Figueira AJ et al., 2022 J. Mol. Biol.). Our investigation additionally explored the impact of such S100B multimers on the generation of Aβ42 intermediate oligomers (AβO). For this, we fitted Aβ42 aggregation traces to mathematical models describing the mechanisms of Aβ42 fibrillation (Meisl G et al., 2016 Nat. Protoc). This revealed that dimeric and tetrameric S100B inhibit Aβ42 nucleation catalysed by fibril surfaces, decreasing the reactive influx towards oligomers down to <10% and reducing the total amounts of AβO by 30-60% (Figueira AJ et al., 2023 Front. Neurosci.).

Taken together, our findings highlight S100B multimers as versatile and complementary inhibitors of Aβ42 neurotoxic oligomerization and aggregation, hinting their pivotal role in the regulation of AD synaptic proteostasis.

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