CALCIUM-INDUCED HETERODIMERIZATION OF S100A8 WITH S100A1 TRIGGERS AMYLOID FIBRILLATION

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S100 is a family of calcium-binding proteins, consisting of isoforms with structural similarity but functional diversity [1]. S100 proteins regulate various proteins involved in cellular functions like calcium homeostasis, cell growth, differentiation, cytoskeleton dynamics, and energy metabolism [2]. Several members are known to be important in neurodegeneration by signaling neuroinflammation and forming amyloid fibrils. One of them is S100A9, which is well-studied, but the roles of S100A1 and S100A8 remain relatively unexplored.

S100A1 is predominantly expressed in the brain, skeletal and cardiac muscles [3]. S100A1 interacts with tau, RAGE, and RyR - proteins that participate Alzheimer

's disease (AD) cascade [4]. Another family member S100A8 is mostly found in neutrophils and monocytes [5] and plays a role in neurological disease pathology as well. S100A8 homodimers can independently induce neuroinflammation [6] and their overexpression in AD patients leads to activation of microglia [7, 8]. However, it is known that S100A8 can form a heterodimer with S100A9 called calcprotectin [9], but intereaction with S100A1 is still not investigated. Both S100A1 and S100A8 are expressed in the cerebral cortex as per the Human Protein Atlas (https://www.proteinatlas.org/) [10] and share structural similarities [1]. Thus, our main goal was to elucidate their potential complex formation.

To explore the aggregation kinetics of the S100A1/A8 complex, we employed the Thioflavin T Fluorescence Assay, unveiling calcium concentration-dependent amyloid formation. In addition, Atomic Force Microscopy (AFM) was used to visualize the S100A1/A8 fibrils and, Differential Scanning Fluorimetry (DSF) to quantify protein stabilities. In conclusion, our research contributes new findings to the understanding of S100A1 and S100A8 aggregation dynamics, offering valuable insights into their relevance to various diseases.

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