Role of pro-inflammatory S100A9 protein in amyloid-neuroinflammatory cascade in Alzheimer’s disease and traumatic brain injury

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S100A9 properties was studied under various *ex vivo* and *in vitro* conditions. First, human and mouse tissues with TBI and AD were subjected to microscopic, immunohistochemical and immunofluorescent techniques. Then, aged mouse treated with native, oligomeric and fibrillar S100A9 was also studied by using behavioral and neurochemical analysis. Moreover, S100A9 was established as a biomarker of dementia progression and compared with others such as Aβ42 and tau-proteins, by studying cerebrospinal fluid (CSF) samples from different stages of dementia. Finally, *in vitro* experiments on S100A9 amyloidogenesis, co-aggregation with Aβ40 and Aβ42, digestion and cytotoxicity were also performed by using spectroscopic, atomic force microscopy and cell biology methods.

We have found that S100A9-driven amyloid-neuroinflammatory cascade serves as a link between TBI and AD. S100A9 contributes to the plaque formation and intraneuronal responses in AD, being a part of the amyloid-neuroinflammatory cascade. In TBI we have found that extensive S100A9 neuronal production and amyloid self-assembly is triggered immediately after injury, leading to apoptotic pathways and neuronal loss. S100A9 is an integral component of both TBI precursor-plaques, formed prior to Aβ deposition, and AD plaques, characterized by different degree of amyloid maturation, indicating that all plaques are associated with inflammation. Both intra- and extracellular amyloid-neuroinflammatory cascades are intertwined and showed similar tendencies in human and mouse tissues in TBI and AD. *Ex vivo* findings are further supported by *in vitro* experiments on S100A9 amyloidogenesis, digestion and cytotoxicity. Importantly, being highly amyloidogenic itself, S100A9 can trigger and aggravate Aβ amyloid self-assembly and significantly contribute to amyloid cytotoxicity. Moreover, the CSF dynamics of S100A9 levels matches very closely the content of Aβ in AD, vascular dementia and mild cognitive impairment due to AD, emphasizing the involvement of S100A9 together with Aβ in the amyloid-neuroinflammatory cascade in these ailments.

**Keywords**

Traumatic brain injury, Alzheimer’s disease, Aβ, S100A9, Amyloid, Cytotoxicity, Neuroinflammation.