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

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Abstract
Over the past decade traumatic brain injury (TBI) has become the focus of research due to growing epidemiological and clinical evidences that TBI incidences are strong risk factors for Alzheimer's disease (AD). Major pathological hallmarks of AD are massive accumulations of amyloid-β peptide (Aβ) toxic oligomers and plaques. Neuroinflammation is also considered as a common denominator in AD. S100A9 is a multifunctional cytokine with diverse roles in the cell signaling pathways associated with inflammation and cancers. A widespread expression of S100A9 was also reported in many other ailments involving inflammatory processes, such as AD, malaria, cerebral ischemia and TBI, implying that S100A9 may be a universal biomarker of inflammation. The distinctive feature of S100A9 compared to other pro-inflammatory cytokines is its ability to self-assemble into amyloids, which may lead to the loss of its signaling functions and acquired amyloid cytotoxicity, exceeding that of Aβ.

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 fibrillary 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 $A\beta_{42}$ and tau-proteins, by studying cerebrospinal fluid (CSF) samples from different stages of dementia. Finally, *in vitro* experiments on S100A9 amyloidogenesis, co-aggregation with $A\beta_{40}$ and $A\beta_{42,}$ 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.

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