Scavenger receptor-A deficiency impairs immune response of microglia and astrocytes potentiating Alzheimer’s disease pathophysiology


Abstract

Late onset Alzheimer disease’s (LOAD) main risk factor is aging. Although it is not well known which age-related factors are involved in its development, evidence points out to the involvement of an impaired amyloid-β (Aβ) clearance in the aged brain among possible causes. Glial cells are the main scavengers of the brain, where Scavenger Receptor class A (SR-A) emerges as a relevant player in AD because of its participation in Aβ uptake and in the modulation of glial cell inflammatory response. Here, we show that SR-A expression is reduced in the hippocampus of aged animals and APP/PS1 mice. Given that Aβ deposition increases in the aging brain, we generated a triple transgenic mouse, which accumulates Aβ and is knockout for SR-A (APP/PS1/SR-A−/−) to evaluate Aβ accumulation and the inflammatory outcome of SR-A depletion in the aged brain. The lifespan of APP/PS1/SR-A−/− mice was greatly reduced, accompanied by a 3-fold increase in plasmatic pro-inflammatory cytokines, and reduced performance in a working memory behavioral assessment. Microglia and astrocytes lacking SR-A displayed impaired oxidative response and nitric oxide production, produced up to 7-fold more pro-inflammatory cytokines and showed a 12-fold reduction in anti-inflammatory cytokines release, with conspicuous changes in lipopolysaccharide-induced glial activation. Isolated microglia from young and adult mice lacking SR-A showed a 50% reduction in phagocytic activity. Our results indicate that reduced expression of SR-A can deregulate glial inflammatory response and potentiate Aβ accumulation, two mechanisms that could contribute to AD progression.

Keywords

Aging, Beta-amyloid plaques, Glial cells, Neurodegenerative diseases, Neuroinflammation, Scavenger receptor