

Inflammasome Activation: A Potential Mechanism for Cognitive Impairment

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The inflammatory process plays a crucial role in the maintenance of the central nervous system (CNS) homeostasis, essential for the functioning of neuronal cells, mainly through the active protection against various noxious stimuli such as neurotropic viral infections and/or traumatic injury, promoting tissue regeneration [1]. However, the persistence and/or unbalance of the inflammatory response can trigger a state of chronic inflammation, which may lead to cell function impairment or even cell death [2].

Interleukin (IL)-1 β and IL-18 are among the pro-inflammatory cytokines involved in the pathogenesis of CNS diseases. These cytokines are synthesized as precursor proteins and their activation depends on a maturation process executed by a multiprotein complex called inflammasome [3]. The inflammasome was first described in 2002 [4], and it is generally composed of i) a sensor/receptor protein located in the cytosol that works as a platform for the formation of the complex, ii) an adapter protein, ASC [apoptosis-associated speck-like protein containing a CARD (caspase recruitment domain)], and iii) an effector protein, caspase-1. So far, four conventional or canonical inflammasomes have been described which process pro-IL-1 β and pro-IL-18 via caspase-1: NLRP1 (NLR family protein, containing pyrin domain 1), NLRP3, IPAF (IL-1-converting enzyme protease-activation factor) and AIM2 (absent in melanoma 2).

Although the inflammasome activation is essential for host defense, IL-1 β processing and secretion must be tightly regulated due to its strong pro-inflammatory activity. Recent studies have suggested that unbalanced inflammasome activation may be involved in the pathogenesis of various diseases with inflammatory component, including the common neurodegenerative diseases, Parkinson's disease and Alzheimer's disease (AD) [5-7]. In this scenario, the upregulation of inflammasome components, such as the NLRP3 receptor, caspase-1 and IL-1 β , has been described in post-mortem brain tissue from aged and/or AD patients [7,8] and in blood from cognitively impaired amyloid-positive patients [9]. Thus, the understanding of the involvement of the excessive inflammasome activation in the pathophysiology of aging or neurological/neurodegenerative diseases will open new horizons to identify more sensitive and responsive targets for therapy.

The most common form of dementing illnesses is Alzheimer's-type dementia. According to the World Health Organization, there was 47.5 million people diagnosed with AD or other closely related dementing illness in 2015 [10]. Amyloid beta (A β) has been proposed to be a causative factor in the development of AD. Besides, it is a well-known activator of the NLRP3 inflammasome. For example, the double transgenic (Tg) mice overexpressing mutant forms of amyloid- β precursor protein (APP) and presenilin 1 (PS1) - a genetic model for AD which develop amyloid plaques and behavioral deficits around 6 - 7 months of age - shows increased IL-1 β , active caspase-1 and NLRP3 or NLRP1 content in cortex and/or hippocampus, indicating inflammasome activation [7,11,12]. Moreover, the knocking down of NLRP3 or caspase-1 protects APP/PS1 mice from memory deficits and completely prevents hippocampal synaptic plasticity impairment, probably by the induction of microglial A β phagocytosis [7].

In line with this, the silencing of NLRP1 and caspase-1 significantly improves spatial learning and memory assessed by the Morris water maze test (MWM) in APP/PS1 mice [11]. Furthermore, it has been demonstrated that AIM2 deletion does not change the defective short-term memory and spatial learning, observed through cued Y-maze and Barnes maze test, neither IL-1 β expression in total brain from 5XFAD mice, a more rapidly progressing animal line created by combining five AD-related mutations, even though, it reduces APP expression, A β deposition and microglial activation in hippocampus and cortex [13]. The knockout of another inflammasome component has also shown to rescue from memory impairments in mice. In line with this, it has been shown that the deletion of ASC preserves hippocampal-dependent spatial acquisition and reference memory evaluated by MWM in the 5XFAD transgenic mice [14].

The activation of the inflammasome with cognitive decline has also been demonstrated in other conditions, including aging or lipopolysaccharide (LPS)-induced neuroinflammation. For example, aged rats (18-month-old) with impaired hippocampal dependent spatial learning presents increased content of caspase-1 and caspase-11, in addition to upregulation of the ATP purinergic receptor, P2X₇, and the associated pores, pannexin-1, in the brain [15]. In this context, it has been shown that ATP-induced K⁺ efflux through the P2X₇ receptors triggers the inflammasome activation in murine macrophages [16]. Thus, rats treated with probenecid - a pannexin 1 inhibitor with capacity to block the inflammasome activity - presents reduced content of caspase-1, P2X₇ receptors and of pannexin-1 in the hippocampus with a improved hippocampal dependent spatial learning task [15].

On the other hand, the association of low dose LPS (10 μ g/kg) with high fat diet potentially impairs the development of context fear memory and increases the hippocampal content of NLRP3 and IL-1 β [17]. Another recent work demonstrated that the challenge with higher doses of LPS (5 mg/kg) induces hippocampal inflammasome activation three days after the toxin administration, identified by increased IL-1 β , caspase-1 and NLRP3, and long lasting (28 days) cognitive impairment observed through the novel object recognition test. Interestingly, the use of Ac-YVAD-CMK (N-acetyl-tyrosyl-valyl-alanyl-aspartyl chloromethyl ketone), compound that irreversibly blocks NLRP3 inflammasome assembly, prevents both inflammasome activation and cognitive impairment in LPS-exposed animals [18]. These studies showed that the inflammasome may be activated in the CSN during inflammatory conditions and might play a role on the cognitive decline.

Considering the serious cognitive impairment observed in neurodegenerative diseases, the inflammasome inhibition represents a potential target for the development of effective therapies. Thus, cognitive enhancer molecules have been studied as potential inflammasome inhibitors. For instance, our research group has recently showed that the pteridine neopterin - widely used as a sensitive marker for the activation of the immune system, facilitates the acquisition of aversive memory and the generation of hippocampal long-term potentiation in naïve rodents [19]. This effects seems to be mediated by inhibiting the activation of the inflammasome, since neopterin decreases LPS-induced caspase-1 gene expression in human primary neurons [20]. Another example is the cyclooxygenase and lipoxygenase inhibitor flavocoxid, which improves learning and memory performances, decreases NLRP3 and IL-1 β protein content and A β deposition in the brain cortex of the triple-transgenic 3xTg-AD mice (3 months old) [21]. Also, the main active component isolated from the traditional Chinese medicinal herb *Astragalus membranaceus*, Astragaloside IV, decreases the hippocampal NLRP3, cleaved caspase-1 and IL-1 β content and protects mice from the cognitive impairment induced by transient cerebral ischemia and reperfusion [22].

In conclusion, most attention has been driven to the role of NLRP3 and NLRP1 inflammasomes in the cognitive impairment observed in conditions coursing with inflammation. The association of inflammasome activation and cognitive decline has been strongly suggested by genetic and pharmacological tools for inflammasome inhibition. Thus, further investigation is necessary to confirm the involvement of the inflammasome in the pathophysiology of neuroinflammatory conditions characterized by cognitive impairment, and raise the inflammasome inhibition as a promising target for therapy research.

Bibliography

1. Butovsky O., *et al.* "Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells". *Molecular and Cellular Neuroscience* 31.1 (2006): 149-160.
2. Hsieh HL and Yang CM. "Role of redox signaling in neuroinflammation and neurodegenerative diseases". *BioMed Research International* (2013): 484613.
3. Thornberry NA., *et al.* "A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes". *Nature* 356.6372 (1992): 768-774.
4. Martinon F., *et al.* "The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta". *Molecular Cell* 10.2 (2002): 417-426.
5. Codolo G., *et al.* "Triggering of inflammasome by aggregated alpha-synuclein, an inflammatory response in synucleinopathies". *PLoS One* 8.1 (2013): e55375.
6. Halle A., *et al.* "The NALP3 inflammasome is involved in the innate immune response to amyloid-beta". *Nature Immunology* 9.8 (2008): 857-865.
7. Heneka MT., *et al.* "NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice". *Nature* 493.7434 (2013): 674-678.
8. Cribbs DH., *et al.* "Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: a microarray study". *Journal of Neuroinflammation* 9 (2012): 179.
9. Cattaneo A., *et al.* "Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly". *Neurobiology of Aging* 49 (2017): 60-68.
10. WHO. "The epidemiology and impact of dementia. Current state and future trends" (2015).
11. Tan MS., *et al.* "Amyloid-beta induces NLRP1-dependent neuronal pyroptosis in models of Alzheimer's disease". *Cell Death and Disease* 5 (2014): e1382.
12. Zhang HR., *et al.* "Paeoniflorin Attenuates Amyloidogenesis and the Inflammatory Responses in a Transgenic Mouse Model of Alzheimer's Disease". *Neurochemical Research* 40.8 (2015): 1583-1592.
13. Wu PJ., *et al.* "Deletion of the Inflammasome Sensor Aim2 Mitigates Abeta Deposition and Microglial Activation but Increases Inflammatory Cytokine Expression in an Alzheimer Disease Mouse Model". *Neuroimmunomodulation* 24.1 (2017): 29-39.
14. Couturier J., *et al.* "Activation of phagocytic activity in astrocytes by reduced expression of the inflammasome component ASC and its implication in a mouse model of Alzheimer disease". *Journal of Neuroinflammation* 13 (2016): 20.
15. Mawhinney LJ., *et al.* "Heightened inflammasome activation is linked to age-related cognitive impairment in Fischer 344 rats". *BMC Neuroscience* 12 (2011): 123.
16. Franchi L., *et al.* "Differential requirement of P2X7 receptor and intracellular K⁺ for caspase-1 activation induced by intracellular and extracellular bacteria". *Journal of Biological Chemistry* 282.26 (2007): 18810-18818.
17. Sobesky JL., *et al.* "Glucocorticoids Mediate Short-Term High-Fat Diet Induction of Neuroinflammatory Priming, the NLRP3 Inflammasome, and the Danger Signal HMGB1". *eNeuro* 3.4 (2016).
18. Zhu W., *et al.* "NLRP3 inflammasome activation contributes to long-term behavioral alterations in mice injected with lipopolysaccharide". *Neuroscience* 343 (2017): 77-84.

19. Ghisoni K., *et al.* "Neopterin acts as an endogenous cognitive enhancer". *Brain, Behavior, and Immunity* 56 (2016): 156-164.
20. Martins RP, *et al.* "Treating depression with exercise: The inflammasome inhibition perspective". *Journal of Systems and Integrative Neuroscience* 3.1 (2016): 1-8.
21. Bitto A., *et al.* "Effects of COX1-2/5-LOX blockade in Alzheimer transgenic 3xTg-AD mice". *Inflammation Research* 66.5 (2017): 389-398.
22. Li M., *et al.* "Astragaloside IV attenuates cognitive impairments induced by transient cerebral ischemia and reperfusion in mice via anti-inflammatory mechanisms". *Neuroscience Letters* 639 (2017): 114-119.

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