Progress in Neurobiology 87 (2009) 181–194

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Inflammation in Alzheimer's disease: Amyloid-β oligomers trigger innate immunity defence via pattern recognition receptors

Antero Salminen [a,b,*], Johanna Ojala [a], Anu Kauppinen [a], Kai Kaarniranta [c,d], Tiina Suuronen [a]

[a] Department of Neurology, Institute of Clinical Medicine, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland
[b] Department of Neurology, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland
[c] Department of Ophthalmology, Institute of Clinical Medicine, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland
[d] Department of Ophthalmology, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland

ARTICLE INFO

Article history:
Received 12 September 2008
Received in revised form 11 December 2008
Accepted 8 January 2009

Keywords:
Alzheimer's disease
Amyloid
Complement system
Inflammasome
Inflammation
Innate immunity
RAGE
TLR

ABSTRACT

The inflammatory process has a fundamental role in the pathogenesis of Alzheimer's disease (AD). Recent studies indicate that inflammation is not merely a bystander in neurodegeneration but a powerful pathogenetic force in the disease process. Increased production of amyloid-β peptide species can activate the innate immunity system via pattern recognition receptors (PRRs) and evoke Alzheimer's pathology. We will focus on the role of innate immunity system of brain in the initiation and the propagation of inflammatory process in AD. We examine here in detail the significance of amyloid-β oligomers and fibrils as danger-associated molecular patterns (DAMPs) in the activation of a wide array of PRRs in glial cells and neurons, such as Toll-like, NOD-like, formyl peptide, RAGE and scavenger receptors along with complement and pentraxin systems. We also characterize the signaling pathways triggered by different PRRs in evoking inflammatory responses. In addition, we will discuss whether AD pathology could be the outcome of chronic activation of the innate immunity defence in the brain of AD patients.

Contents

* Corresponding author at: Department of Neurology, Institute of Clinical Medicine, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland. Fax: +358 17162048.
E-mail address: antero.salminen@uku.fi (A. Salminen).

Abbreviations: AD, Alzheimer 's disease; ADDL, amyloid-β derived diffusible ligand; APP, amyloid-β precursor protein; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; DAMP, danger-associated molecular pattern; FPR, N-formyl peptide receptors; HMGB, high mobility group box; HSP, heat shock protein; IDE, insulin degrading enzyme; IL, interleukin; IRF, interferon regulatory factor; JNK, c-Jun NH2-terminal kinase; LPS, lipopolysaccharide; LRP, low-density lipoprotein receptor-related protein; LTP, long-term potentiation; MAC, membrane attack complexes; NEP, neprilysin; NLR, NOD-like receptors; NSAID, nonsteroidal anti-inflammatory drug; PAMP, pathogen-associated molecular pattern; PECAM-1, platelet endothelial cell adhesion molecule; PRR, pattern recognition receptor; PTX, pentraxin; RAGE, receptor for advanced glycation end product; TLR, Toll-like receptor; TREM, triggering receptors expressed on myeloid cell.

0301-0082/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2009.01.001

1. Inflammation in the pathogenesis of Alzheimer's disease (AD)

There is a consensus that inflammation is involved in the pathogenesis of Alzheimer's disease (AD) (Neuroinflammation Working Group, 2000). However, the role of inflammation in the pathogenetic process is still a matter of debate, and it has been argued that neuroinflammation seems to be associated with AD pathology. One hundred years ago, Fischer (1910), according to Eikelenboom et al. (2006), proposed that the deposition of a peculiar foreign substance in the human cortex could induce a local inflammatory reaction followed by regenerative changes in the surrounding neurons. This statement still holds true although inflammation has also been considered as a secondary, bystander response to the neuronal degeneration and death. Moreover, some studies indicate that inflammation has neuroprotective, beneficial effects in AD. The role of the inflammatory process in AD, evidence for its presence and ultimate significance, has been topics covered in detailed reviews (McGeer and McGeer, 2003; Eikelenboom et al., 2006; Wyss-Coray, 2006; Heneka and O'Banion, 2007).

Twenty years ago, this "peculiar foreign substance" was identified as fibrillated amyloid-β peptides (see Tanzi and Bertram, 2005) which can be recognized and phagocytozed by glial cells, and therefore should not be aggregated in brain. However, amyloid-β peptides can oligomerize and aggregate to neuritic plaques which do not seem to be recognized by glial cells. Amyloid plaques also accumulate during aging, and the stage of AD does not correlate with the level of neuritic plaques (Eikelenboom et al., 2006). Furthermore, the amounts of amyloid plaques and neurofibrillary tangles, another hallmark of AD, are not increased equally and the regulatory interactions are matter of debate. It seems that amyloid-β peptide aggregation and tau protein phosphorylation and tangle formation cannot explain by themselves the AD pathology but some missing link seems to regulate the pathogenetic process and progressive dementia in AD.

There is strong evidence implicating the inflammatory process in the pathology encountered in the AD brain. Examination of postmortem brains of AD patients reveals the abundant presence of inflammatory mediators, such as proinflammatory cytokines and chemokines, e.g. IL-1, IL-6, TNFα, MIP-1β, complement activation products, and oxygen radicals (Neuroinflammation Working Group, 2000; McGeer and McGeer, 2003; Heneka and O'Banion, 2007; Rojo et al., 2008). Histopathology shows increased numbers of active astro- and microglial cells. Inflammatory processes are present also in transgenic AD mice which produce an abundance of human amyloid-β peptides and develop amyloid plaques (Hoozemans et al., 2006; Wyss-Coray, 2006). However, several clinical trials with anti-inflammatory NSAIDs (nonsteroidal anti-inflammatory drugs) have not shown any significant improvement in progressive dementia (Rojo et al., 2008). NSAIDs affect only a few of the factors in inflammatory process, and as we will discuss later (see Section 5), the chronic nature of inflammation may induce immunosuppression of microglia via innate immunity signaling.

In this review, we will focus on the role of innate immunity system of brain in the initiation and propagation of inflammatory process in AD. In particular, we examine in detail the significance of amyloid-β species as danger-associated molecular patterns (DAMPs) in the activation of pattern recognition receptors (PRRs) in both glial cells and neurons. In addition, we point out that AD pathology seems be the outcome of the activation of innate immunity defence in brain.

2. Innate immunity: guardian against pathogens and danger insults via pattern recognition receptors

Discrimination of self and non-self has been one of the fundamental forces in evolution, both in unicellular and multicellular organisms (Danilova, 2006). Host-defence has been based on the recognition of pathogen structures (Akira et al., 2006). Different strategies have evolved to recognize pathogen-associated molecular structures, abbreviated to PAMPs. Another requirement for successful evolution has been the sensing of the pathogen-free, self-derived danger signals and tissue injuries, in this case called danger-associated molecular structures (DAMPs). Interestingly, organisms utilize the same pattern recognition receptors (PRRs) to defend themselves against both environmental and inherent threats, i.e. PAMPs and DAMPs. The first, perhaps original, host-defence mechanism, based on germline-encoded receptors, is called the innate immunity system (Danilova, 2006). During evolution, higher organisms have supplemented the innate immunity defence with the adaptive immunity which is based on the immunological memory carried by specialized immune cells (Danilova, 2006; Pancer and Cooper, 2006).

Some of the host-defence mechanisms, such as phagocytosis, RNA interference, and anti-microbial peptide defence, originated in unicellular organisms (Danilova, 2006). Multicellular organisms then developed the PRRs and later the specialized immune cell network. The innate immunity system involves many types of PRRs which have different locations in cells, or they can be secreted, as is the case for the complement components (see Section 4.6).

The activation of innate immunity is a double-edged sword; it provides a rapid defence against a variety of dangerous conditions, compared to the adaptive immune response, but during chronic insults, it may become harmful to the brain (Eikelenboom et al., 2006; Wyss-Coray, 2006). It seems that the clearance system of the brain, including astrocytes and microglial cells, is not able to dispose effectively of amyloid-β oligomers and fibrils which can activate signaling via PRRs and establish a chronic inflammatory response. This immune attack along with direct neurotoxic effects of amyloid-β species triggers a plethora of new DAMPs which subsequently aggravate the inflammation-driven AD pathogenesis.

3. Amyloid-β oligomers and fibrils trigger the inflammatory process in AD

Different research approaches have confirmed the central role of amyloid-β oligomers and fibrils in the pathogenesis of AD (Haass and Selkoe, 2007; Walsh and Selkoe, 2007; Tanzi and Bertram, 2005; Klein, 2002). The processing of amyloid-β precursor protein (APP) by β- and γ-secretases produces amyloid-β peptides, of which Aβ1–42 is especially toxic since it is spontaneously prone to undergo oligomerization and fibrillation processes. Recent studies have revealed that the soluble amyloid-β oligomers (ADDL, amyloid-β derived diffusible ligand) are the most toxic of the amyloid-β species to neurons, in particular the trimeric and tetrameric oligomers, which are stable and can target synapses leading to synaptic dysfunction, and ultimately the loss of synaptic integrity (De Felice et al., 2007; Haass and Selkoe, 2007; Walsh and Selkoe, 2007; Salminen et al., 2008). Amyloid-β oligomers and fibrils can cause direct neuronal injuries, but since they are foreign molecular structures, they can also activate the PRRs of the innate immunity system and induce inflammatory responses (see Sections 3 and 4). Several studies have demonstrated that amyloid-β species can interact with neuronal membranes to create ion channels, so-called Aβ channels, which can mediate ion fluxes (Arispe et al., 2007). In a similar manner to the bacterial pore-forming toxins, the pores formed by amyloid-β species are believed to cause potassium efflux which can activate inflammasomes and IL-1β secretion (see Section 4.2).

The processing of APP to amyloid-β peptides is a normal physiological process in neurons. However, an increase in the production of amyloid-β 1–42 peptides, e.g. in the case of genetic