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Review Article

Complex role of chemokine mediators in animal models of Alzheimer's Disease


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ABSTRACT

Chemokines are a family of cytokines, first described to play a role in the immune system. However, neurons and glial cells also express chemokines and their receptors. In the central nervous system, chemokines are involved in several neural functions, in particular in the control of cell communications and neuronal activity. In pathological conditions, chemokines participate in neuroinflammatory and neurodegenerative processes. In Alzheimer's disease (AD), chemokines play a role in the development of the two main lesions, amyloid β plaques and neurofibrillary tangles. In addition, they contribute to the inflammatory response by recruiting T cells and controlling microglia/macrophages activation. Actually, targeting inflammatory pathways seems a promising therapeutic approach for the treatment of AD patients. This review summarizes our current knowledge on the roles of chemokines in AD animal models and the underlying mechanisms in which they take part. Better knowledge of the role of chemokines and their cellular receptors in AD could open new therapeutic perspectives.

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, with an increasing prevalence due to an aging population. AD is a fatal brain disease and currently, there is no cure or treatment which delays or stops the progression of AD. This neurodegenerative disease is characterized by two main lesions: senile plaques and neurofibrillary tangles. The exact processes that cause the disease are still poorly understood. They might involve toxic oligomers of amyloid β (Aβ) peptides and/or the formation of amyloid (senile) plaques composed of extracellular aggregates of Aβ peptides, and/or rely on the formation of neurofibrillary tangles composed of intraneuronal aggregates of hyperphosphorylated Tau protein. The Aβ peptides are generated by the sequential cleavage of APP by two enzymes, the β-amyloid cleavage enzyme and the γ secretase complex composed of presenilin (PS), nicastrin, presenilin enhancer 2 and anterior pharynx-defective 1. Less than 1% of AD cases are caused by mutation in APP and PS genes. Mutations in the gene encoding Tau have not been identified in AD cases. However, Tau mutations found in other Tauopathies are co-expressed with APP and PS bearing AD familial mutations to model both neurofibrillary tangles and Aβ plaques in transgenic animals [1].

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Alzheimer's disease and inflammation

Genetic studies have also identified polymorphisms, linked to AD, in genes involved in the innate immune system [2–5]. In AD patients, many activated microglial cells and astrocytes have been shown to be associated with lesions and inflammatory molecules. Microglial cells are the resident immune cells of the central nervous system (CNS) and derive from myeloid progenitors from the yolk sac before embryonic day 8 and maintain in the brain by self-renewal [6]. Microglia participate in the immune response in AD by activating the complement cascade and producing inflammatory cytokines such as IL-1β, IL-6 and TNF-α [7]. Early recruitment of microglia seems beneficial in AD by promoting phagocytosis and clearance of Aβ peptides. However, as disease progresses, microglia are overwhelmed by the excessive amount of Aβ and become more pro-inflammatory [8]. These chronic inflammatory processes lead to alteration of microglial functions creating a vicious circle. Consequently, microglia are unable to restrict the formation of Aβ plaques [9]. Thus, several studies on inflammatory mediators and immune pathways revealed that inflammatory and immunological processes are central to the progression of AD [10,11].

Chemokines

Among pro-inflammatory molecules, chemokines are a subfamily of chemotactic cytokines. Chemokines are a large family of over 50 small proteins. Chemokines exert their functions through chemokines receptors that belong to the superfamily of G-protein-coupled receptors. Chemokines were first named according to their biological functions. Since 2000, chemokines were classified in 4 subfamilies based on their structural shapes related to the number and spacing of conserved cysteine residues at the N-terminal domain (CXC, CC, CX3C and C) [12]. Chemokines bind to different receptors and several distinct chemokines share common receptor. Chemokines were first described to contribute to numerous aspects of immune function as recruitment of immune cells but they have also important roles in the CNS such as brain development, neuroinflammation and neuroendocrine functions [13]. CNS cells constitutively express chemokine receptors while chemokines are mainly produced during diverse pathological states [14]. In this review, we did not detail results on the expression of chemokines and chemokines receptor in AD patients and AD models. In general, most of them were overexpressed during the pathology with the exception of CX3CL1/CX3CR1 [15], for review see Refs. [14,16]. We preferred to focus on the molecular mechanisms triggered by chemokines receptors activation that contribute to the development of the disease.

Chemokines and animal models of Alzheimer's disease

CX3CR1

In the CNS, microglia constitutively express the receptor CX3CR1 and neurons its unique ligand CX3CL1 as a transmembrane protein. The interaction between CX3CL1 (also named fractalkine) and CX3CR1 is important in neuronal-microglial communication, throughout the life span, allowing neurons to regulate microglia activation [17]. Microglia control synaptic pruning during development, survey neuronal damages as well as sensing the presence of danger signals. CX3CL1 can be cleaved by a disintegrin and metalloprotease (ADAM10, 17) or a cysteine protease cathepsin S and subsequently induces the recruitment of leucocytes expressing CX3CR1 from the periphery, such as monocytes. In the CNS, CX3CL1/CX3CR1 signalling controls the production of growth factor and cytokines, in particular IL-1β [18], microglial phagocytic activity but also proliferation and survival of neural progenitor cells [17]. Globally, neuron controls microglial functions through this interaction. On the other hand, disruption of CX3CL1/CX3CR1 pathway in physiological conditions leads to impairment of hippocampal neuronal functions (reduction of adult hippocampal neurogenesis, impairment in long-term potentiation (LTP), and deficits in contextual fear conditioning and Morris water maze tests) suggesting a role in cognitive deficits present in AD [19–21]. In AD model, CX3CR1 & CX3CL1 have opposite roles on the Aβ and Tau pathologies. Deletion of CX3CR1 enhances Tau phosphorylation and aggregation of hyperphosphorylated Tau that increase behavioral impairments in the humanized Tau transgenic mice. The authors propose a model where CX3CR1-defiency induces an increase of IL-1β release that binds to IL1 receptor on neurons and activates the p38 MAPkinase leading to hyperphosphorylation of Tau [22]. This result was confirmed in another Tau model of AD i.e. the Tg4510 mice which express the human Tau containing the P301L mutation [23]. Overexpression of soluble CX3CL1 using adeno-associated viral vector (AAV) reduces Tau phosphorylation, microglia activation and neuronal loss observed in this model.

In Aβ models of AD, the results are more divergent and can be explained by the different animal models used. Overall, the data suggest a protective effect of CX3CR1 deficit on Aβ lesions. These studies were performed in three different Aβ models of AD: (1) TgCRND8 which expresses the human APP containing KM670/671NL and V717F mutations; (2) the double transgenic model APP/PS1 expressing the human APP containing K670M/N671L mutations and PS1 harboring the L166P mutation; (3) the R1.40 transgenic line which contains a yeast artificial chromosome (YAC) expressing the human APP containing K670M/N671L mutations. In these models, the introduction of CX3CR1 deficiency was shown to increase phagocytosis and reduce Aβ lesions [24,25]. In these studies, the memory deficits were not assessed, thus the overall beneficial vs. pathological role of CX3CL1/CX3CR1 on cognitive functions were not determined. In contrast, using the J20 transgenic mouse model in which the human APP containing KM670/671NL and V717F mutations are expressed under the control of the PDGF-β promoter, Cho et al. did not observe any effects on Aβ load but an increase in memory deficits associated with higher levels of phospho-Tau [15]. CX3CR1-deficiency in APP/PS1 mice also induces hyperphosphorylation of Tau, thus the beneficial effect of CX3CR1 on Tau pathology could be predominant compared to the detrimental effect on Aβ deposits [26]. These effects on the levels of Aβ peptides and phospho-Tau were also observed in APP/PS1 mice by knocking-out the ligand CX3CL1, confirming

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