Short Conceptual Overview

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Alzheimer's disease as an inflammatory disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative condition characterized by the formation of amyloid-β plaques, aggregated and hyperphosphorylated tau protein, activated microglia and neuronal cell death, ultimately leading to progressive dementia. In this short review, we focus on neuroinflammation in AD. Specifically, we describe the participation of microglia, as well as other factors that may contribute to inflammation, in neurodegeneration.

Keywords: Alzheimer's disease; beta amyloid peptide (Aβ); inflammation; microglia; tau.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. It is characterized by the presence of two aberrant structures within the patient's brain, namely senile plaques and neurofibrillary tangles (NFTs). In addition, it causes the loss of neuronal function and neuronal death in the later stages of the disease (1).

The main component of senile plaques and NFTs are amyloid beta (Aβ) peptide and tau proteins (2), respectively. Aβ is cleaved from the larger amyloid precursor protein (APP) (3). In the familial type of AD (FAD), which has an incidence below 5%, mutations in APP and in presenilin 1 and 2 genes can lead to increased levels of Aβ, which may be related to the onset of the disease (4). For the remaining cases of (sporadic) AD, which typically develops later than familial AD, the cause is largely unknown. Given that the degenerative process of the two forms of the disease are similar, it is thought that they share the same underlying mechanism.

On the basis of these observations, Aβ has become a major pharmacological target for the treatment of the disease. The amyloid cascade-inflammatory hypothesis has been put forward to explain the mechanism underlying Aβ toxicity in AD (5–11). This hypothesis proposes that Aβ induces an inflammatory response that is enhanced by the presence of tau. An excess of soluble Aβ species, as well as aggregated Aβ and hyperphosphorylated tau proteins, interferes with neuronal function and triggers the inflammatory activity of microglia, some of the primary events being those that initiate AD pathology. It has even been discussed whether a pro-inflammatory process could precede AD (12, 13). The inflammatory response is driven mainly by activated microglia (14). The activation of these cells has been reported in both AD patients and animal models of this disease (15), and it is accompanied by increased levels of specific chemokines and cytokines (16). In addition, the protective effects of non-steroidal anti-inflammatory drugs (NSAIDs) against AD development (17) further support the neuroinflammation hypothesis of AD (5). Finally, as the disease progresses, neurodegeneration ensues, interfering with the properties of the central nervous system (CNS) and thus affecting neuronal function, as well as the structure and survival of the neurons themselves.

Microglia

Microglia are glial cells located in the CNS. They play a macrophage-like role in the immune defense of this system (18–21). These cells were named by the Spanish neuroscientist Pío del Río Hortega about a century ago (22, 23). He postulated that microglia serve as macrophages by phagocytosing toxic elements in the CNS.

The origin of microglia differs from that of other types of brain glia or macroglia. In the mouse brain, microglia originate from myeloid progenitors in the yolk sac that migrate into the brain during early embryonic stages, before the blood-brain barrier is formed (24). Under

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physiological conditions, microglia proliferate throughout embryogenesis and self-renew constantly throughout life to maintain cell numbers, without a contribution from bone marrow-derived macrophages (25).

Recent evidence shows that microglia are highly dynamic. Under both physiological and pathological conditions, they monitor their environment and regulate tissue homeostasis through scavenging functions (26). Therefore, resident microglia have functions related to immune surveillance (27); adult neurogenesis and refinement of synaptic networks such as synapse pruning, promotion or removal apoptosis, secretion of growth factors, among others (28). During the regulation of brain homeostasis, microglia can undergo changes in their metabolism and morphology (24, 29). In this regard, two main microglia types, namely resting and activated, have been described (Figure 1A–D). The former show long cytoplasmic extensions that are in continuous movement. The latter change shape to become an activated and mobile amoeboid, which can be recognized by the expression of ionized calcium binding adapter molecule 1 (Iba1) or cluster of differentiation (CD) 68 (CD68) markers. The transition of a microglial cell from the resting to the activated type and the resulting changes in morphology are promoted by various extracellular cytokines or factors such as lipids or lipopolysaccharides (LPS) (30, 31). Also, a transition to senescent glia could take place in some pathologies like AD (13).

Activated microglia, like peripheral macrophages, are often classified into inflammatory (M1) and alternatively activated (M2) phenotypes (32) (Figure 1A). However, these cells show high levels of diversity and plasticity and their classification into an M1 or M2 polarized state may be an oversimplification (14, 33, 34). Recently, it has been proposed that microglia switch continuously between phenotypes (35, 36). However, the M1 phenotype

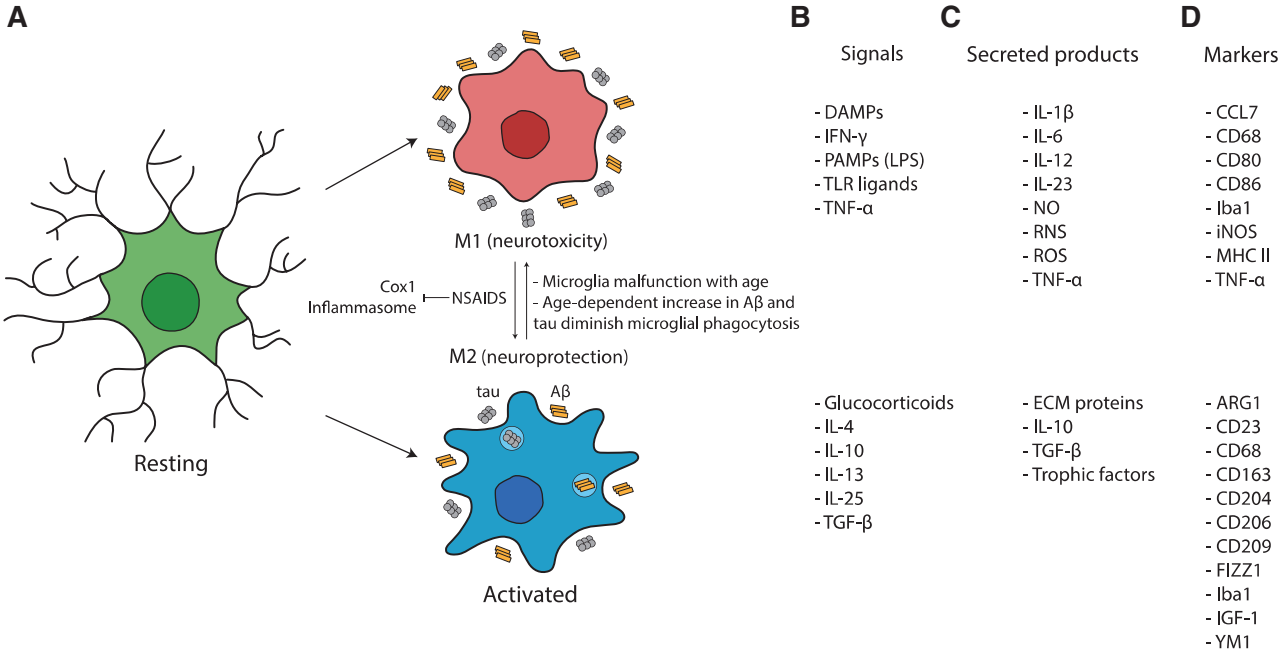

Figure 1: Diagram of polarization states of microglia.
(A–B) Resting microglia may turn into distinct phenotypes depending on the signals that they receive. (C) M1 classical state releases pro-inflammatory cytokines and cytotoxic substances inducing neurological damage. On the other hand, the M2 alternative state produces trophic factors and anti-inflammatory cytokines that have a neuroprotective role in the CNS. (D) Several proteins have been proposed as specific markers to differentiate between M1 and M2 states. During the progression of neurodegenerative diseases, there is an imbalance of M1/M2 populations, the M1 phenotype being more predominant at late stages. Moreover, it is known that the functions and morphology of microglia are altered during aging. For example, phagocytic capacity in AD is decreased due to the increasing amounts of Aβ and tau. NSAIDs have been studied as a therapeutic treatment to reduce the M1/M2 imbalance, by decreasing pro-inflammation and attenuating neuron loss. AD, Alzheimer's disease; ARG1, arginase 1; Aβ, amyloid β peptide; CCL7, chemokine (C-C motif) ligand 7; CD, cluster of differentiation; CNS, central nervous system; Cox1, cyclooxygenase1; DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; FIZZ1, found in inflammatory zone 1; Iba1, ionized calcium-binding adapter molecule 1; IFN-γ, interferon γ; IGF-1, insulin growth factor 1; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MHC II, major histocompatibility complex II; NO, nitric oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; PAMPs, pathogen-associated molecular patterns; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF-β, transforming growth factor β; TLR, toll-like receptor; TNF-α, tumor necrosis factor α; YM1, chitinase-like 3.

is induced by means of interferon (IFN)-γ and LPS stimulation, among others, and the M2 phenotype by means of interleukin (IL)-4, IL-10, and IL-13 (31, 37), etc. (Figure 1B). M1 microglia are associated with the production and release of pro-inflammatory cytokines, namely tumor necrosis factor (TNF)-α, IL-6, IL-23, IL-1β, IL-12, nitric oxide (NO), and chemokines, among others (38) (Figure 1C). In contrast, M2 microglia express anti-inflammatory molecules, such as IL-10 and transforming growth factor (TGF)-β, and extracellular matrix molecules (39). In addition, it has been proposed that M1 microglia predominate at the site of injury under pathological situations, whereas M2 microglia appear later at a stage more related to repair processes (34). In most cases, microglia in AD patients exhibit mixed activation phenotypes. Indeed, cortical tissue from the Tg2576 mouse and individuals with AD show a mixed profile of alternative activation and classical activation genes (40).

Neurodegenerative diseases are associated with elderly people. In this regard, it has also been hypothesized that aging leads to the dysfunction or dystrophia of these cells (34). Nevertheless, a larger reduction in process length and arborized area in AD compared to aged-matched control microglia has recently been described (41).

Activation of microglia

Bacterial LPS is the major outer surface membrane component present in almost all Gram-negative bacteria, and it is an extremely strong stimulator of innate or natural immunity. LPS can bind to microglia to induce the M1 phenotype, which secretes pro-inflammatory cytokines (31) that promote the inflammatory response. The secretion of these molecules can be prevented by anti-inflammatory therapeutic agents, specifically by NSAIDs (42) (Figure 1A). NSAIDs exert their effects by inhibiting the activity of cyclooxygenase (COX) enzymes COX1 and COX2 (43). Ibuprofen is a NSAID and therefore has the capacity to inhibit COX1 and COX2. In this regard, the potential of ibuprofen to inhibit the effects of LPS in mouse models has been addressed (44). COX1 is expressed mainly in microglial cells and COX2 in neurons (45). COX protein expression has not been reported in astrocytes (46). However, the inhibition of COX1 does not totally block the inflammatory response.

This observation suggests that NSAIDs could initiate other elements involved in the inflammatory response. One such element is the multi-protein complex known as the inflammasome (47–49). Inflammasomes have been linked to a variety of auto-inflammatory and auto-immune diseases, including neurodegenerative diseases and metabolic disorders (50). Therefore, the inflammatory cytokine IL-1β secreted by activated microglia is synthesized as an inactive precursor and it requires the action of caspase 1 to become active (51). Increased amounts of cleaved caspase-1 have been reported in hippocampal and cortical lysates from AD patients compared to controls. This finding is consistent with chronic inflammasome activation (47). The best characterized inflammasome-forming pattern recognition receptor and the one most commonly associated with AD is NLRP3 (NLR family, pyrin-domain containing 3) (47). Previous activation of caspase-1 requires the NLRP3 inflammasome (52). The NLRP3/caspase-1 axis plays an important role in AD pathogenesis, and therefore inhibition of the NLRP3 inflammasome emerges as a novel therapeutic intervention for neurological diseases that course with inflammation.

Role of Aβ in brain inflammation

In animal models overexpressing Aβ, inflammatory responses to amyloidosis could take place (53, 54). In this amyloidosis microglia could exert neuroprotective activity by degrading Aβ (55). In AD, these cells have a reduced capacity for Aβ clearance, which results in additional accumulation of this peptide (56). Microglia-mediated clearance of Aβ occurs through the TLR4, the same receptor that is used for LPS action (57). Thus, Aβ (mainly in an aggregated form) is a TLR4 ligand, and chronic exposure of this receptor to Aβ can result in TLR signaling dysfunction and inflammation (57, 58). Aβ aggregates interact with other microglial receptors like CD14, CD36, CD47, the receptor for advanced glycation end products (RAGE), and some integrins (59–62). It has been proposed that the binding of Aβ to CD36 regulates inflammasome activation (63). In addition, Aβ peptide may activate the NLRP3 inflammasome in microglia (64). More recently, it has been reported that Aβ activates microglia through its interaction with the APP present in the membrane of these cells (65). This finding defines a novel function of APP in microglial regulation of the inflammatory response in AD (65).

Role of tau in brain inflammation

Tau is a neuronal microtubule-associated protein whose main function is to stabilize microtubules (66). The pathological aggregations of hyperphosphorylated tau

are the defining histopathological features of AD and other tauopathies. Recent research has shown that NFTs themselves are not the most toxic form of tau, but rather the smaller aggregates, called tau oligomers, which are likely to initiate neurodegeneration in tauopathies. Oligomeric tau can be released into the extracellular space and can spread throughout the brain. Activated microglia are frequently present in the proximity of NFTs in the hippocampus of AD patients, thereby indicating a close relationship between the inflammatory response and tau neurofibrillary lesions. Furthermore, tau can be phagocytosed by microglia (67). This finding would support the notion that impaired clearance of extracellular tau (by microglia) contributes to the spread of pathological tau, as shown in AD (68).

In animal models of tauopathies, tau dysfunction may result in changes in neuroinflammatory gene regulation (69). Deficits in tau function affect various neuronal functions, such as the secretion of proteins like fractalkine (CX3CL1) (70, 71). CX3CL1 secreted by neurons can bind to its receptor in microglia (CX3CR1), and this process maintains microglia in an 'off' state (72), thereby inhibiting the release of inflammatory cytokines (73, 74). The deficiency of CX3CR1 in microglia results in increased secretion of IL-1β. This pro-inflammatory cytokine interacts with neurons, thereby enhancing tau neuronal pathology via p38MAPK (75).

A main tau modification, occurring in AD, is its phosphorylation. Tau hyperphosphorylation could be toxic, independently if it forms toxic aggregates or could remain in soluble form (76). In this way, tau toxicity could result in an inflammatory process that could be prevented by the inhibition of tau kinases, like GSK3 (77). However, tau phosphorylation at different residues could result in different toxicity levels and even a site-specific phosphorylation of tau could inhibit amyloid toxicity, in a mouse model (78).

Other factors modulate inflammation

In recent years, genome-wide association studies (GWAS) have identified a large number of risk genes for AD. In this regard, the R47H mutation in Triggering receptor expressed on myeloid cells 2 (TREM2) has been reported as a risk for this disease. TREM2 is a transmembrane glycoprotein that is expressed exclusively by immune cells in the brain. Mutations in TREM2 are associated with microglial dystrophy, decreased phagocytosis, and an increased pro-inflammatory reactive phenotype. These features increase the risk of AD, as previously described (79, 80). It has been shown that TREM2 deficiency increases LPS-induced IL-6 and IL-1β mRNA levels in microglia. This observation thus indicates that TREM2 restrains microglia activation (81).

Environmental factors contribute to the regulation of microglia. An example of this is the communication from gut to brain (29, 30, 82). The human intestine contains many microbial cells that secrete factors, which, after crossing the blood-brain barrier, reach the CNS to interact with microglia. In this way, microbiota could have the capacity to modulate behavioral and physiological abnormalities associated with neuronal disorders (30).

Allergic diseases are generally accompanied by chronic systemic inflammation. The effects of allergy on AD have not been addressed, but epidemiological studies suggest that the presence of allergic diseases, especially asthma, is associated with an almost two-fold increase in the risk of developing any form of dementia, including AD, later in life (83, 84). Asthma is an inflammatory disease of the airways, and it is characterized by airway eosinophilia, in which the CCL11 (eotaxin-1) chemokine plays a crucial role. Eotaxin-1 is a key molecule in eosinophil chemoattraction and activation in asthma pathogenesis (85). Of note, eotaxin-1 levels increase throughout life, thus being a molecular effector of aging, the largest risk factor for developing AD (86). It has been shown that plasma eotaxin-1 levels are correlated with AD patients. Therefore, low to moderate eotaxin-1 levels elicit a normal or protective response, while higher levels ultimately lead to neurodegeneration and memory impairment (87).

Studies in mice revealed an association between allergy and increased phosphorylation of tau (88). More recently, it has been described that allergic long-term inflammation results in a reduction in the number of activated microglia at the dentate gyrus, together with enhanced neurogenesis in that brain region (89).

Taken together, all these observations support the notion that cross-talk between peripheral tissues and the CNS could regulate microglial activation, and, in some cases, might result in the onset of neurodegeneration.

Conclusions

Neuroinflammation is one of the main triggers of neurodegeneration. Research into the factors and pathways able to induce the first steps of the inflammatory response would lead to the identification of potential therapeutic targets through which to halt the progression of AD.

List of abbreviations

AD	Alzheimer's disease
Aβ	beta amyloid peptide
NFT	neurofibrillary tangles
SP	senile plaques
APP	amyloid precursor protein
NAIDS	non-steroidal anti-inflammatory drugs
CD	cluster of differentiation
LPS	lipopolysaccharides
IL	interleukin
TNF-α	tumor necrosis factor α
TGF-β	transforming growth factor β
COX	cyclooxygenase
RAGE	receptor for advanced glycation end products
GWAS	genome-wide association study
TREM2	triffering receptor expressed in myeloid cells 2

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