Short Conceptual Overview

Marta Bolós, Juan Ramón Perea and Jesús Avila*

Alzheimer's disease as an inflammatory disease

DOI 10.1515/bmc-2016-0029

Received December 7, 2016; accepted January 10, 2017

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 (A β); 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 (A β) peptide and tau proteins (2), respectively. A β 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 A β , 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, A β 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 A β toxicity in AD (5–11). This hypothesis proposes that A β induces an inflammatory response that is enhanced by the presence of tau. An excess of soluble A β species, as well as aggregated A β 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

*Corresponding author: **Jesús Avila**, Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Valderrebollo 5, E-28041-Madrid, Spain; and Centro de Biología Molecular "Severo Ochoa" CSIC-UAM, Nicolás Cabrera 1, E-28049-Madrid, Spain, e-mail: jesus.avila@csic.es; javila@cbm.csic.es

Marta Bolós and Juan Ramón Perea: Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Valderrebollo 5, E-28041-Madrid, Spain; and Centro de Biología Molecular "Severo Ochoa" CSIC-UAM, Nicolás Cabrera 1, E-28049-Madrid, Spain. <http://orcid.org/0000-0001-7607-8814> (J.R. Perea)

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 A β 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; A β , 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-1 β , 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 dystrophy 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-1 β 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 A β in brain inflammation

In animal models overexpressing A β , inflammatory responses to amyloidosis could take place (53, 54). In this amyloidosis microglia could exert neuroprotective activity by degrading A β (55). In AD, these cells have a reduced capacity for A β clearance, which results in additional accumulation of this peptide (56). Microglia-mediated clearance of A β occurs through the TLR4, the same receptor that is used for LPS action (57). Thus, A β (mainly in an aggregated form) is a TLR4 ligand, and chronic exposure of this receptor to A β can result in TLR signaling dysfunction and inflammation (57, 58). A β 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 A β to CD36 regulates inflammasome activation (63). In addition, A β peptide may activate the NLRP3 inflammasome in microglia (64). More recently, it has been reported that A β 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-1 β . 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-1 β 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
A β	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	triggering receptor expressed in myeloid cells 2

References

- Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Psych genchl Med* 1907; 64: 146–8.
- Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. *Lancet* 2016; 388: 505–17.
- Goldgaber D, Lerman MI, McBride OW, Saffiotti U, Gajdusek DC. Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease. *Science* 1987; 235: 877–80.
- Tanzi RE. The genetics of Alzheimer disease. *Cold Spring Harb Perspect Med* 2012; 2. pii: a006296. doi: 10.1101/cshperspect.a006296.
- McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. *Acta Neuropathol* 2013; 126: 479–97.
- Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. *Nat Rev Neurosci* 2015; 16: 358–72.
- Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mrak R, Mackenzie IR, McGeer PL, O'Banion MK, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strommeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T. Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000; 21: 383–421.
- Lee YJ, Han SB, Nam SY, Oh KW, Hong JT. Inflammation and Alzheimer's disease. *Arch Pharm Res* 2010; 33: 1539–56.
- Holmes C. Review: systemic inflammation and Alzheimer's disease. *Neuropathol Appl Neurobiol* 2013; 39: 51–68.
- Perry VH. Contribution of systemic inflammation to chronic neurodegeneration. *Acta Neuropathol* 2010; 120: 277–86.
- Sardi F, Fassina L, Venturini L, Inguscio M, Guerriero F, Rolfo E, Ricevuti G. Alzheimer's disease, autoimmunity and inflammation. The good, the bad and the ugly. *Autoimmun Rev* 2011; 11: 149–53.
- Ferretti MT, Cuellar AC. Does a pro-inflammatory process precede Alzheimer's disease and mild cognitive impairment? *Curr Alzheimer Res* 2011; 8: 164–74.
- Streit WJ, Braak H, Xue QS, Bechmann I. Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. *Acta Neuropathol* 2009; 118: 475–85.
- Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science* 2016; 353: 777–83.
- Cagnin A, Brooks DJ, Kennedy AM, Gunn RN, Myers R, Turkheimer FE, Jones T, Banati RB. In vivo measurement of activated microglia in dementia. *Lancet* 2001; 358: 461–7.
- Swardfager W, Lancot K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry* 2010; 68: 930–41.
- Vlad SC, Miller DR, Kowall NW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology* 2008; 70: 1672–7.
- Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep* 2014; 6: 13.
- Streit WJ. Microglia and neuroprotection: implications for Alzheimer's disease. *Brain Res Brain Res Rev* 2005; 48: 234–9.
- Graeber MB, Streit WJ. Microglia: biology and pathology. *Acta Neuropathol* 2010; 119: 89–105.
- Graeber MB, Li W, Rodriguez ML. Role of microglia in CNS inflammation. *FEBS Lett* 2011; 585: 3798–805.
- Tremblay ME, Lecours C, Samson L, Sanchez-Zafra V, Sierra A. From the Cajal alumni Achucarro and Rio-Hortega to the rediscovery of never-resting microglia. *Front Neuroanat* 2015; 9: 45.
- Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. *Physiol Rev* 2011; 91: 461–553.
- Ginhoux F, Lim S, Hoeffel G, Low D, Huber T. Origin and differentiation of microglia. *Front Cell Neurosci* 2013; 7: 45.
- Elmore MR, Najafi AR, Koike MA, Dagher NN, Spangenberg EE, Rice RA, Kitazawa M, Matusow B, Nguyen H, West BL, Green KN. Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. *Neuron* 2014; 82: 380–97.
- Ransohoff RM, Brown MA. Innate immunity in the central nervous system. *J Clin Invest* 2012; 122: 1164–71.
- Matcovitch-Natan O, Winter DR, Giladi A, Vargas Aguilar S, Spinrad A, Sarrazin S, Ben-Yehuda H, David E, Zelada González F, Perrin P, Keren-Shaul H, Gury M, Lara-Astaiso D, Thaïs CA, Cohen M, Bahar Halpern K, Baruch K, Deczkowska A, Lorenzo-Vivas E, Itzkovitz S, Elinav E, Sieweke MH, Schwartz M, Amit I. Microglia development follows a stepwise program to regulate brain homeostasis. *Science* 2016; 353: aad8670.
- Ransohoff RM, El Khoury J. Microglia in Health and Disease. *Cold Spring Harb Perspect Biol* 2016; 8: a020560.
- Erny D, Hrabé de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Mhlahkoiv T, Jakobshagen K, Buch T, Schwierzeck V, Utermöhlen O, Chun E, Garrett WS, McCoy KD, Diefenbach A, Staeheli P, Stecher B, Amit I, Prinz M. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* 2015; 18: 965–77.
- Mosher KI, Wyss-Coray T. Go with your gut: microbiota meet microglia. *Nat Neurosci* 2015; 18: 930–1.
- Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. *Br J Pharmacol* 2016; 173: 649–65.
- Boche D, Perry VH, Nicoll JA. Activation patterns of microglia and their identification in the human brain. *Neuropathol Appl Neurobiol* 2013; 39: 3–18.
- Ransohoff RM. A polarizing question: do M1 and M2 microglia exist? *Nat Neurosci* 2016; 19: 987–91.

34. Tang Y, Le W. Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. *Mol Neurobiol* 2016; 53: 1181–94.
35. Town T, Nikolic V, Tan J. The microglial “activation” continuum: from innate to adaptive responses. *J Neuroinflamm*. 2005; 2: 24.
36. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhatsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP. Neuroinflammation in Alzheimer’s disease. *Lancet Neurol* 2015; 14: 388–405.
37. Miron VE, Boyd A, Zhao JW, Yuen TJ, Ruckh JM, Shadrach JL, van Wijngaarden P, Wagers AJ, Williams A, Franklin RJ, French-Constant C. M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. *Nat Neurosci* 2013; 16: 1211–8.
38. Loane DJ, Byrnes KR. Role of microglia in neurotrauma. *Neurotherapeutics* 2010; 7: 366–77.
39. Michell-Robinson MA, Touil H, Healy LM, Owen DR, Durafour BA, Bar-Or A, Antel JP, Moore CS. Roles of microglia in brain development, tissue maintenance and repair. *Brain* 2015; 138(Pt 5): 1138–59.
40. Colton CA, Mott RT, Sharpe H, Xu Q, Van Nostrand WE, Vitek MP. Expression profiles for macrophage alternative activation genes in AD and in mouse models of AD. *J Neuroinflamm* 2006; 3: 27.
41. Davies DS, Ma J, Jegathees T, Goldsberry AC. Microglia show altered morphology and reduced arborisation in human brain during aging and Alzheimer’s disease. *Brain Pathol* 2016.
42. Llorens-Martin M, Jurado-Arjona J, Bolos M, Pallas-Bazarra N, Avila J. Forced swimming sabotages the morphological and synaptic maturation of newborn granule neurons and triggers a unique pro-inflammatory milieu in the hippocampus. *Brain Behav Immun* 2016; 53: 242–54.
43. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971; 231: 232–5.
44. Moriguchi T, Teter B, Yang F, Lim GP, Boudinot S, Boudinot FD, Frautschy SA, Cole GM. Ibuprofen suppresses interleukin-1 β induction of pro-amyloidogenic α 1-antichymotrypsin to ameliorate beta-amyloid (A β) pathology in Alzheimer’s models. *Neuropsychopharmacology* 2005; 30: 1111–20.
45. Deininger MH, Schluesener HJ. Cyclooxygenases-1 and -2 are differentially localized to microglia and endothelium in rat EAE and glioma. *J Neuroimmunol*. 1999; 95(1–2): 202–8.
46. Hoozemans JJ, Rozemuller AJ, Janssen I, De Groot CJ, Veerhuis R, Eikelenboom P. Cyclooxygenase expression in microglia and neurons in Alzheimer’s disease and control brain. *Acta Neuropathol* 2001; 101: 2–8.
47. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, Griep A, Axt D, Remus A, Tzeng T-C, Gelpi E, Halle A, Korte M, Latz E, Golenbock D. NLRP3 is activated in Alzheimer’s disease and contributes to pathology in APP/PS1 mice. *Nature* 2013; 493: 674–8.
48. Walsh JG, Muruve DA, Power C. Inflammasomes in the CNS. *Nat Rev Neurosci* 2014; 15: 84–97.
49. Pan Y, Chen XY, Zhang QY, Kong LD. Microglial NLRP3 inflammasome activation mediates IL-1 β -related inflammation in prefrontal cortex of depressive rats. *Brain Behav Immun* 2014; 41: 90–100.
50. Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature* 2012; 481: 278–86.
51. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med* 2015; 21: 677–87.
52. Daniels MJ, Rivers-Auty J, Schilling T, Spencer NG, Watremez W, Fasolino V, Booth SJ, White CS, Baldwin AG, Freeman S, Wong R, Latta C, Yu S, Jackson J, Fischer N, Koziel V, Pillot T, Bagnall J, Allan SM, Paszek P, Galea J, Harte MK, Eder C, Lawrence CB, Brough D. Fenamate NSAIDs inhibit the NLRP3 inflammasome and protect against Alzheimer’s disease in rodent models. *Nat Commun* 2016; 7: 12504.
53. Matsuoka Y, Picciano M, Malester B, LaFrancois J, Zehr C, Daeschner JM, Olschowka JA, Fonseca MI, O’Banion MK, Tenner AJ, Lemere CA, Duff K. Inflammatory responses to amyloidosis in a transgenic mouse model of Alzheimer’s disease. *Am J Pathol* 2001; 158: 1345–54.
54. Wirz KT, Bossers K, Stargardt A, Kamphuis W, Swaab DF, Hol EM, Verhaagen J. Cortical β -amyloid protein triggers an immune response, but no synaptic changes in the APP^{swE}/PS1^{dE9} Alzheimer’s disease mouse model. *Neurobiol Aging* 2013; 34: 1328–42.
55. Takata K, Kitamura Y, Saeki M, Terada M, Kagitani S, Kitamura R, Fujikawa Y, Maelicke A, Tomimoto H, Taniguchi T, Shimohama S. Galantamine-induced amyloid- β clearance mediated via stimulation of microglial nicotinic acetylcholine receptors. *J Biol Chem* 2010; 285: 40180–91.
56. Lee CY, Landreth GE. The role of microglia in amyloid clearance from the AD brain. *J Neural Transm (Vienna)* 2010; 117: 949–60.
57. Go M, Kou J, Lim JE, Yang J, Fukuchi KI. Microglial response to LPS increases in wild-type mice during aging but diminishes in an Alzheimer’s mouse model: Implication of TLR4 signaling in disease progression. *Biochem Biophys Res Commun* 2016; 479: 331–7.
58. Hines DJ, Choi HB, Hines RM, Phillips AG, MacVicar BA. Prevention of LPS-induced microglia activation, cytokine production and sickness behavior with TLR4 receptor interfering peptides. *PLoS One* 2013; 8: e60388.
59. Du Yan S, Zhu H, Fu J, Yan SF, Roher A, Tourtellotte WW, Rajavashisth T, Chen X, Godman GC, Stern D, Schmidt AM. Amyloid- β peptide-receptor for advanced glycation endproduct interaction elicits neuronal expression of macrophage-colony stimulating factor: a proinflammatory pathway in Alzheimer disease. *Proc Natl Acad Sci USA* 1997; 94: 5296–301.
60. Stewart CR, Stuart LM, Wilkinson K, van Gils JM, Deng J, Halle A, Rayner KJ, Boyer L, Zhong R, Frazier WA, Lacy-Hulbert A, El Khoury J, Golenbock DT, Moore KJ. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. *Nat Immunol* 2010; 11: 155–61.
61. Koenigsknecht J, Landreth G. Microglial phagocytosis of fibrillar β -amyloid through a β 1 integrin-dependent mechanism. *J Neurosci* 2004; 24: 9838–46.
62. Fassbender K, Walter S, Kuhl S, Landmann R, Ishii K, Bertsch T, Stalder AK, Muehlhauser F, Liu Y, Ulmer AJ, Rivest S, Lentschat A, Gulbins E, Jucker M, Staufenbiel M, Brechtel K, Walter J, Multhaup G, Penke B, Adachi Y, Hartmann T, Beyreuther K. The LPS receptor (CD14) links innate immunity with Alzheimer’s disease. *FASEB J* 2004; 18: 203–5.
63. Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhalawon B, Carpenter SB, Becker CE, Ediriweera HN, Mullick AE, Golenbock

- DT, Stuart LM, Latz E, Fitzgerald KA, Moore KJ. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nat Immunol* 2013; 14: 812–20.
64. Gold M, El Khoury J. β -Amyloid, microglia, and the inflammasome in Alzheimer's disease. *Semin Immunopathol* 2015; 37: 607–11.
 65. Manocha GD, Floden AM, Rausch K, Kulas JA, McGregor BA, Rojanathammanee L, Puig KR, Puig KL, Karki S, Nichols MR, Darland DC, Porter JE, Combs CK. APP regulates microglial phenotype in a mouse model of Alzheimer's Disease. *J Neurosci* 2016; 36: 8471–86.
 66. Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. *Physiol Rev* 2004; 84: 361–84.
 67. Bolos M, Llorens-Martin M, Jurado-Arjona J, Hernandez F, Rabano A, Avila J. Direct evidence of internalization of tau by microglia in vitro and in vivo. *J Alzheimers Dis* 2015; 50: 77–87.
 68. Maphis N, Xu G, Kokiko-Cochran ON, Jiang S, Cardona A, Ransohoff RM, Lamb BT, Bhaskar K. Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. *Brain* 2015; 138(Pt 6): 1738–55.
 69. Lopez-Gonzalez I, Aso E, Carmona M, Armand-Ugon M, Blanco R, Naudi A, Cabré R, Portero-Otin M, Pamplona R, Ferrer I. Neuroinflammatory gene regulation, mitochondrial function, oxidative stress, and brain lipid modifications with disease progression in tau P301S transgenic mice as a model of frontotemporal lobar degeneration-tau. *J Neuropathol Exp Neurol* 2015; 74: 975–99.
 70. Chen P, Zhao W, Guo Y, Xu J, Yin M. CX3CL1/CX3CR1 in Alzheimer's disease: a target for neuroprotection. *Biomed Res Int* 2016; 2016: 8090918.
 71. Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. *Neuron* 2010; 68: 19–31.
 72. Biber K, Neumann H, Inoue K, Boddeke HW. Neuronal 'On' and 'Off' signals control microglia. *Trends Neurosci* 2007; 30: 596–602.
 73. Cardona AE, Pioro EP, Sasse ME, Kostenko V, Cardona SM, Dijkstra IM, Huang D, Kidd G, Dombrowski S, Dutta R, Lee JC, Cook DN, Jung S, Lira SA, Littman DR, Ransohoff RM. Control of microglial neurotoxicity by the fractalkine receptor. *Nat Neurosci* 2006; 9: 917–24.
 74. Sheridan GK, Murphy KJ. Neuron-glia crosstalk in health and disease: fractalkine and CX3CR1 take centre stage. *Open Biol* 2013; 3: 130181.
 75. O'Sullivan SA, Gasparini F, Mir AK, Dev KK. Fractalkine shedding is mediated by p38 and the ADAM10 protease under pro-inflammatory conditions in human astrocytes. *J Neuroinflamm* 2016; 13: 189.
 76. Llorens-Martin M, Jurado J, Hernandez F, Avila J. GSK-3 β , a pivotal kinase in Alzheimer disease. *Front Mol Neurosci* 2014; 7: 46.
 77. Licht-Murava A, Paz R, Vaks L, Avrahami L, Plotkin B, Eisenstein M, Eldar-Finkelman H. A unique type of GSK-3 inhibitor brings new opportunities to the clinic. *Sci Signal* 2016; 9: ra110.
 78. Ittner A, Chua SW, Bertz J, Volkerling A, van der Hoven J, Gladbach A, Przybyla M, Bi M, van Hummel A, Stevens CH, Ippati S, Suh LS, Macmillan A, Sutherland G, Kril JJ, Silva AP, Mackay J, Poljak A, Delerue F, Ke YD, Ittner LM. Site-specific phosphorylation of tau inhibits amyloid-beta toxicity in Alzheimer's mice. *Science* 2016; 354: 904–8.
 79. Walter J. The Triggering receptor expressed on myeloid cells 2: a molecular link of neuroinflammation and neurodegenerative diseases. *J Biol Chem* 2016; 291: 4334–41.
 80. Tanzi RE. TREM2 and risk of Alzheimer's disease – friend or foe? *N Engl J Med* 2015; 372: 2564–5.
 81. Zhong L, Chen XF, Zhang ZL, Wang Z, Shi XZ, Xu K, Zhang YW, Xu H, Bu G. DAP12 stabilizes the C-terminal fragment of the triggering receptor expressed on myeloid cells-2 (TREM2) and protects against LPS-induced pro-inflammatory response. *J Biol Chem* 2015; 290: 15866–77.
 82. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 2013; 155: 1451–63.
 83. Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. *Curr Alzheimer Res.* 2013; 10: 549–55.
 84. Chen MH, Li CT, Tsai CF, Lin WC, Chang WH, Chen TJ, Pan TL, Su TP, Bai YM. Risk of dementia among patients with asthma: a nationwide longitudinal study. *J Am Med Dir Assoc* 2014; 15: 763–7.
 85. Wu D, Zhou J, Bi H, Li L, Gao W, Huang M, Adcock IM, Barnes PJ, Yao X. CCL11 as a potential diagnostic marker for asthma? *J Asthma* 2014; 51: 847–54.
 86. Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park J-S, Couillard-Després S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 2011; 477: 90–4.
 87. Lalli MA, Bettcher BM, Arcila ML, Garcia G, Guzman C, Madrigal L, Ramirez L, Acosta-Urbe J, Baena A, Wojta KJ, Coppola G, Fitch R, de Both MD, Huentelman MJ, Reiman EM, Brunkow ME, Glusman G, Roach JC, Kao AW, Lopera F, Kosik KS. Whole-genome sequencing suggests a chemokine gene cluster that modifies age at onset in familial Alzheimer's disease. *Mol Psychiatry* 2015; 20: 1294–300.
 88. Sarlus H, Hoglund CO, Karshikoff B, Wang X, Lekander M, Schultzberg M, Oprica M. Allergy influences the inflammatory status of the brain and enhances tau-phosphorylation. *J Cell Mol Med* 2012; 16: 2401–12.
 89. Klein B, Mrowetz H, Thalhammer J, Scheiblhofer S, Weiss R, Aigner L. Allergy enhances neurogenesis and modulates microglial activation in the hippocampus. *Front Cell Neurosci* 2016; 10: 169.