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Review

Does the Interplay Between Aging and Neuroinflammation Modulate Alzheimer's Disease Clinical Phenotypes? A Clinico-Pathological Perspective

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Abstract.

Alzheimer's disease (AD) is a chronic neurodegenerative disorder and is the most common cause of dementia worldwide. Cumulative data suggests that neuroinflammation plays a prominent and early role in AD, and there is compelling data from different research groups of age-associated dysregulation of the neuroimmune system. From the clinical point of view, despite clinical resemblance and neuropathological findings, there are important differences between the group of patients with sporadic early-onset (<65 years old) and late-onset AD (>65 years old). Thus, it seems important to understand the age-dependent relationship between neuroinflammation and the underlying biology of AD in order to identify potential explanations for clinical heterogeneity, interpret biomarkers, and promote the best treatment to different clinical AD phenotypes. The study of the delicate balance between pro-inflammatory or anti-inflammatory sides of immune players in the different ages of onset of AD would be important to understand treatment efficacy in clinical trials and eventually, not only direct treatment to early disease stages, but also the possibility of establishing different treatment approaches depending on the age of the patient. In this review, we would like to summarize what is currently known about the interplay between "normal" age associated inflammatory changes and AD pathological mechanisms, and also the potential differences between early-onset and late-onset AD taking into account the age-related neuroimmune background at disease onset.

Keywords: Aging, Alzheimer's disease, inflammation, microglia, phenotype

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder and is the most common cause of dementia worldwide. The two major neuropathological hallmarks of the disease are senile plaques, which are mainly composed of extracellular deposits of amyloid-β (Aβ) and neurofibrillary tangles, which consist of intracellular aggregates of aberrantly phosphorylated tau protein. This is accompanied by neuronal and synaptic loss, dendritic and axonal changes, and inflammatory reaction

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lesions [1, 2]. Cumulative data suggests that neuroinflammation plays a prominent and early role in AD [3–8]. Microglia cells are the predominant resident immune cells in the central nervous system (CNS) [9]. Recently, some studies highlighted the biological process of age-related changes associated with microglial cells [10–12] and suggest that microglial senescence can be directly associated to neurofibrillary degeneration [13]. From the clinical point of view, despite clinical resemblance and neuropathological findings, there are important differences between the group of patients with sporadic early-onset (<65 years old, EOAD) and late-onset AD (>65 years old, LOAD). Thus, it seems important to understand the age-dependent relationship between neuroinflammation and the underlying biology of AD in order to identify potential explanations for clinical heterogeneity, interpret biomarkers, and promote the best treatment to different clinical AD phenotypes.

In this article, we will discuss the current knowledge regarding the interplay between "normal" age associated inflammatory changes and AD pathological mechanisms. In addition, we will discuss the potential differences between EOAD and LOAD taking into account the age-related neuroimmune background at disease onset. We will give particular emphasis to microglia due to their predominant role in the immunological process within the CNS.

BRAIN IMMUNE SYSTEM

Microglia are the resident immune cells of the CNS and considered the tissue-resident macrophages. These cells were first described by Nissl in 1899, who distinguished microglia from other neural cells based on the shape and their nuclei [14]. Microglia cells arise from myeloid precursors and constitute an autonomous population distinct from the peripheral circulating mononuclear phagocytes [15]. These cells account for up to 16% of total cell CNS population and this is dependent on the brain region [9]. There is limited replication and turnover of microglia, suggesting that microglia are a very long-lived and stable cell population [9, 12]. Microglia can provide several macrophage-related activities that provide an innate immune response as the first and main form of active immune defense in the brain [9]. The term microglial activation encloses the process where microglia change shape, molecular signature, and cellular physiology in order to respond to injury or disease [16]. Resting microglia are characterized by a small cell body, highly ramified processes with weak expression of associated cell surface marker antigens [17]. In contrast, activated microglia display shortened and extensively branched processes and hypertrophy of cell body [18]. The definition of resting microglia does not mean a passive spectator in the healthy adult CNS. *In vivo* two-photon microscopy imaging studies showed that microglia survey the brain parenchyma by constantly extending and retracting their processes, and react rapidly to brain injury or insult, and are more properly termed "surveillant" [19–21]. The functions of microglia in the normal healthy brain beyond immune surveillance are unclear, but recently more sophisticated functions were described such as participating actively in the maintenance and plasticity of neuronal circuits and contributing to the protection and remodeling of synapses [22, 23].

Microglial activation states have been classically described as activated (M1) or alternatively activated (M2) [24]. The M1 phenotype is characterized by production of proinflammatory cytokines, such as IL-1β, tumor necrosis factor alpha (TNFα), and IFN-γ, whereas in the M2 phenotype microglia secrete anti-inflammatory cytokines, such as IL-4, IL-10, and transforming growth factor-β, which downregulate inflammation and promote tissue remodeling/repair and angiogenesis [25]. However, this categorizing system relays on peripheral macrophages studies, which do not recapitulate all microglial functions and is likely an oversimplification [21].

The second type of neuroimmune cells is the perivascular macrophages [26]. They seem to be derived from circulating macrophages, and are able to perform all the known functions of peripheral macrophages; they undergo complete turnover approximately every 3 months [27, 28]. Finally, the circulating blood monocyte can enter the CNS, but it is not clear how often it happens under non-inflammatory conditions. In conditions of disrupted blood-brain barrier, and when properly stimulated, they can differentiate into microglia-like cells or perivascular macrophages morphologically and phenotypically [26].

Astrocytes are the most abundant glial cells in the CNS and their function is critical for the support of neuronal homeostasis. The term astrogliosis describes a wide range of both molecular and functional changes in astrocytes aimed to neuroprotection and repair of injured neural tissue [29, 30]. Recently it has been shown that that reactive astrogliosis and glial

scar formation play essential roles in regulating CNS inflammation [29]. Reactive astrocytes in response to different kinds of insult can produce molecules with either pro- or anti-inflammatory potential. Additionally, reactive astrocytes can exert both pro- and anti-inflammatory effects on microglia [31, 32].

NEUROINFLAMMATION IN BRAIN AGING

There is clinical and experimental evidence that neuroinflammation in the aged brain is characterized by a shift toward a pro-inflammatory state [9, 33]. *In vivo* imaging studies using ^{11}-C-*R*-PK1195 PET ligand, which is upregulated in activated microglia cells, showed an increase in the specific binding with age in several cortical and subcortical structures, indicating that activated microglia gradually appear in the aging human brain [34]. In parallel, age senescent alterations can contribute to a dysfunctional microglia [12, 35, 36]. In the next paragraphs, we will address these apparent competitive perspectives of age-related neuroinflammation.

Inflammation in the brain is defined by upregulated astrocyte and microglial cell reactivity in association with increased levels of circulating cytokines such as TNFα, IL-1β, and IFN-γ [37–39]. With aging, microglia phenotype shifts progressively toward the activated form, together with enhanced sensitivity to inflammatory stimuli (priming phenomena) [9, 40]. In normal human brain aging, microglia is characterized by upregulation of glial activation markers such as IL-1α [41] and major histocompatibility complex II (MHC II) [42]. MHC II is important because it is conserved across species and is interpreted to indicate microglial priming [9]. There is compelling evidence from different research groups and aging models, that following different types of challenge (bacteria, virus, stress, surgical intervention), aged animals exhibited a clear and exaggerated neuroinflammatory response, when compared to young adult animals [33, 43–46]. These studies provided evidence that during lifespan, episodes of systemic inflammation and cytokine stimulation can "instruct" microglia and increase their reactivity [23, 33]. Interestingly, some of these sensitized neuroinflammatory responses are specific to the hippocampal formation, which is important for memory function [33]. Microglia from the aged CNS could be described as hyper-vigilant to disturbances in central homeostasis with less capability of shifting among functional states.

Proteins expressed in CNS microenvironment, which are known to inhibit microglia activation or pro-inflammatory immune responses, were implicated in the mechanism how microglia becomes chronically sensitized during normal aging [47]. In fact, some lines of research describe various proteins that activate anti-inflammatory signals following ligand receptor interactions [48], particularly CD200 [49–51] and fractalkine (CX3CL1) [51–53]; interestingly, both are preferentially expressed in neurons. These proteins inhibit microglia through their cognate receptor, which is expressed predominantly in myelomonocytic cell types. During aging, the expression of levels of these ligands decreases concurrently with increases in microglial activation status. More recently, another line of research suggests that significant and prolonged elevation in hippocampal corticosterone (the endogenous glucocorticoid in rodents) leads to microglial priming [51]. However, the simplistic view that aging CNS shifts microglial polarization from alternative M2 state to the classical, proinflammatory state, should be interpreted cautiously because many studies found that both M1 markers and M2 markers are increased in aged mice [12]. For example, active microglia from aged mice actually had higher levels of IL-10 production (an anti-inflammatory cytokine) than those of adult mice and lower expression of TGFβ (an inflammatory cytokine) [54]. In this case, the maintenance of inflammatory response could be attributed to an impaired response to IL-10 in the aged brain [9]. Furthermore, primed microglia phenomena have been described mainly in mouse models [9, 55], and less in human brain research [56]. More recently, research studies showed that the cerebrospinal fluid (CSF) levels of YKL-40 (a microglial marker) increase in normal aging [57–59].

Together with this perspective that microglia becomes primed and more reactive with age, others showed that microglia becomes senescent and less reactive with age [10, 11, 13]. In the healthy young CNS, microglia have a typical ramified morphology and are distributed throughout the neural parenchyma in a "space-filling" manner [60]. Due to the prolonged lifespan of CNS microglia, they are more susceptible to accumulate aging-related changes [61], such as in the distribution, morphology, and behavior [12, 60] (Table 1). Many microglial cells in the aged brain show dystrophic features indicative of age-related alterations. This dystrophic microglia have de-ramification or decrease arborization of their processes, loss of finely branched cytoplasmic process,

Table 1
Summary of principal changes associated to microglial aging (adapted from Wong [60] and Wyss-Coray [6])

Changes in aged microglia
Changes in microglial distribution
Replicative senescence (reduced mitotic activity in response to CNS injuries)
Decreases in regularity in distribution
Changes in morphology
Decrease in individual microglial ramification (dendritic arbor area, branching, and total process length)
Appearance of morphological changes suggestive of increase activation state (shortened and extensively branched processes and hypertrophy of cell body)
Appearance of dystrophic microglia (deramified, fragmented, or tortuous processes, cytoplasmic beading/spheroid formation)
Changes in microglial dynamic behavior and function
Decrease in the motility and migration process
Changes in intercellular signaling and marker expression (MHC II, CD11b)
Impaired phagocytosis
Impaired proteostasis

cytoplasmic beading/spheroid formation, and shortened and twisted cytoplasmic processes, and in some instances there is partial or complete cytoplasmic fragmentation [38]. The meaning of these morphological changes or why they happen is still to be understood.

Age-related changes were also described in astrocytes, particularly emphasizing that aged astrocytes show characteristics of the senescence-associated secretory phenotype, which involves increased secretion of inflammatory components [62].

In summary, aged microglia are primed with exaggerated and prolonged responses to inflammatory stimuli and also display dysfunctional dystrophic age associated features. Yet, it is still to be determined if microglia activation is the cause of neurodegeneration or a secondary reactive (beneficial) process; or if the neurodegeneration is actually secondary to microglia senescence and associated loss of microglial protection.

NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

After two decades of the amyloid cascade hypotheses proposed by Hardy and Higgins [63], multiple lines of research still support the Aβ aggregation as the critical step that initiates AD pathology. However, despite required, it seems that Aβ aggregation is not sufficient for the development of the neuropathological and clinical syndrome of AD [64]. Several research studies report links between AD and genes regulating immunity as well as the expression of immune factors in blood, CSF, and brain tissue [8, 65–68]. There is compelling data that neuroinflammation in AD is not a passive mechanism activated by senile plaques and neurofibrillary tangles, but instead contributes, as much or even more, to pathogenesis as do plaques and tangles [65, 68, 69]. Epidemiological studies indicate that systemic markers of the innate immunity are risk factors of LOAD [70–73] and more recently, inflammation in AD gained strong support from genome-wide association studies that identified genes involved in inflammation that are associated with increased risk of developing AD [74], including TREM2 [75, 76] and CD33 [77, 78]. Prospective cohorts' studies suggested that elevations in inflammatory mediators may be present years before clinical disease onset [70, 79, 80]. However, other longitudinal studies did not report associations between inflammation and AD risk [81, 82]. Furthermore, non-steroidal anti-inflammatory drug (NSAID) epidemiology and clinical trials showed mostly negative results, playing against the importance of inflammation in AD pathogenesis. However, these disappointing results are no surprising taking into account that normal physiological cytokine regulation of glia activation and microglial phenotypes are highly dependent of the context and the disease stage [65]. More recently, studies have consistently found an increase in CSF YKL-40 levels in AD. They also found a correlation between CSF YKL-40 levels with markers of neurodegeneration, such as tau, and with at-risk $\varepsilon 4$ carriers during mid middle age [57–59].

Neuropathological studies have shown the presence of a broad variety of inflammation-related proteins (complement factors, acute-phase proteins, proinflammatory cytokines) and clusters of activated microglia around amyloid plaques (Fig. 1) in AD subjects and also AD mice models [8], and these findings have been implicated in the neurodegeneration process [4, 83]. Neuropathological studies also showed

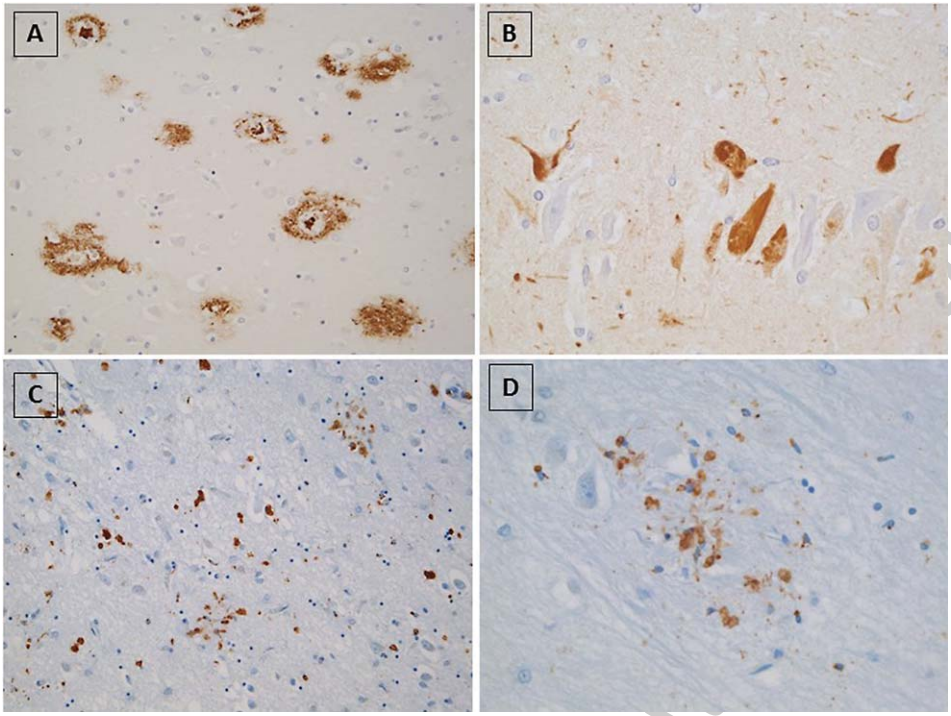

Fig. 1. Alzheimer's disease neuropathology. A) Senile plaques and globose diffuse deposits demonstrated with anti-Aβ antibody (M 0804, Dako). B) Neurofibrillary tangles demonstrated by phosphorylated tau protein immunohistochemistry (PHF-Tau; AT8, Thermo Scientific). C) Diffuse distribution of activated microglia in the cortex with clustering within and around amyloid plaques. D) Higher magnification of amyloid plaque with activated microglial in the CA4 region of the hippocampus (C and D: CD68 immunohistochemistry; PGM1 clone, Dako).

that the neuroinflammatory response in the neocortex is present in the early stages of AD pathology and precedes the late stage, tau-related pathology [84]. Furthermore, microglial activation has been shown to progress with the clinical stage of dementia, with neuropathological stage of disease severity, and with stage of progression of Aβ plaques [67, 85, 86]. *In vivo* imaging studies, using ^{11}-C-*R*-PK1195 PET ligand, showed that activated microglia accumulate near the amyloid plaque pathology, and that activated microglia burden correlates with cognitive decline [87].

The pathological accumulation of Aβ is considered the key factor that drives neuroinflammation responses in AD [65]. The chronic deposition of Aβ stimulates the persistent activation of microglial cells in AD [88]. Microglia undergoes a progressive switch from a neuroprotective M2 status to a classically activated phenotype M1, characterized by production of proinflammatory cytokines [89]. The persistent microglia activation and consequently microglia-derived cytokine overexpression, caused by continuous formation of Aβ and positive feedback loops between inflammation and amyloid-β protein precursor processing, can increase Aβ production and decrease Aβ clearance, ultimately causing neuronal damage [65, 86, 89]. In addition, ongoing exposure to Aβ, chemokines, cytokines, and other inflammatory mediators can be responsible for the functional impairment of microglial cells seen at plaque sites [11, 90] and thus impede the protective role of microglia in Aβ clearance [91]. Recently, Kim et al. [92] showed that soluble Aβ oligomers impair synaptic plasticity and cause synaptic loss in mouse AD models and brains of AD patients binding to the murine PirB (paired immunoglobulin-like receptor B) and its human ortholog LilrB2 (leucocyte immunoglobulin-like receptor B2) receptors, respectively. The PirB receptor was first described exclusively in the immune system but is now know to be expressed by neurons.

Microglia can have different roles and effects depending on the particular disease stage and which brain region is affected in each model [65]. AD mouse models studies showed that in younger ages, together with the appearance of the first Aβ plaques, the microglia is activated toward the alternative state and at older ages, together with the increased

accumulation of extracellular oligomeric Aβ, there is a widespread microglial activation toward the classic phenotype [93]. Recently, Sudduth et al. described that in the early-stage AD brains there is an apparent polarization toward either M1 or M2 brain inflammatory states [94]. The M2 polarized group had great number of neuritic plaques, eventually reflecting disease progression. The heterogeneity found in the early stage AD can influence the response to therapeutic agents that act on immune system and inflammation [94]. The neuropathological study of AD patients that had undergone active Aβ vaccination as part of the AN1792 trial showed significantly reduced levels of Aβ and reduction of aggregated tau in neural processes (not in neurofibrillary tangles), and, although there was no difference on total microglial load, there were reduced levels of a range of activated microglial species when compared to patients who died from AD without treatment [95, 96]. These findings suggest that downregulation of microglial activation through Aβ immunotherapy possibly reduces the inflammatory component of the neurodegeneration of AD [95]. However, a different line of research supports that aging-related microglial degeneration and loss of microglial neuroprotection rather than microglial activation contributes to the onset of sporadic AD [11]. A role for peripheral-derived macrophage cells in AD pathophysiology have recently come under attention [97]. There is extensive evidence that blood-derived monocytes can phagocytose Aβ [98] and that these cells can be recruited to the AD brain, albeit in low numbers [99].

Reactive astrocytes tend to accumulate around fibrillar amyloid plaques [100]. Similar to microglia, astrocytes release cytokines and other potentially cytotoxic molecules after exposure to Aβ thus aggravating the neuroinflammatory response [65]. Glial cell activation can be an early event in AD process, even preceding Aβ deposition. Recently, Rodriguez-Vieitez and colleagues [101], using a PET tracer for astrocytes (^{11}C-deuterium-L-deprenyl), showed prominent initially high and then declining astrocytosis in autosomal dominant AD carriers, contrasting with the increasing Aβ plaque load during disease progression. This study provided *in vivo* evidence that astrocyte activation is a very early feature of, at least familial, AD pathology [101]. Other lines of research have linked senescent astrocytes to the increase risk of sporadic AD [102].

In summary, the role of microglia remains controversial in AD pathogenesis and the question of whether activated microglia aids in promoting clearance of toxic Aβ species or if their proinflammatory profile exacerbates pathology is currently a topic of debate [103]. Although there is broad evidence of a large immune response component in AD, the issue of which activation phenotype affects the onset or progression of the disease and, consequently, which should be the therapeutic target remains to be determined [104]. Furthermore, the questions regarding the role of excessive astrogliosis or astrocyte senescent loss of function in AD pathogenesis remains to be solved [100].

EARLY AND LATE-ONSET ALZHEIMER'S DISEASE

Regardless of the clinical resemblance and neuropathological findings, important differences between EOAD and LOAD patients have been reported. The separation of EOAD from LOAD at 65 years old is a conventional cutoff point indicative of a sociological partition in terms of employment and retirement, but there is no specific biological significance to use this specific age, and there is a range of disease features that do not respect this arbitrary division [105, 106]. However, this arbitrary cutoff point has been used widely by different research groups and allowed the uniform study of AD patients with different ages of onset.

Clinical presentation

Whether age of onset defines the clinical presentation of AD has been a matter of debate for decades and reports on this issue are often contradictory. Nonetheless, some differences have been consistently recognized. Earlier onset is associated with a worse prognosis and a faster progression. Younger-onset patients have comparatively worst outcomes in the Mini-Mental State Examination at baseline, show a steeper cognitive and functional decline, and seem to have higher mortality risks when compared to older-onset patients [107–109]. In addition, different patterns of cognitive deficits are apparent; non-amnestic presentations are more often found in early-onset disease, described in 33–64% of EOAD compared to 6–12.5% of LOAD patients [105, 110].

Earlier neuropsychological studies have shown that younger patients have more language disability when compared to older-onset patients [111–113]. The risk of having language difficulties detected by caregivers has also been shown to nearly duplicate for each 10-year decrease in AD patients' age [114].

Other groups have recognized a greater impairment in measures of attention, praxis, and visuo-contruction tasks in EOAD [115–117]. On the other hand, LOAD patients seem to consistently have preferential memory involvement [118–120]. To explore the relation between this clinical duality and pathologic features, Murray et al. [121] divided a cohort of AD patients into "hippocampal sparing", "limbic predominant", and "typical AD" according to neurofibrillary pathology distribution. They have shown that a younger age of onset (mean 63 years) was associated with greater neurofibrillary tangle burden in cortical association areas and that older age (mean 76 years) was more often associated with limbic predominant pathology. The hippocampal sparing group had greater prevalence of atypical presentations and a faster cognitive decline, similar to what has been described in EOAD.

Seizures and extrapyramidal features seem to be more frequent in EOAD [111, 122]. There are contradictory reports in other symptoms in both groups. For example, there are reports of higher anxiety levels in EOAD [123], while others have shown greater neuropsychiatric and behavioral symptoms in LOAD, including anxiety, depression, agitation, hallucinations, and delusions [124, 125].

Limited research has been reported into sex differences in brain aging, particularly neuroinflammation process. However, gender effect is an interesting issue due to the differences of the neuroendocrine milieu and its possible relation to inflammation cascades (particularly steroid-related pathways). The dynamic change in hormonal status in women during the menopause transition may promote a dysregulation of cellular processes involved in hypothalamic-pituitary-adrenal axis and thus have potential implications on stress-mediated neurotoxicity [126]. It is also important to recognize the importance of immunological differences in males and females within the CNS at different development time points and their possible relevance for the susceptibility in the development of neurological conditions later in life [127]. A recent work in mice by Mangold and colleagues showed a greater induction of MHC class I components and receptors with aging with this finding being greater in females than in males [128]. However, despite the prevalence of AD being greater in women, the prevailing view has been that this difference is due to the fact that women live longer than men on average, and older age is the greatest risk factor for AD. Many studies of incidence of AD have found no significant difference between men and women in the proportion who develop AD at any given age [129].

Biomarkers

Magnetic resonance imaging (MRI) studies show that younger-onset patients have greater generalized neocortical atrophy than LOAD subjects when compared to healthy controls [118, 130]. This is in accordance with glucose metabolism studies, which demonstrate a premature decline in glucose metabolism and a more severe and widespread hypometabolism in EOAD [131]. Regarding regional differences, older patients tend to have a more circumscribed involvement, with preferential reduction in the hippocampus and related structures, including the amygdala [132] and retrosplenial and temporoparietal junction volumes [130], while younger patients tend to have a greater temporoparietal and parietooccipital grey matter atrophy [115, 120]. White matter atrophy mimics this pattern [133]. Moreover, both perfusion and glucose metabolism studies have shown a predilection for temporo-parietal-occipital association areas in EOAD versus medial temporal cortex susceptibility in LOAD [119, 134]. Interestingly, another study has shown no significant difference in total or regional amyloid burden, measured by Pittsburg compound-B PET, despite showing decreased glucose metabolism in bilateral temporoparietal and occipital cortex in EOAD. This finding suggests that both early Aβ and increased susceptibility to pathology in younger onset patients might be responsible for cortical dysfunction in EOAD [135]. The greater involvement of hippocampal-related structures in LOAD is also apparent in functional connectivity studies that have shown that older patients have decreased activation of the anteromedial temporal network, correlating with poorer performance in memory tasks; EOAD was associated with less activation of the dorsolateral prefrontal network, manifested by worse performance on executive function tasks [118].

CSF pathophysiological markers for AD include decrease levels of $A\beta_{1-42}$ and increase levels of total tau and hyperphosphorylated tau. The use of these biomarkers combined is associated with significant sensitivity and specificity in the diagnosis of AD [136]. There is some evidence that EOAD patients have a greater reduction of $A\beta_{1-42}$ (and corresponding greater elevation of tau) than LOAD patients when compared to young and old controls, respectively, although no differences emerge in the direct comparison between EOAD and LOAD [137]. Others have reported lower levels of $A\beta_{1-42}$ in EOAD [138] or no differences [120, 139]. A study comparing CSF biomarkers along different EOAD subtypes,

including amnestic, logopenic progressive aphasia and posterior cortical atrophy found no differences in the Aβ levels, but showed that posterior cortical atrophy had lower levels of total tau and phosphorylated tau [140].

Genetics

Amyloid precursor protein, presenilin 1, and presenilin 2 mutations can cause autosomal dominant AD, and although they may be present in up 71% of familial cases, they account for only about 1–5% of all AD patients. These patients typically have an early or very early-onset disease (<45 years) [136, 141, 142]. A well-recognized genetic risk factor for AD is the APOE ε4 allele. It is usually associated with greater hippocampal atrophy and a poorer performance in memory based tasks [121, 142] and it decreases the age of onset by up to 2.45 years for each copy of the allele [142, 143]. Conversely, non-APOE ε4 patients tend to have greater structural and clinical involvement of non-hippocampal, neocortical areas [121]. ApoE ε4 allele carriers among AD patients are most frequently found in the 60–69-year-old range [144], therefore including both older EOAD patients and younger LOAD patients. The ApoE ε2 allele is less frequently found in AD patients than in normal controls and there seems to be no difference in its prevalence between EOAD and LOAD [144]. Genome wide association studies have identified several other risk genes for LOAD. The association between nine of them (PICALM, CLU, CR1, BIN1, CD2AP, EPHA1, MS4A4A, CD33, and ABCA7) has been shown to account for 1.1% of age of onset variation, versus 3.9% of variation provided by ApoE. The most significant association was found for the CR1, BIN1, and PICALM genes [143]. Another candidate gene that may have an impact on age of onset is DCHS2, a gene expressed in the cerebral cortex [145]. Yet, and surprisingly, these genetic variants do not seem to bring significant value for the distinction between EOAD and LOAD, as they simply seem to anticipate pathology.

INTERPLAY BETWEEN BRAIN AGING, NEUROINFLAMMATION, AND AD PHENOTYPES

AD prevalence is strongly associated with increasing age and aging changes in microglia have been hypothesized to play a prominent role in disease pathogenesis [60]. Recently, the consistent pattern of increases in YKL-40 level with aging supports the concept that neuroinflammation is a process that occurs normally with aging [57–59]. The additional finding of a stronger association with at-risk ε4 carriers during mid middle age suggests that this age-related process may be further exacerbated in the presence of insults including amyloid deposition and neuronal injury [59]. There are important clinical differences between sporadic EOAD and LOAD. Taking into account the data regarding the importance of neuroinflammation in the pathogenesis of AD, particularly the role of microglia, and the differences of the neuroimmunological milieu of the aged brain, it is conceivable that the neuroinflammation associated to the AD can, at least in the beginning, differ between these two groups and contribute for the clinical differences. Not many studies have addressed this issue.

Hoozemans et al. [146] compared the presence of microglia and astrocytes, in clinically and pathologically confirmed AD and non-demented control cases in relation to age. In their study they suggested that the association between neuroinflammation and AD is much stronger in relatively young patients as compared to the older patients (age at death <80 versus >80 years old). Microglial activation increases with the neuropathological stage and disease severity [67, 85]. A key issue would be to know if inflammation differs between these two groups (EOAD versus LOAD) at different pathological and clinically AD stages.

Another remarkable finding is that, in contrast to AD, activated microglia is not found in the similar-appearing Aβ diffuse deposits of the brains of neurologically normal elderly individuals [147]. One of the possibilities is that for those unusual elderly individuals with only diffuse Aβ deposits there is an inherent difference in the responsiveness of microglia [86]. Interestingly, plaque-associated microglia were not seen in diffuse plaque-only young Down's syndrome brain [148]. This subgroup of cases was from very young patients (between 12 and 29 years old), possible supporting the notion that Aβ inflammatory response can also differ in the very young. More recently, a study showed that in Down's syndrome patients with AD pathology (>40 years old), there is a distinct neuroinflammatory phenotype compared to sporadic AD due to microglia bias toward an M2b phenotype [149]. Clinicopathological studies from brain donation programs showed that the presence of moderate and severe AD type pathology changes is more associated to dementia in younger old persons

than in older old persons [150]. These findings suggest that additional factors are involved in the clinical expression of dementia in the oldest old, such as variable tolerance to neuropathological lesions [150]. We speculate that different neuroinflammation apparatus in this age can partial explain this discrepancy.

The study of inflammatory cytokines in CSF as biomarkers of AD has shown very different and contradictory results between different research groups [89]. The analysis of different neuroinflammation-related proteins in the blood, including several interleukines (IL-1α, Il-1β, IL-6, IL-10), α2-macroglobulin, brain-derived neurotrophic factor (BDNF), complement factor H, and heat shock protein 90 (Hsp90) has not shown significant differences between EOAD and LOAD, but studies are scarce and with small samples [151, 152]. TNFα levels have been shown to be both higher and lower in EOAD [152, 153].

Some of the risk loci in modifying age of disease onset identified in genome wide association studies have recognized roles in the immune system, including phagocytosis and immune cell trafficking [154]. Both CLU and CR1 encode for proteins that regulate complement activation; EPHA1, mostly expressed in leukocytes, is involved in T cell regulation; ABCA7 is highly expressed in the hippocampal neurons and in microglia and is involved in Aβ processing; and CD33, overexpressed in AD patient's microglia, encodes for an endocytic receptor that takes part in cell-cell interactions and in immune cell regulation [154, 155]. TREM2, another loci associated to increase risk for AD identified, is involved in immune response [75]. There are studies that found a significantly earlier symptom of onset in patients with TREM2 variants [156], but others found only an association to shortened disease duration and not to age of onset [76]. Aβ cerebral amyloid angiopathy (CAA) and particularly Aβ related angiitis (ABRA), is other AD related clinical feature that bridges AD, inflammation and age. CAA describes a group of biochemically and genetically diverse disorders, which have in common the deposition of amyloid in media and adventitia of cortical and leptomeningeal vessels [157]. Sporadic CAA and AD have overlapping biology with shared risk factors [158]. Aβ vascular deposition affects about 30% of the otherwise normal elderly and over 90% of those with AD, in whom CAA tends also to be more severe [157, 159]. ABRA is characterized by a vasculitic transmural, often granulomatous, inflammatory infiltrates affecting leptomeningeal and cortical vessels

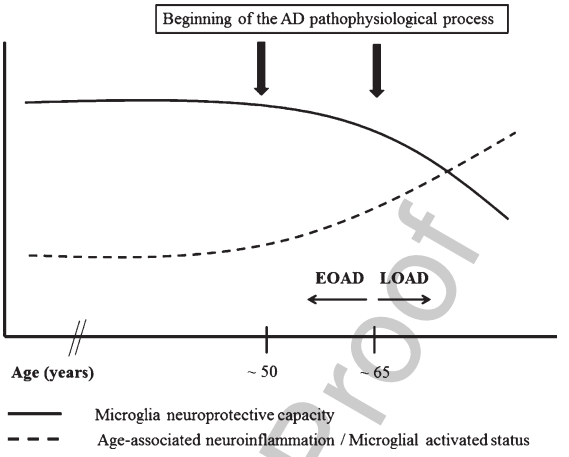

Fig. 2. Diagram illustrating age associated microglia dynamics and temporal Alzheimer's disease onset. Arrows exemplify two time points for the beginning of AD biomarkers [Aβ accumulation (CSF/PET), sequentially followed by tau-mediated neuronal injury (CSF)] at the preclinical stage.

that have abundant Aβ deposition within the vessel walls [159, 160]. The recent finding of autoantibodies against $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ forms of amyloid in the CSF of two patients with ABRA and inflammation associated to CAA [161, 162], together with the description of meningoencephalitis caused by active or passive immunotherapeutic approaches to reduce Aβ burden in AD [163], suggests that an immune response directed against Aβ may represent a common disease mechanism shared by ABRA and in complications of therapy for AD [160]. The mean age of presentation of ABRA is lower than that of sporadic non-inflammatory Aβ-related CAA (66 versus 76 years, respectively) [159, 160]. These findings support a role for the interactions between age, and inflammation in AD related pathophysiology and clinical expression.

In summary, the pathophysiological mechanisms underlying the clinical differences between EOAD and LOAD are still not well known, but the differences of neuroinflammation characteristics with aging can help to partially explain it (Fig. 2).

CONCLUSION

Understanding both sides of microglial and astrocytosis inflammation process at functional and molecular level will be necessary for the development of treatment strategies for AD and aging [12].

Additionally, the study of this delicate balance in the different ages of onset of AD would be important

to understand treatment efficacy in clinical trials and eventually, not only direct treatment to early disease stages, but also the possibility of establishing different treatment approaches in light of the age of the patient. The boost on AD diagnostic biomarkers will increase diagnostic certainty in life for the diagnosis of dementia with AD pathology. This refinement will allow the increased recognition of the more often atypical clinical presentations in EOAD and thus increase the knowledge (epidemiology, clinical progression, biomarkers studies, neuroinflammation associated process, etc.) for a possible better understanding of this complex disorder.

DISCLOSURE STATEMENT

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REFERENCES

[1] Cummings JL (2004) Alzheimer's disease. *N Engl J Med* **351**, 56-67.

[2] Taipa R, Pinho J, Melo-Pires M (2012) Clinico-pathological correlates of the most common neurodegenerative dementias. *Front Neurol* **3**, 68.

[3] Rogers J, Webster S, Lue LF, Brachova L, Civin WH, Emmerling M, Shivers B, Walker D, McGeer P (1996) Inflammation and Alzheimer's disease pathogenesis. *Neurobiol Aging* **17**, 681-686.

[4] 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, Strohmeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T (2000) Inflammation and Alzheimer's disease. *Neurobiol Aging* **21**, 383-421.

[5] McGeer PL, Rogers J, McGeer EG (2006) Inflammation, anti-inflammatory agents and Alzheimer disease: The last 12 years. *J Alzheimers Dis* **9**, 271-276.

[6] Wyss-Coray T (2006) Inflammation in Alzheimer disease: Driving force, bystander or beneficial response? *Nat Med* **12**, 1005-1015.

[7] Heneka MT, O'Banion MK (2007) Inflammatory processes in Alzheimer's disease. *J Neuroimmunol* **184**, 69-91.

[8] Eikelenboom P, Exel E, Hoozemans JJ, Veerhuis R, Rozemuller AJ, Gool WA (2010) Neuroinflammation - an early event in both the history and pathogenesis of Alzheimer's disease. *Neurodegener Dis* **7**, 38-41.

[9] Norden DM, Godbout JP (2013) Review: Microglia of the aged brain: Primed to be activated and resistant to regulation. *Neuropathol Appl Neurobiol* **39**, 19-34.

[10] Flanary BE, Sammons NW, Nguyen C, Walker D, Streit WJ (2007) Evidence that aging and amyloid promote microglial cell senescence. *Rejuvenation Res* **10**, 61-74.

[11] Streit WJ, Braak H, Xue QS, Bechmann I (2009) Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. *Acta Neuropathol* **118**, 475-485.

[12] Mosher KI, Wyss-Coray T (2014) Microglial dysfunction in brain aging and Alzheimer's disease. *Biochem Pharmacol* **88**, 594-604.

[13] Streit WJ, Xue QS, Tischer J, Bechmann I (2014) Microglial pathology. *Acta Neuropathol Commun* **2**, 142.

[14] Nissl F (1899) Ueber einige Beziehungen zwischen Nervenzellerkrankungen und gliosen Erscheinungen bei verschiedenen Psychosen. *Archiv Psychiatrie* **32**, 1-22.

[15] Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM, Merad M (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* **330**, 841-845.

[16] Kettenmann H, Hanisch UK, Noda M, Verkhratsky A (2011) Physiology of microglia. *Physiol Rev* **91**, 461-553.

[17] Derecki NC, Katzmarski N, Kipnis J, Meyer-Luehmann M (2014) Microglia as a critical player in both developmental and late-life CNS pathologies. *Acta Neuropathol* **128**, 333-345.

[18] Perry VH, Nicoll JA, Holmes C (2010) Microglia in neurodegenerative disease. *Nat Rev Neurol* **6**, 193-201.

[19] Nimmerjahn A, Kirchhoff F, Helmchen F (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma *in vivo*. *Science* **308**, 1314-1318.

[20] Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB (2005) ATP mediates rapid microglial response to local brain injury *in vivo*. *Nat Neurosci* **8**, 752-758.

[21] Malm TJ, Jay TR, Landreth GE (2014) The evolving biology of microglia in Alzheimer's disease. *Neurotherapeutics* **12**, 81-93.

[22] Ji K, Akgul G, Wollmuth LP, Tsirka SE (2013) Microglia actively regulate the number of functional synapses. *PLoS One* **8**, e56293.

[23] Lourbopoulos A, Ertürk A, Hellal F (2015) Microglia in action: How aging and injury can change the brain's guardians. *Front Cell Neurosci* **9**, 54.

[24] Martinez FO, Sica A, Mantovani A, Locati M (2008) Macrophage activation and polarization. *Front Biosci* **13**, 453-461.

[25] Czeh M, Gressens P, Kaindl AM (2011) The yin and yang of microglia. *Dev Neurosci* **33**, 199-209.

[26] Hickman SE, El Khoury J (2013) The neuroimmune system in Alzheimer's disease: The glass is half full. *J Alzheimers Dis* **33**(Suppl 1), S295-S302.

[27] Audoy-Rémus J, Richard JF, Soulet D, Zhou H, Kubes P, Vallières L (2008) Rod-Shaped monocytes patrol the brain vasculature and give rise to perivascular macrophages under the influence of proinflammatory cytokines and angiopoietin-2. *J Neurosci* **28**, 10187-10199.

[28] Bechmann I, Priller J, Kovac A, Böntert M, Wehner T, Klett FF, Bohsung J, Stuschke M, Dirnagl U, Nitsch R (2001) Immune surveillance of mouse brain perivascular spaces by blood-borne macrophages. *Eur J Neurosci* **14**, 1651-1658.

[29] Sofroniew MV, Vinters HV (2010) Astrocytes: Biology and pathology. *Acta Neuropathol* **119**, 7-35.

[30] Osborn LM, Kamphuis W, Wadman WJ, Hol EM (2016) Astrogliosis: An integral player in the pathogenesis

of Alzheimer's disease. *Prog Neurobiol*, doi: 10.1016/j.pneurobio.2016.01.001

[31] Farina C, Aloisi F, Meinl E (2007) Astrocytes are active players in cerebral innate immunity. *Trends Immunol* **28**, 138-145.

[32] Burda JE, Sofroniew MV (2014) Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron* **81**, 229-248.

[33] Barrientos RM, Frank MG, Watkins LR, Maier SF (2010) Memory impairments in healthy aging: Role of aging-induced microglial sensitization. *Aging Dis* **1**, 212-231.

[34] Schuitemaker A, van der Doef TF, Boellaard R, van der Flier WM, Yaqub M, Windhorst AD, Barkhof F, Jonker C, Kloet RW, Lammertsma AA, Scheltens P, van Berckel BN (2012) Microglial activation in healthy aging. *Neurobiol Aging* **33**, 1067-1072.

[35] Harry GJ (2013) Microglia during development and aging. *Pharmacol Ther* **139**, 313-326.

[36] Conde JR, Streit WJ (2006) Microglia in the aging brain. *J Neuropathol Exp Neurol* **65**, 199-203.

[37] McGeer PL, McGeer EG (2001) Inflammation, autotoxicity and Alzheimer disease. *Neurobiol Aging* **22**, 799-809.

[38] Streit WJ, Mrak RE, Griffin WS (2004) Microglia and neuroinflammation: A pathological perspective. *J Neuroinflammation* **1**, 14.

[39] Ojo JO, Rezaie P, Gabbott PL, Stewart MG (2015) Impact of age-related neuroglial cell responses on hippocampal deterioration. *Front Aging Neurosci* **7**, 57.

[40] Perry VH, Teeling J (2013) Microglia and macrophages of the central nervous system: The contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Semin Immunopathol* **35**, 601-612.

[41] Sheng JG, Mrak RE, Griffin WS (1998) Enlarged and phagocytic, but not primed, interleukin-1 alpha-immunoreactive microglia increase with age in normal human brain. *Acta Neuropathol* **95**, 229-234.

[42] Sobel RA, Ames MB (1988) Major histocompatibility complex molecule expression in the human central nervous system: Immunhistochemical analysis of 40 patients. *J Neuropathol Exp Neurol* **47**, 19-28.

[43] Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, Johnson RW (2005) Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. *FASEB J* **19**, 1329-3131.

[44] Abraham J, Jang S, Godbout JP, Chen J, Kelley KW, Dantzer R, Johnson RW (2008) Aging sensitizes mice to behavioral deficits induced by central HIV-1 gp120. *Neurobiol Aging* **29**, 614-621.

[45] Buchanan JB, Sparkman NL, Chen J, Johnson RW (2008) Cognitive and neuroinflammatory consequences of mild repeated stress are exacerbated in aged mice. *Psychoneuroendocrinology* **33**, 755-765.

[46] Rosczyk HA, Sparkman NL, Johnson RW (2008) Neuroinflammation and cognitive function in aged mice following minor surgery. *Exp Gerontol* **43**, 840-846.

[47] Biber K, Neumann H, Inoue K, Boddeke HW (2007) Neuronal "On" and "Off" signals control microglia. *Trends Neurosci* **30**, 596-602.

[48] Griffiths MR, Gasque P, Neal JW (2009) The multiple roles of the innate immune system in the regulation of apoptosis and inflammation in the brain. *J Neuropathol Exp Neurol* **68**, 217-226.

[49] Hoek RM, Ruuls SR, Murphy CA, Wright GJ, Goddard R, Zurawski SM, Blom B, Homola ME, Streit WJ, Brown MH, Barclay AN, Sedgwick JD (2000) Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science* **290**, 1768-1771.

[50] Lyons A, Downer EJ, Crotty S, Nolan YM, Mills KH, Lynch MA (2007) CD200 ligand receptor interaction modulates microglial activation *in vivo* and *in vitro*: A role for IL-4. *J Neurosci* **27**, 8309-8313.

[51] Barrientos RM, Kitt MM, Watkins LR, Maier SF (2015) Neuroinflammation in the normal aging hippocampus. *Neuroscience* **309**, 84-99.

[52] Corona AW1, Huang Y, O'Connor JC, Dantzer R, Kelley KW, Popovich PG, Godbout JP (2010) Fractalkine receptor (CX3CR1) deficiency sensitizes mice to the behavioral changes induced by lipopolysaccharide. *J Neuroinflammation* **7**, 93.

[53] Wynne AM, Henry CJ, Huang Y, Cleland A, Godbout JP (2010) Protracted downregulation of CX3CR1 on microglia of aged mice after lipopolysaccharide challenge. *Brain Behav Immun* **24**, 1190-1201.

[54] Sierra A, Gottfried-Blackmore AC, McEwen BS, Bulloch K (2007) Microglia derived from aging mice exhibit an altered inflammatory profile. *Glia* **55**, 412-424.

[55] Raj DD, Jaarsma D, Holtman IR, Olah M, Ferreira FM, Schaafsma W, Brouwer N, Meijer MM, de Waard MC, van der Pluijm I, Brandt R, Kreft KL, Laman JD, de Haan G, Biber KP, Hoeijmakers JH, Eggen BJ, Boddeke HW (2014) Priming of microglia in a DNA-repair deficient model of accelerated aging. *Neurobiol Aging* **35**, 2147-2160.

[56] Sheng JG, Mrak RE, Griffin WS (1997) Neuritic plaque evolution in Alzheimer's disease is accompanied by transition of activated microglia from primed to enlarged to phagocytic forms. *Acta Neuropathol* **94**, 1-5.

[57] Olsson B, Hertze J, Lautner R, Zetterberg H, Nägga K, Höglund K, Basun H, Annas P, Lannfelt L, Andreasen N, Minthon L, Blennow K, Hansson O (2013) Microglial markers are elevated in the prodromal phase of Alzheimer's disease and vascular dementia. *J Alzheimers Dis* **33**, 45-53.

[58] Alcolea D, Martínez-Lage P, Sánchez-Juan P, Olazarán J, Antúnez C, Izagirre A, Ecay-Torres M, Estanga A, Clerigué M, Guisasola MC, Sánchez Ruiz D, Marín Muñoz J, Calero M, Blesa R, Clarimón J, Carmona-Iragui M, Morenas-Rodríguez E, Rodríguez-Rodríguez E, Vázquez Higuera JL, Fortea J, Lleó A (2015) Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. *Neurology* **85**, 626-633.

[59] Sutphen CL, Jasielec MS, Shah AR, Macy EM, Xiong C, Vlassenko AG, Benzinger TL, Stoops EE, Vanderstichele HM, Brix B, Darby HD, Vandijck ML, Ladenson JH, Morris JC, Holtzman DM, Fagan AM (2015) Longitudinal cerebrospinal fluid biomarker changes in preclinical Alzheimer disease during middle age. *JAMA Neurol* **72**, 1029-1042.

[60] Wong WT (2013) Microglial aging in the healthy CNS: Phenotypes, drivers and rejuvenation. *Front Cell Neurosci* **7**, 22.

[61] Gehrmann J, Banati RB (1995) Microglial turnover in the injured CNS: Activated microglia undergo delayed DNA fragmentation following peripheral nerve injury. *J Neuropathol Exp Neurol* **54**, 680-688.

[62] Salminen A, Ojala, Kaarniranta K, Haapasalo A, Hiltunen M, Soininen H (2011) Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. *Eur J Neurosci* **34**, 3-11.

[63] Hardy JA, Higgins GA (1992) Alzheimer's disease: The amyloid cascade hypothesis. *Science* **256**, 184-185.

[64] Musiek ES, Holtzman DM (2015) Three dimensions of the amyloid hypothesis: Time, space and "wingmen". *Nat Neurosci* **18**, 800-806.

[65] 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, Verkhratsky 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 (2015) Neuroinflammation in Alzheimer's disease. *Lancet Neurol* **14**, 388-405.

[66] International Genomics of Alzheimer's Disease Consortium (IGAP) (2015) Convergent genetic and expression data implicate immunity in Alzheimer's disease. *Alzheimers Dement* **11**, 658-671.

[67] Xiang Z, Haroutunian V, Ho L, Purohit D, Pasinetti GM (2006) Microglia activation in the brain as inflammatory biomarker of Alzheimer's disease neuropathology and clinical dementia. *Dis Markers* **22**, 95-102.

[68] Mhatre SD, Tsai CA, Rubin AJ, James ML, Andreasson KI (2015) Microglial malfunction: The third rail in the development of Alzheimer's disease. *Trends Neurosci* **38**, 621-636.

[69] Zhang B, Gaiteri C, Bodea LG, Wang Z, McElwee J, Podtelezhnikov AA, Zhang C, Xie T, Tran L, Dobrin R, Fluder E, Clurman B, Melquist S, Narayanan M, Suver C, Shah H, Mahajan M, Gillis T, Mysore J, MacDonald ME, Lamb JR, Bennett DA, Molony C, Stone DJ, Gudnason V, Myers AJ, Schadt EE, Neumann H, Zhu J, Emilsson V (2013) Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell* **153**, 707-720.

[70] Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ (2002) Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol* **52**, 168-174.

[71] Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, Launer L, Kuller L, Rubin S, Harris T (2003) Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* **61**, 76-80.

[72] Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC, Eikelenboom P (2005) Serum inflammatory proteins and cognitive decline in older persons. *Neurology* **64**, 1371-1377.

[73] Wichmann MA, Cruickshanks KJ, Carlsson CM, Chappell R, Fischer ME, Klein BE, Klein R, Tsai MY, Schubert CR (2014) Long-term systemic inflammation and cognitive impairment in a population-based cohort. *J Am Geriatr Soc* **62**, 1683-1691.

[74] Schellenberg GD, Montine TJ (2012) The genetics and neuropathology of Alzheimer's disease. *Acta Neuropathol* **124**, 305-323.

[75] Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J; Alzheimer Genetic Analysis Group (2013) TREM2 variants in Alzheimer's disease. *N Engl J Med* **368**, 117-127.

[76] Korvatska O, Leverenz JB, Jayadev S, McMillan P, Kurtz I, Guo X, Rumbaugh M, Matsushita M, Girirajan S, Dorschner MO, Kiianitsa K, Yu CE, Brkanac Z, Garden GA, Raskind WH, Bird TD (2015) R47H variant of TREM2 associated with Alzheimer disease in a large late-onset family: Clinical, genetic, and neuropathological study. *JAMA Neurol* **72**, 920-927.

[77] Bradshaw EM, Chibnik LB, Keenan BT, Ottoboni L, Raj T, Tang A, Rosenkrantz LL, Imboywa S, Lee M, Von Korff A; Alzheimer Disease Neuroimaging Initiative, Morris MC, Evans DA, Johnson K, Sperling RA, Schneider JA, Bennett DA, De Jager PL (2012) CD33 Alzheimer's disease locus: Altered monocyte function and amyloid biology. *Nat Neurosci* **16**, 848-850.

[78] Griciuc A, Serrano-Pozo A, Parrado AR, Lesinski AN, Asselin CN, Mullin K, Hooli B, Choi SH, Hyman BT, Tanzi RE (2013) Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. *Neuron* **78**, 631-643.

[79] Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, Stijnen T, Hofman A, Witteman JC, Breteler MM (2004) Inflammatory proteins in plasma and the risk of dementia: The rotterdam study. *Arch Neurol* **61**, 668-672.

[80] Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, Benjamin EJ, Au R, Kiel DP, Wolf PA, Seshadri S (2007) Inflammatory markers and the risk of Alzheimer disease: The Framingham Study. *Neurology* **68**, 1902-1908.

[81] Ravaglia G, Forti P, Maioli F, Chiappelli M, Montesi F, Tumini E, Mariani E, Licastro F, Patterson C (2007) Blood inflammatory markers and risk of dementia: The Conselice Study of Brain Aging. *Neurobiol Aging* **28**, 1810-1820.

[82] Sundelof J, Kilander L, Helmersson J, Larsson A, Ronnemaa E, Degerman-Gunnarsson M, Basun H, Lannfelt L, Basu S (2009) Systemic inflammation and the risk of Alzheimer's disease and dementia: A prospective population-based study. *J Alzheimers Dis* **18**, 79-87.

[83] Meda L, Cassatella MA, Szendrei GI, Otvos L Jr, Baron P, Villalba M, Ferrari D, Rossi F (1995) Activation of microglial cells by beta-amyloid protein and interferon-gamma. *Nature* **374**, 647-650.

[84] Webster B, Hansen L, Adame A, Crews L, Torrance M, Thal L, Masliah E (2006) Astroglial activation of extracellular-regulated kinase in early stages of Alzheimer's disease. *J Neuropathol Exp Neurol* **65**, 142-151.

[85] Vehmas AK, Kawas CH, Stewart WF, Troncoso JC (2003) Immune reactive cells in senile plaques and cognitive decline in Alzheimer's disease. *Neurobiol Aging* **24**, 321-331.

[86] Mrak RE (2012) Microglia in Alzheimer brain: A neuropathological perspective. *Int J Alzheimers Dis* 2012, 165021.

[87] Edison P, Archer HA, Gerhard A, Hinz R, Pavese N, Turkheimer FE, Hammers A, Tai YF, Fox N, Kennedy A, Rossor M, Brooks DJ (2008) Microglia, amyloid, and cognition in Alzheimer's disease: An [^{11}C](R)PK11195-PET and [^{11}C]PIB-PET study. *Neurobiol Dis* **32**, 412-419.

[88] Prinz M, Priller J, Sisodia SS, Ransohoff RM (2011) Heterogeneity of CNS myeloid cells and their roles in neurodegeneration. *Nature Neurosci* **14**, 1227-1235.

[89] Wang WY, Tan MS, Yu JT, Tan L (2015) Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann Transl Med* **3**, 136.

[90] Krabbe G, Halle A, Matyash V, Rinnenthal JL, Eom GD, Bernhardt U, Miller KR, Prokop S, Kettenmann H, Heppner FL (2013) Functional impairment of microglia coincides with Beta-amyloid deposition in mice with Alzheimer-like pathology. *PLoS One* **8**, e60921.

[91] Hickman SE, Allison EK, El Khoury J (2008) Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J Neurosci* **28**, 8354-8360.

[92] Kim T, Vidal GS, Djurisic M, William CM, Birnbaum ME, Garcia KC, Hyman BT, Shatz CJ (2003) Human LilrB2 is a β-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. *Science* **341**, 1399-404.

[93] Jimenez S, Baglietto-Vargas D, Caballero C, Moreno-Gonzalez I, Torres M, Sanchez-Varo R, Ruano D, Vizuete M, Gutierrez A, Vitorica J (2008) Inflammatory response in the hippocampus of PS1M146L/APP751SL mouse model of Alzheimer's disease: Age-dependent switch in the microglial phenotype from alternative to classic. *J Neurosci* **28**, 11650-11661.

[94] Sudduth TL, Schmitt FA, Nelson PT, Wilcock DM (2013) Neuroinflammatory phenotype in early Alzheimer's disease. *Neurobiol Aging* **34**, 1051-1059.

[95] Boche D, Donald J, Love S, Harris S, Neal JW, Holmes C, Nicoll JA (2010) Reduction of aggregated Tau in neuronal processes but not in the cell bodies after Abeta42 immunisation in Alzheimer's disease. *Acta Neuropathol* **120**, 13-20.

[96] Zotova E, Bharambe V, Cheaveau M, Morgan W, Holmes C, Harris S, Neal JW, Love S, Nicoll JA, Boche D (2013) Inflammatory components in human Alzheimer's disease and after active amyloid-β42 immunization. *Brain* **136**, 2677-2696.

[97] El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, Luster AD (2007) Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nat Med* **13**, 432-438.

[98] Hohsfield LA, Humpel C (2015) Migration of blood cells to β-amyloid plaques in Alzheimer's disease. *Exp Gerontol* **65**, 8-15.

[99] Lampron A, Pimentel-Coelho PM, Rivest S (2013) Migration of bone marrow-derived cells into the central nervous system in models of neurodegeneration. *J Comp Neurol* **521**, 3863-3876.

[100] Medeiros R, LaFerla FM (2013) Astrocytes: Conductors of the Alzheimer disease neuroinflammatory symphony. *Exp Neurol* **239**, 133-138.

[101] Rodriguez-Vieitez E, Saint-Aubert L, Carter SF, Almkvist O, Farid K, Schöll M, Chiotis K, Thordardottir S, Graff C, Wall A, Långström B, Nordberg A (2016) Diverging longitudinal changes in astrocytosis and amyloid PET in autosomal dominant Alzheimer's disease. *Brain* **139**, 922-936.

[102] Bhat R, Crowe EP, Bitto A, Moh M, Katsetos CD, Garcia FU, Johnson FB, Trojanowski JQ, Sell C, Torres C (2012) Astrocyte senescence as a component of Alzheimer's disease. *PLoS One* **7**, e45069.

[103] Schott JM, Revesz T (2013) Inflammation in Alzheimer's disease: Insights from immunotherapy. *Brain* **136**, 2654-2656.

[104] Varnum MM, Ikezu T (2012) The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alzheimer's disease brain. *Arch Immunol* **60**, 251-256.

[105] Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA (2010) Early versus late-onset Alzheimer's disease: More than age alone. *J Alzheimers Dis* **19**, 1401-1408.

[106] Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD (2010) The diagnosis of young-onset dementia. *Lancet Neurol* **9**,793-806.

[107] Jacobs D, Sano M, Marder K, Bell K, Bylsma F, Lafleche G, Albert M, Brandt J, Stern Y (1994) Age at onset of Alzheimer's disease: Relation to pattern of cognitive dysfunction and rate of decline. *Neurology* **44**, 1215-1220.

[108] Koedam EL, Pijnenburg YA, Deeg DJ, Baak MM, van der Vlies AE, Scheltens P, van der Flier WM (2008) Early-onset dementia is associated with higher mortality. *Dement Geriatr Cogn Disord* **26**, 147-152.

[109] Panegyres PK, Chen HY (2013) Differences between early and late onset Alzheimer's disease. *Am J Neurodegener Dis* **2**, 300-306.

[110] Mendez MF, Lee AS, Joshi A, Shapira JS (2012) Nonamnestic presentations of early-onset Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **27**, 413-420.

[111] Chui HC, Teng EL, Henderson VW, Moy AC (1985) Clinical subtypes of dementia of the Alzheimer type. *Neurology* **35**, 1544-1550.

[112] Filley CM, Kelly J, Heaton RK (1986) Neuropsychologic features of early- and late-onset Alzheimer's disease. *Arch Neurol* **43**, 574-576.

[113] Seltzer B, Sherwin I (1983) A comparison of clinical features in early- and late-onset primary degenerative dementia. One entity or two? *Arch Neurol* **40**, 143-146.

[114] Koss E, Edland S, Fillenbaum G, Mohs R, Clark C, Galasko D, Morris JC (1996) Clinical and neuropsychological differences between patients with earlier and later onset of Alzheimer's disease: A CERAD analysis, Part XII. *Neurology* **46**, 136-141.

[115] Frisoni GB, Testa C, Sabattoli F, Beltramello A, Soininen H, Laakso MP (2005) Structural correlates of early and late onset Alzheimer's disease: Voxel based morphometric study. *J Neurol Neurosurg Psychiatr* **76**, 112-114.

[116] Fujimori M, Imamura T, Yamashita H, Hirono N, Ikejiri Y, Shimomura T, Mori E (1998) Age at onset and visuocognitive disturbances in Alzheimer disease. *Alzheimer Dis Assoc Disord* **12**, 163-166.

[117] Suribhatla S, Baillon S, Dennis M, Marudkar M, Muhammad S, Munro D, Spreadbury C, Lindesay J (2004) Neuropsychological performance in early and late onset Alzheimer's disease: Comparisons in a memory clinic population. *Int J Geriatr Psychiatry* **19**, 1140-1147.

[118] Gour N, Felician O, Didic M, Koric L, Gueriot C, Chanoine V, Confort-Gouny S, Guye M, Ceccaldi M, Ranjeva JP (2014) Functional connectivity changes differ in early and late-onset alzheimer's disease. *Hum Brain Mapp* **35**, 2978-2994.

[119] Kaiser NC, Melrose RJ, Liu C, Sultzer DL, Jimenez E, Su M, Monserratt L, Mendez MF (2012) Neuropsychological and neuroimaging markers in early versus late-onset Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **27**, 520-529.

[120] Möller C, Vrenken H, Jiskoot L, Versteeg A, Barkhof F, Scheltens P, van der Flier WM (2013) Different patterns of gray matter atrophy in early- and late-onset Alzheimer's disease. *Neurobiol Aging* **34**, 2014-2022.

[121] Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW (2011) Neuropathologically defined subtypes of Alzheimer's disease with distinct

clinical characteristics: A retrospective study. *Lancet Neurol* **10**, 785-796.

[122] Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, Albert M, Brandt J, Stern Y (2006) Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia* **47**, 867-872.

[123] Porter VR, Buxton WG, Fairbanks LA, Strickland T, O'Connor SM, Rosenberg-Thompson S, Cummings JL (2003) Frequency and characteristics of anxiety among patients with Alzheimer's disease and related dementias. *J Neuropsychiatry Clin Neurosci* **15**, 180-186.

[124] Toyota Y, Ikeda M, Shinagawa S, Matsumoto T, Matsumoto N, Hokoishi K, Fukuhara R, Ishikawa T, Mori T, Adachi H, Komori K, Tanabe H (2007) Comparison of behavioral and psychological symptoms in early-onset and late-onset Alzheimer's disease. *Int J Geriatr Psychiatry* **22**, 896-901.

[125] van Vliet D, de Vugt ME, Aalten P, Bakker C, Pijnenburg YA, Vernooij-Dassen MJ, Koopmans RT, Verhey FR (2012) Prevalence of neuropsychiatric symptoms in young-onset compared to late-onset Alzheimer's disease - part 1: Findings of the two-year longitudinal NeedYD-study. *Dement Geriatr Cogn Disord* **34**, 319-327.

[126] Bale TL, Epperson CN (2015) Sex differences and stress across the lifespan. *Nat Neurosci* **18**, 1413-1420.

[127] Hanamsagar R, Bilbo SD (2015) Sex differences in neurodevelopmental and neurodegenerative disorders: Focus on microglial function and neuroinflammation during development. *J Steroid Biochem Mol Biol*. doi: 10.1016/j.jsbmb.2015.09.039

[128] Mangold CA, Masser DR, Stanford DR, Bixler GV, Pisupati A, Giles CB, Wren JD, Ford MM, Sonntag WE, Freeman WM (2016) CNS-wide sexually dimorphic induction of the major histocompatibility complex 1 pathway with aging. *J Gerontol A Biol Sci Med Sci*, doi: 10.1093/gerona/glv232

[129] Alzheimer's, Association (2015) Alzheimer's disease facts and figures. *Alzheimers Dement* **11**, 332-384.

[130] Frisoni GB, Pievani M, Testa C, Sabattoli F, Bresciani L, Bonetti M, Beltramello A, Hayashi KM, Toga AW, Thompson PM (2007) The topography of grey matter involvement in early and late onset Alzheimer's disease. *Brain* **130**, 720-730.

[131] Kim EJ, Cho SS, Jeong Y, Park KC, Kang SJ, Kang E, Kim SE, Lee KH, Na DL (2005) Glucose metabolism in early onset versus late onset Alzheimer's disease: An SPM analysis of 120 patients. *Brain* **128**, 1790-1801.

[132] Cavedo E, Pievani M, Boccardi M, Galluzzi S, Bocchetta M, Bonetti M, Thompson PM, Frisoni GB (2014) Medial temporal atrophy in early and late-onset Alzheimer's disease. *Neurobiol Aging* **35**, 2004-2012.

[133] Canu E, Frisoni GB, Agosta F, Pievani M, Bonetti M, Filippi M (2012) Early and late onset Alzheimer's disease patients have distinct patterns of white matter damage. *Neurobiol Aging* **33**, 1023-1033.

[134] Kemp PM, Holmes C, Hoffmann SM, Bolt L, Holmes R, Rowden J, Fleming JS (2003) Alzheimer's disease: Differences in technetium-99m HMPAO SPECT scan findings between early onset and late onset dementia. *J Neurol Neurosurg Psychiatry* **74**, 715-719.

[135] Rabinovici GD, Furst AJ, Alkalay A, Racine CA, O'Neil JP, Janabi M, Baker SL, Agarwal N, Bonasera SJ, Mormino EC, Weiner MW, Gorno-Tempini ML, Rosen HJ, Miller BL, Jagust WJ (2010) Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. *Brain* **133**, 512-528.

[136] Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (2011) Alzheimer's disease. *Lancet* **377**, 1019-1031.

[137] Bouwman FH, Schoonenboom NS, Verwey NA, van Elk EJ, Kok A, Blankenstein MA, Scheltens P, van der Flier WM (2009) CSF biomarker levels in early and late onset Alzheimer's disease. *Neurobiol Aging* **30**, 1895-1901.

[138] Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, Vanderstichele H, Vanmechelen E, Blennow K (1999) Cerebrospinal fluid β-amyloid (1-42) in Alzheimer disease: Differences between early- and late-onset Alzheimer disease and stability during the course of disease. *Arch Neurol* **56**, 1895-1901.

[139] Ossenkoppele R, Mattsson N, Teunissen CE, Barkhof F, Pijnenburg Y, Scheltens P, van der Flier WM, Rabinovici GD (2015) Cerebrospinal fluid biomarkers and cerebral atrophy in distinct clinical variants of probable Alzheimer's disease. *Neurobiol Aging* **36**, 2340-2347.

[140] Teng E, Yamasaki TR, Tran M, Hsiao JJ, Sultzer DL, Mendez MF (2014) Cerebrospinal fluid biomarkers in clinical subtypes of early-onset Alzheimer's disease. *Dement Geriatr Cogn Disord* **37**, 307-314.

[141] Campion D, Dumanchin C, Hannequin D, Dubois B, Belliard S, Puel M, Thomas-Anterion C, Michon A, Martin C, Charbonnier F, Raux G, Camuzat A, Penet C, Mesnage V, Martinez M, Clerget-Darpoux F, Brice A, Frebourg T (1999) Early-onset autosomal dominant Alzheimer disease: Prevalence, genetic heterogeneity, and mutation spectrum. *Am J Hum Genet* **65**, 664-670.

[142] van der Flier WM, Pijnenburg YA, Fox NC, Scheltens P (2011) Early-onset versus late-onset Alzheimer's disease: The case of the missing APOE ε4 allele. *Lancet Neurol* **10**, 280-288.

[143] Naj AC, Jun G, Reitz C, Kunkle BW, Perry W, Park YS, Beecham GW, Rajbhandary RA, Hamilton-Nelson KL, Wang LS, Kauwe JS, Huentelman MJ, Myers AJ, Bird TD, Boeve BF, Baldwin CT, Jarvik GP, Crane PK, Rogaeva E, Barmada MM, Demirci FY, Cruchaga C, Kramer PL, Ertekin-Taner N, Hardy J, Graff-Radford NR, Green RC, Larson EB, St George-Hyslop PH, Buxbaum JD, Evans DA, Schneider JA, Lunetta KL, Kamboh MI, Saykin AJ, Reiman EM, De Jager PL, Bennett DA, Morris JC, Montine TJ, Goate AM, Blacker D, Tsuang DW, Hakonarson H, Kukull WA, Foroud TM, Martin ER, Haines JL, Mayeux RP, Farrer LA, Schellenberg GD, Pericak-Vance MA, Alzheimer Disease Genetics Consortium, Albert MS, Albin RL, Apostolova LG, Arnold SE, Barber R, Barnes LL, Beach TG, Becker JT, Beekly D, Bigio EH, Bowen JD, Boxer A, Burke JR, Cairns NJ, Cantwell LB, Cao C, Carlson CS, Carney RM, Carrasquillo MM, Carroll SL, Chui HC, Clark DG, Corneveaux J, Cribbs DH, Crocco EA, DeCarli C, DeKosky ST, Dick M, Dickson DW, Duara R, Faber KM, Fallon KB, Farlow MR, Ferris S, Frosch MP, Galasko DR, Ganguli M, Gearing M, Geschwind DH, Ghetti B, Gilbert JR, Glass JD, Growdon JH, Hamilton RL, Harrell LE, Head E, Honig LS, Hulette CM, Hyman BT, Jicha GA, Jin LW, Karydas A, Kaye JA, Kim R, Koo EH, Kowall NW, Kramer JH, LaFerla FM, Lah JJ, Leverenz JB, Levey AI, Li G, Lieberman AP, Lin CF, Lopez OL, Lyketsos CG, Mack WJ, Martiniuk F, Mash DC, Masliah E, McCormick WC, McCurry SM, McDavid AN, McKee AC, Mesulam M, Miller BL, Miller CA, Miller JW, Murrell JR, Olichney JM, Pankratz VS, Parisi

JE, Paulson HL, Peskind E, Petersen RC, Pierce A, Poon WW, Potter H, Quinn JF, Raj A, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosen HJ, Rosenberg RN, Sano M, Schneider LS, Seeley WW, Smith AG, Sonnen JA, Spina S, Stern RA, Tanzi RE, Thornton-Wells TA, Trojanowski JQ, Troncoso JC, Valladares O, Van Deerlin VM, Van Eldik LJ, Vardarajan BN, Vinters HV, Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Williamson J, Wishnek S, Woltjer RL, Wright CB, Younkin SG, Yu CE, Yu L (2014) Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease. *JAMA Neurol* **71**, 1394-1404.

[144] Davidson Y, Gibbons L, Pritchard A, Hardicre J, Wren J, Stopford C, Julien C, Thompson J, Payton A, Pickering-Brown SM, Pendleton N, Horan MA, Burns A, Purandare N, Lendon CL, Neary D, Snowden JS, Mann DM (2007) Apolipoprotein E ε4 allele frequency and age at onset of Alzheimer's disease. *Dement Geriatr Cogn Disord* **23**, 60-66.

[145] Kamboh MI, Barmada MM, Demirci FY, Minster RL, Carrasquillo MM, Pankratz VS, Younkin SG, Saykin AJ; Alzheimer's Disease Neuroimaging Initiative, Sweet RA, Feingold E, DeKosky ST, Lopez OL (2012) Genome-wide association analysis of age-at-onset in Alzheimer's disease. *Mol Psychiatry* **17**, 1340-1346.

[146] Hoozemans JJ, Rozemuller AJ, van Haastert ES, Eikelenboom P, van Gool WA (2011) Neuroinflammation in Alzheimer's disease wanes with age. *J Neuroinflammation* **8**, 171.

[147] Mackenzie IR, Hao C, Munoz DG (1995) Role of microglia in senile plaque formation. *Neurobiol Aging* **16**, 797-804.

[148] Stoltzner SE, Grenfell TJ, Mori C, Wisniewski KE, Wisniewski TM, Selkoe DJ, Lemere CA (2000) Temporal accrual of complement proteins in amyloid plaques in Down's syndrome with Alzheimer's disease. *Am J Pathol* **156**, 489-499.

[149] Wilcock DM, Hurban J, Helman AM, Sudduth TL, McCarty KL, Beckett TL, Ferrell JC, Murphy MP, Abner EL, Schmitt FA, Head E (2105) Down syndrome individuals with Alzheimer's disease have a distinct neuroinflammatory phenotype compared to sporadic Alzheimer's disease. *Neurobiol Aging* **36**, 2468-2474.

[150] Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C, Medical Research Council Cognitive Function, Ageing Study (2009) Age, neuropathology, and dementia. *N Engl J Med* **360**, 2302-2309.

[151] Dursun E, Gezen-Ak D, Hanağası H, Bilgiç B, Lohmann E, Ertan S, Atasoy İL, Alaylıoğlu M, Araz ÖS, Önal B, Gündüz A, Apaydın H, Kızıltan G, Ulutin T, Gürvit H, Yılmazer S (2015) The interleukin 1 alpha, interleukin 1 beta, interleukin 6 and alpha-2-macroglobulin serum levels in patients with early or late onset Alzheimer's disease, mild cognitive impairment or Parkinson's disease. *J Neuroimmunol* **283**, 50-57.

[152] Gezen-Ak D, Dursun E, Hanağası H, Bilgiç B, Lohman E, Araz ÖS, Atasoy IL, Alaylıoğlu M, Önal B, Gürvit H, Yılmazer S (2013) BDNF, TNFα, HSP90, CFH, and IL-10 serum levels in patients with early or late onset Alzheimer's disease or mild cognitive impairment. *J Alzheimers Dis* **37**, 185-195.

[153] Alvarez XA, Franco A, Fernández-Novoa L, Cacabelos R (1996) Blood levels of histamine, IL-1 beta, and TNF-alpha in patients with mild to moderate Alzheimer disease. *Mol Chem Neuropathol* **29**, 237-252.

[154] Rosenthal S, Kamboh I (2014) Late-onset Alzheimer's disease genes and the potentially implicated pathways. *Curr Genet Med Rep* **2**, 85-101.

[155] Nuutinen T, Suuronen T, Kauppinen A, Salminen A (2009) Clusterin: A forgotten player in Alzheimer's disease. *Brain Res Rev* **61**, 89-104.

[156] Slattery CF, Beck JA, Harper L, Adamson G, Abdi Z, Uphill J, Campbell T, Druyeh R, Mahoney CJ, Rohrer JD, Kenny J, Lowe J, Leung KK, Barnes J, Clegg SL, Blair M, Nicholas JM, Guerreiro RJ, Rowe JB, Ponto C, Zerr I, Kretzschmar H, Gambetti P, Crutch SJ, Warren JD, Rossor MN, Fox NC, Collinge J, Schott JM, Mead S (2014) R47H TREM2 variant increases risk of typical early-onset Alzheimer's disease but not of prion or frontotemporal dementia. *Alzheimers Dement* **10**, 602-608.

[157] Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, Ghiso J (2009) Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. *Acta Neuropathol* **118**, 115-130.

[158] Yamada M (2002) Risk factors for cerebral amyloid angiopathy in the elderly. *Ann N Y Acad Sci* **977**, 37-44.

[159] Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, Ellison D, Hilton DA, Williams TL, MacKenzie JM, Xuereb JH, Love S (2005) Abeta-related angiitis: Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* **128**, 500-515.

[160] Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C (2013) Aβ-related angiitis: Comparison with CAA without inflammation and primary CNS vasculitis. *Neurology* **81**, 1596-1603.

[161] DiFrancesco JC, Brioschi M, Brighina L, Ruffmann C, Saracchi E, Costantino G, Galimberti G, Conti E, Curtò NA, Marzorati L, Remida P, Tagliavini F, Savoiardo M, Ferrarese C (2011) Anti-Aβ autoantibodies in the CSF of a patient with CAA-related inflammation: A case report. *Neurology* **76**, 842-844.

[162] Hermann DM, Keyvani K, van de Nes J, Weimar C, Wiltfang J, Nitsch RM, Szodorai A (2011) Brain-reactive β-amyloid antibodies in primary CNS angiitis with cerebral amyloid angiopathy. *Neurology* **77**, 503-505.

[163] Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C (2003) Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology* **61**, 46-54.