Neurobiology of Stress 9 (2018) 9–21

Contents lists available at ScienceDirect

Neurobiology of Stress

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

Chronic stress as a risk factor for Alzheimer's disease: Roles of microglia-mediated synaptic remodeling, inflammation, and oxidative stress

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ARTICLE INFO

Keywords:
Microglia
Stress
Alzheimer's disease
Neurodegeneration
Neuroinflammation
Synaptic remodeling
Microglial phenotypes
Dark microglia

ABSTRACT

Microglia are the predominant immune cells of the central nervous system (CNS) that exert key physiological roles required for maintaining CNS homeostasis, notably in response to chronic stress, as well as mediating synaptic plasticity, learning and memory. The repeated exposure to stress confers a higher risk of developing neurodegenerative diseases including sporadic Alzheimer's disease (AD). While microglia have been causally linked to amyloid beta (Aβ) accumulation, tau pathology, neurodegeneration, and synaptic loss in AD, they were also attributed beneficial roles, notably in the phagocytic elimination of Aβ. In this review, we discuss the interactions between chronic stress and AD pathology, overview the roles played by microglia in AD, especially focusing on chronic stress as an environmental risk factor modulating their function, and present recently-described microglial phenotypes associated with neuroprotection in AD. These microglial phenotypes observed under both chronic stress and AD pathology may provide novel opportunities for the development of better-targeted therapeutic interventions.

1. Introduction: microglia and Alzheimer's disease

Microglia are known to rapidly respond to alterations in brain homeostasis during stress, trauma, disease or pathology (Matcovitch-Natan et al., 2016; Tian et al., 2017). They are the resident, predominant immune cells of the CNS, which although initially thought to be responsible for orchestrating neuroinflammation and causing neurodegeneration (Cartier et al., 2014), were also recently attributed important roles in the maintenance of CNS homeostasis and remodeling of neuronal circuits across development and experience-dependent plasticity (Derecki et al., 2014; Ransohoff and El Khoury, 2015; Tay et al., 2017). Microglial ability to sense neuronal activity allows them to regulate synaptic plasticity, learning and memory mechanisms, and hence determine cognitive abilities (Morris et al., 2013; Sipe et al., 2016). For instance, brain derived neurotrophic factor (BDNF) produced by microglia was shown to modulate motor learning-dependent synapse formation in mice (Parkhurst et al., 2013). In addition, $CX_3CR1^{CreER}/ROSA26^{iDTR}$-flox mice treated with tamoxifen to induce expression of the diphtheria toxin receptor selectively in microglia, and receiving diphtheria toxin to deplete these cells, showed decreased motor learning-induced dendritic spine formation, and reduced levels of synaptic proteins VGlut1 and GluA2 from glutamatergic synapses in the motor cortex (Parkhurst et al., 2013).

Reactive 'microgliosis' in terms of abnormal morphology (e.g. a shift from a ramified to an amoeboid morphology), exacerbated immunoreactivity for ionized calcium-binding adapter molecule 1 (IBA1), and increased proliferation is a prominent feature of AD pathology, especially observed around amyloid plaques in postmortem brain tissue. Similarly, positron emission tomography scans of AD patients using the TSPO tracer [^{11}C]-PK_{11195} revealed exacerbated glial activity (Edison et al., 2008; Perlmutter et al., 1992; Rozemuller et al., 1992; Serrano-Pozo et al., 2011b). Investigating microglial implication in AD onset and progression is becoming increasingly important given the various roles that these immune cells can play. While microglia were

Abbreviations: Aβ, Amyloid beta; ABCA7, ATP-binding cassette transporter A7; AD, Alzheimer's disease; APOE, Apolipoprotein E; APP, amyloid precursor protein; BDNF, brain derived neurotrophic factor; CD11b, cluster of differentiation molecule 11B; CD33, cluster of differentiation 33; CNS, central nervous system; CR, complement receptor; CRF, corticotropin releasing factor; DAM, disease associated microglia; DAP12, DNAX-activation protein 12; FAD, Familial Alzheimer's disease; FCRLS, Fc receptor-like S scavenger receptor; GR, glucocorticoid receptor; HPA axis, hypothalamic pituitary adrenocortical axis; IBA1, ionized calcium-binding adapter molecule 1; IL, interleukin; LTP, long-term potentiation; MGnD, **m**icro**g**lia with a **n**euro**d**egenerative phenotype; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; NADPH, nicotinamide adenine dinucleotide phosphate; NFT, neurofibrillary tangles; PS, presenilin; ROS, reactive oxygen species; TGFβ, transforming growth factor β; TLR, Toll-like receptors; TMEM119, transmembrane protein 119; TNFα, tumor necrosis factor-α; TREM2, triggering receptor expressed in myeloid cells 2; TYROBP, TYRO protein tyrosine kinase binding protein

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https://doi.org/10.1016/j.ynstr.2018.05.003
Received 18 January 2018; Received in revised form 23 February 2018; Accepted 14 May 2018
Available online 19 May 2018

causally linked to neuroinflammation, Aβ accumulation (see Box 1), and tau pathology, as well as implicated in neuronal and synaptic loss (Fuhrmann et al., 2010; Morris et al., 2013), they were also shown to actively participate in the phagocytic clearance of Aβ and protection of neuronal tissue (Ard et al., 1996; Grathwohl et al., 2009; Majumdar et al., 2011; Maphis et al., 2015).

AD is a debilitating, progressive neurodegenerative disease and the most common cause of dementia worldwide (van der Flier and Scheltens, 2005). It is characterized by a slow, progressive cognitive dysfunction, memory decline, and gradual disturbances in reasoning, language, and physical abilities (Holtzman et al., 2011). In AD, the presence of extracellular Aβ deposits and intracellular neurofibrillary tangles (NFTs) are main hallmarks that lead to neuronal dysfunction, cell death, and loss of synaptic connections, notably due to ensuing inflammation and oxidative stress (Zhao and Zhao, 2013). The imbalance in Aβ homeostasis, i.e. production *versus* clearance of Aβ peptides, leads to their accumulation, aggregation –in either fibrillary, oligomeric, or β-sheet conformations– and deposition within the extracellular space (Sadigh-Eteghad et al., 2015). The extracellular Aβ deposits trigger active 'gliosis' that primarily consists in hyperactive astrocytes and microglia among the surrounding parenchyma (Hardy and Higgins, 1992; Kurz and Perneczky, 2011; Wildsmith et al., 2013). The hyperphosphorylation of tau –a tubulin binding protein that functions to stabilize microtubules in the neurons (Kadavath et al., 2015)– results in its dissociation from microtubules, and aggregation in the form of NFTs inside of neuronal cell bodies and neurites, which also triggers gliosis (Grundke-Iqbal et al., 1986; Kadavath et al., 2015; Serrano-Pozo et al., 2011a). Synaptic and neuronal loss as a result of tau pathology and Aβ deposition have been shown to best correlate with the cognitive impairment seen in AD (Spires-Jones and Hyman, 2014). These pathological features may appear early in subcortical nuclei such as the locus coeruleus, then affect the hippocampus and entorhinal cortex, and eventually spread to other cortical areas as the disease progresses (Braak and Del Tredici, 2011; Glenner and Wong, 1984; Grundke-Iqbal et al., 1986; Hardy and Higgins, 1992; Holtzman et al., 2011; Raber et al., 2004).

AD is a multifactorial disease driven by a combination of genetic and environmental factors, and can therefore be classified into familial (FAD) and sporadic forms (Johns, 2014). FAD comprising about 5% of AD cases is due to mutations in APP, presenilin-1, or presenilin-2 genes that result in the production of aggregation-prone Aβ peptides (Johns, 2014; Lanoiselée et al., 2017). Sporadic forms have no familial history of AD, but may be related to the expression of apolipoprotein E4 (APOE4) involved with the transport of lipids, cholesterol, and other hydrophobic molecules into the brain (Raber et al., 2004). In addition, environmental factors that comprise psychosocial stress confer a high risk of developing neurodegenerative diseases and may play an important role in the etiology of sporadic AD (Alkadhi, 2012; Aznar and Knudsen, 2011; Nation et al., 2011). Genetic risk factors for sporadic AD also include mutations or polymorphisms in several genes expressed by microglia and other myeloid cells (Dos Santos et al., 2017; Efthymiou and Goate, 2017; Jonsson et al., 2013; Malik et al., 2015; Satoh et al., 2017; Sims et al., 2017), stressing the importance of these immune cells. While the brain is home to perivascular macrophages, as well as monocytes derived from the bone marrow that enter the CNS from the circulation, especially during brain injury or systemic inflammation (Guillemin and Brew, 2004; Schwartz et al., 2013; Wohleb et al., 2015), microglia are the predominant immune cell population within the CNS.

The genes associated with sporadic AD include *TREM2* (Guerreiro et al., 2013), which codes for a cell surface protein (Prokop et al., 2015; Sessa et al., 2004). The particular R47H variant of *TREM2* leads to a loss-of-function that impairs TREM2-mediated neuroprotection and increases the risk of developing AD by threefold (Guerreiro et al., 2013; Jonsson et al., 2013; Melchior et al., 2010). Knockdown of TREM2 in the brain of a senescence-accelerated mouse prone 8 (SAMP8) mouse model resulted in cognitive impairment, accompanied by increased expression levels of pro-inflammatory tumor necrosis factor (*TNF)α* and interleukin (*IL*)*-6*, and decreased expression levels of anti-inflammatory *IL-10* (Jiang et al., 2014). The association of TREM2 with its binding partner DAP12, an activating adaptor protein, is important for microglial survival and proliferation in mice, especially through regulation of the Wnt/β-Catenin pathway (Poliani et al., 2015; Zheng et al., 2017). TREM2/DAP12 activity is essential for microglial innate immune responses, including chemotaxis and phagocytosis (Kleinberger et al., 2014; Takahashi et al., 2005; Zhong et al., 2017). TREM2 knockdown using a lentiviral strategy reduced microglial 'efferocytosis' or phagocytosis of apoptotic neurons, while its overexpression increased microglial phagocytic activity in a mouse neuron-microglia co-culture system (Takahashi et al., 2005).

Other genes expressed by microglia that were implicated in sporadic AD include the *ABCA7* gene and its variants rs3764650, rs4147929, and rs3752246 (Cuyvers et al., 2015). The gene encodes a protein thought to regulate lipid homeostasis (as well as Aβ homeostasis possibly) and mediate the formation of phagocytic cups, critical for microglial phagocytosis of apoptotic cells and Aβ (Abe-Dohmae et al., 2004; Jehle et al., 2006; Kim et al., 2013). Increased ABCA7 levels were measured in AD postmortem brains, and also in an AD mouse model knockout for *ABCA7* (J20/Abca7$^{-/-}$ mice) showing significantly increased insoluble Aβ levels and plaque burden in the brain, thus suggesting that ABCA7 exerts a neuroprotective role in AD (Kim et al., 2013; Li et al., 2015).

Through this review, we aim to discuss the consequences of chronic stress on the onset and progression of AD pathology, overview the roles played by microglia in AD, by focusing on chronic stress as an environmental risk factor modulating their function, and present the recently-described microglial phenotypes associated with neuroprotection in AD. These microglial phenotypes observed upon chronic stress and AD pathology may provide novel opportunities for the development of therapeutic applications across different contexts of neurodegeneration.

2. Chronic stress as an environmental risk factor

Stress is our body's natural response to adverse or demanding changes in our environment, developed as a measure to deal and overcome these challenges to our well-being (McEwen, 2005). Allostasis refers to such internal adaptive mechanisms that attempt to restore homeostasis to meet the perceived and anticipated demands posed by the stressful situations (McEwen and Seeman, 1999). Stress, therefore, is crucial for survival, but its response can become maladaptive (Ellis and Del Giudice, 2014). Depending on the actual stressor and the severity of its effects, stress can be either beneficial or detrimental, and the duration and chronicity of the stressors exposure also plays an important role in determining its outcome (McCormick and Hodges, 2017).

While the body can quickly resolve and normalize the effects of acute stress, when it becomes chronic, stress may seriously perturb the physiological and psychological balance of an individual. Repetitive recruitment of the neuroendocrine response to chronic stress can lead to a cumulative disturbance of the internal homeostatic mechanisms. Chronic unpredictable and uncontrollable stressors are generally associated with a high risk of developing cardiovascular diseases, depression, and neurodegenerative disorders that include AD, especially in individuals susceptible to stress and its detrimental effects (Leonard, 2010; Liu et al., 2017).

In individuals that are susceptible to stress, due to the high allostatic load, the once protective coping mechanisms become pathological, whereas in resilient individuals, the adaptive response is successfully used to maintain homeostasis (McEwen, 2000; McEwen and Wingfield, 2007). The biological mechanisms that determine the individual response to stress is the subject of intense research with the aim of promoting stress resilience, given the severe impact that chronic stress has

on human health and the serious burden that it imposes on individuals as well as to the society (Schneiderman et al., 2005; Seib et al., 2014).

Stress is also a consequence of disease, especially when the normal day-to-day activities of the affected individuals are being significantly disrupted as a result of their underlying medical condition, thus causing psychological stress (Donovan et al., 2018). The resulting psychological stress may lead to exacerbated cellular stress due to inflammation and oxidative damage (Hayashi, 2015; Miller and Sadeh, 2014). The molecular mechanisms by which stress leads to altered homeostasis and pathology will be discussed further in this review.

A key physiological system that responds to psychological stress is the hypothalamic-pituitary-adrenocortical (HPA) axis, which comprises a tightly regulated pathway of communication between the paraventricular nucleus of the hypothalamus, the pituitary gland, and the adrenal gland. Stressors exposure results in HPA axis activation that eventually leads to the secretion into the blood stream of glucocorticoid stress hormones: cortisol in humans or corticosterone in rodents (Smith and Vale, 2006). Blood glucocorticoids cross the blood-brain barrier and enter the brain to activate glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), two important signaling pathways having essential roles in mediating the brain response to stress (Scheuer, 2010). While GR is ubiquitously expressed by neurons, microglia, CNS-infiltrating monocytes, astrocytes, and oligodendrocytes, MR expression is restricted to mainly neurons showing limited expression by microglia and astrocytes (Madalena and Lerch, 2017). MR is active in basal conditions, due to its high binding affinity and sensitivity toward the low resting levels of corticosteroids (de Kloet et al., 2000). It mediates the tonic functions of glucocorticoids, including their circadian regulation of learning and memory (de Kloet et al., 2000). GR is mainly active during stressful conditions, due to its low binding affinity for corticosteroids, allowing its response to high corticosterone/cortisol levels (de Kloet et al., 2000; Groeneweg et al., 2012). GR and MR also differ in their relative distribution across the brain; while MR is restricted to the prefrontal cortex (PFC), amygdala, and hippocampus, GR shows an abundant brain-wide expression especially in the PFC, amygdala, hypothalamic paraventricular nucleus, locus coeruleus, hippocampus, and hindbrain (Fuxe et al., 1987; Meaney et al., 1985; Reul and de Kloet, 1986, 1985).

Glucocorticoid signaling through GR and MR ensures a tight control over the HPA axis during an acute stress response, requiring an integrative and coordinated activity of neuroendocrine circuits among the forebrain, hypothalamic, and hindbrain systems in order to mediate adaptive changes at both the physiological and behavioral levels (Myers et al., 2014). However, in conditions of prolonged psychological stress, when the adaptive changes are no longer sufficient to meet the environmental challenges, the HPA axis is chronically activated due to a loss of inhibitory feedback causing a dysregulation of glucocorticoid signaling (Ellis and Del Giudice, 2014; Nicolaides et al., 2015; O'Connor et al., 2017, 2016; Vyas et al., 2016). For instance, rats receiving chronic subcutaneous administration of corticosterone showed a permanent depletion of hippocampal corticosterone receptors, accompanied by loss of hippocampal neurons, similar to that seen during aging (Sapolsky et al., 1985).

The sustained increase in glucocorticoid levels was also proposed to initiate Aβ accumulation and tau pathology in AD (Dong and Csernansky, 2009; Green et al., 2006). The glucocorticoid cascade hypothesis postulates that HPA axis dysfunction may represent a contributing factor in the pathogenesis of AD and other neurodegenerative diseases, but strong clinical evidence is currently lacking (Bao et al., 2008; Franceschi et al., 1991; Swanwick et al., 1998). In support of this hypothesis, AD patients present a ~83% increase in cortisol levels in their cerebrospinal fluid compared to healthy age-matched controls, thus indicating an association between stress and AD (Sapolsky et al., 1985; Swaab et al., 1994; Woolley et al., 1990). Several other human studies revealed that individuals with a life-long history of stress or trauma are at higher risk of developing brain atrophy, dementia, and AD in late-life stages (Johansson, 2014; Johansson et al., 2012, 2010; Wang et al., 2012). These evidence indicate that chronic stressors confer an increased vulnerability to developing neurodegenerative diseases across the lifespan.

Similarly, chronic stress was shown to 'prime' or sensitize microglia to generate heightened, exaggerated responses to a second stimulus occurring later in life (Santos et al., 2016). Studies by our group and others have detailed the effects of chronic stress on microglia using a number of paradigms in rodents, including maternal separation, physical restraint, tail suspension, forced swim or water immersion, social defeat or isolation, and unpredictable modifications of the housing conditions (Calcia et al., 2016; Lehmann et al., 2016; Roque et al., 2016; Sugama et al., 2011, 2007; Wang et al., 2017; Winkler et al., 2017; Wohleb et al., 2018). Overall, these studies revealed that microglia are integral partners in mediating the response of the brain and behavior to stress. In the absence of proper neuron-microglial crosstalk (as observed in Cx3cr1 knockout mice, which are deficient in fractalkine signaling) (see Box 1), chronic unpredictable stress failed to alter microglial morphology and phagocytic activity, as well as short- and long-term synaptic plasticity, including long-term potentiation (LTP, a cellular mechanism proposed to underlie memory formation) (Milior et al., 2016). Cx3cr1 knockout mice also failed to develop anhedonia, which is a measure of depressive-like behavior (Milior et al., 2016). Similar findings of an increased resistance to stress in the Cx3cr1 knockout mice were reported by other groups using different stress paradigms (Hellwig et al., 2016; Rimmerman et al., 2017; Winkler et al., 2017). In addition, microglial depletion, using systemic administration of a colony stimulating factor 1 receptor antagonist, in mice exposed to repeated social defeat stress, prevented anxiety (McKim et al., 2017). Similarly, treatment of rats with minocycline, a well-known modulator of microglial activity, rescued working memory upon exposure to chronic restraint stress (Hinwood et al., 2012). These findings and those from other studies indicate that microglial response to stress may be critical in determining its outcome on resilience or susceptibility, with consequences on the overall brain homeostasis.

3. Consequences of chronic stress on AD pathology

A complex interaction of genetic and environmental factors has been proposed to modulate the etiology and pathogenesis of AD. Meta-analysis studies conducted by Ownby et al. provided strong correlations between individuals' histories of early-life depression and their risk of developing AD later in life (Ownby et al., 2006).

In animal studies, the exposure of male and female 5xFAD mice (in pre-pathological stages; see Fig. 1 for additional information on the AD pathology mouse models mentioned in this review) to chronic restraint stress resulted in increased neurotoxic Aβ42 (see Box 1) levels and plaque deposition in the hippocampus of females only, without changes in the cerebral cortex of both males and females (Devi et al., 2010). This finding suggests a sex- and brain region-specific vulnerability to the detrimental effects of stress. The elevation of blood glucocorticoid levels upon stress could adversely influence Aβ processing, by targeting the amyloid precursor and amyloid precursor-like proteins as shown in rats *in vivo* (Budas et al., 1999). Similarly, exposure of APP-PS1 mice (see Fig. 1) to chronic isolation stress resulted in increased Aβ42/Aβ40 ratios (see Box 1) in the hippocampus while worsening spatial working memory (Huang et al., 2011). Chronic immobilization stress to APP_{V717I}-CT100 mice (overexpressing human APP-CT100 bearing the London mutation (V717I), see Fig. 1) also resulted in impaired performance under the passive avoidance task, increased extracellular Aβ deposits, elevated tau phosphorylation levels, and increased Aβ and APP carboxyl-terminal fragments (APP-CTFs; see Box 1) in the hippocampus, entorhinal, and piriform cortex (Jeong et al., 2006). Also, 3xTg mice (see Fig. 1) subjected to social stress showed increased plasma corticosterone levels accompanied by heightened anxiety compared to age-matched wild-types (Rothman et al., 2012). The 3xTg mice

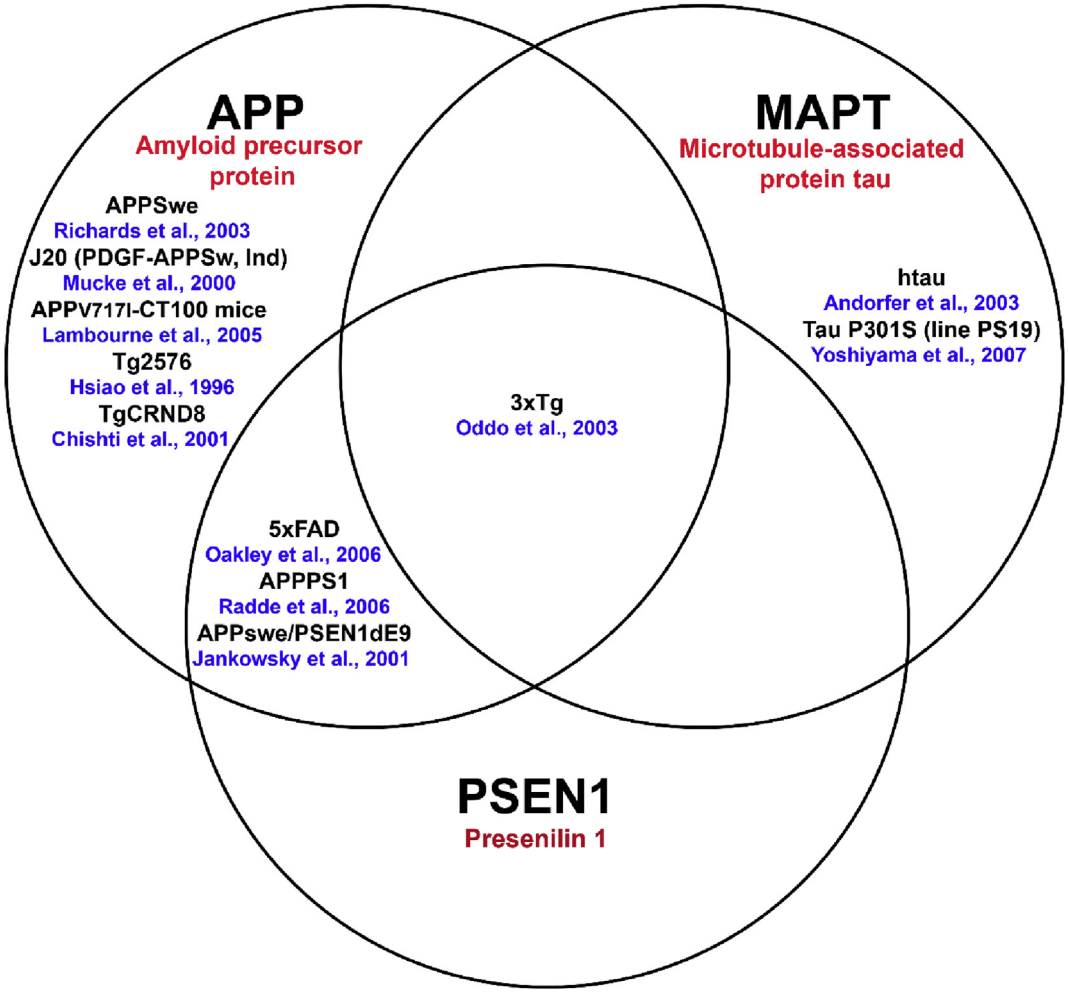

Fig. 1. Overview of the AD pathology mouse models mentioned in the review. Data compiled from Alzforum Alzheimer's disease research model database (https://www.alzforum.org/research-models/alzheimers-disease).

additionally displayed increased levels of Aβ oligomers, intraneuronal Aβ, and decreased levels of BDNF in the hippocampus, but no change in hyperphosphorylated tau (Rothman et al., 2012). Tg2576 mice showed increased Aβ levels and reduced IBA1 immunoreactivity, as well as deficits in spatial and fear memories, while the PS19 mice had elevated levels of hyperphosphorylated tau in the form of insoluble aggregates, with an impairment of fear memory upon chronic restraint and isolation stress (Carroll et al., 2011). These detrimental effects were prevented by pre-stress treatment with an antagonist of the corticotropin releasing factor (CRF) (Carroll et al., 2011). Mice overexpressing CRF (without bearing any mutations associated with AD) similarly displayed increased levels of hyperphosphorylated tau in this study (Carroll et al., 2011) and others (Campbell et al., 2015), supporting the detrimental consequences of chronic stress-mediated HPA axis dysregulation on AD pathogenesis.

Aside from affecting the hallmark features of AD, the exposure of rodents to stress resulted in impaired adult neurogenesis and synaptic plasticity. Tg2576 mice (see Fig. 1) undergoing chronic isolation stress showed an accelerated age-dependent deposition of Aβ, accompanied by reduced hippocampal neurogenesis and decreased contextual memory, compared with their unstressed littermates (Dong et al., 2004). Tran et al. revealed significant alterations of LTP and spatial memory in rats chronically receiving subpathogenic doses of Aβ (subAβ) that were also exposed to repeated social defeat stress. Unstressed rats receiving subAβ did not differ from the controls receiving vehicle (Tran et al., 2011). This effect of social stress on LTP and spatial memory may partly result from the decreased expression levels of different plasticity-related proteins, including calcium calmodulin kinase II and protein kinase C, and increased expression levels of protein phosphatase 2B (calcineurin), which are known to inhibit LTP in the rat hippocampus (Gerges et al., 2004). Cytokines secreted by microglia such as anti-inflammatory IL-10 and TGFβ, and pro-inflammatory TNFα, IL-1β, IL-6, IL-12 and IL-18, could also be implicated (Piirainen et al., 2017). For example, IL-1 regulates learning and memory mechanisms notably through its influence on LTP. The induction of LTP promotes *IL-1* expression while blocking IL-1 impairs maintenance of LTP in the rat hippocampus (Balschun et al., 2003; Schneider et al., 1998). Similarly, IL-18 positively regulates LTP maintenance, while IL-6 negatively regulates LTP maintenance in the rat hippocampus (del Rey et al., 2013). The contribution of inflammatory microglia to AD pathology (Sarlus and Heneka, 2017) will be discussed below.

Chronic stress additionally regulates the synthesis and secretion of neurotrophins that play key roles in synaptic plasticity, learning and memory. A decline in BDNF expression was measured in the hippocampus of wild-type rats in response to chronic restraint stress (Chiba et al., 2012; Smith et al., 1995) and of rodent depression models upon predator stress or repeated social defeat (Roth et al., 2011; Tsankova et al., 2006). A similar decline in blood BDNF levels was detected in patients suffering from depression or showing predisposition to depression, which could be reversed by antidepressant treatment (Karege et al., 2005; Sen et al., 2008; Shimizu et al., 2003; Trajkovska et al., 2008). A reduction in BDNF levels was also observed in AD patients at

preclinical and clinical stages, within the hippocampus and temporal cortex, where the diminished BDNF levels correlated with the pathology severity (Connor et al., 1997; Michalski and Fahnestock, 2003; Peng et al., 2005; Phillips et al., 1991). These data suggest that alterations in neurotrophin signaling, particularly of BDNF, may underlie some of the deleterious effects of chronic stress, and hence influence AD onset and progression. BDNF expression is among other mechanisms regulated by glucocorticoid signaling onto both GR and MR (Suri and Vaidya, 2013). Since microglia express GR and MR, they were proposed to play important roles in facilitating the adaptive response to stress and AD pathology, notably through their remodeling of neuronal circuits (Carrillo-de Sauvage et al., 2013; Chantong et al., 2012; Parkhurst et al., 2013; Sierra et al., 2008; Tanaka et al., 1997; Vyas et al., 2016).

4. Roles of microglia in AD pathology

While microglia exert neuroprotection in AD, especially through their phagocytic clearance of Aβ (ElAli and Rivest, 2016), a loss of their beneficial functions can exacerbate amyloidosis, leading to subsequent inflammation, synaptic loss, and neuronal damage (Gandy and Heppner, 2013; Heppner et al., 2015; Perry and Holmes, 2014; Rivest, 2015). Vice versa, microglial inability to clear abnormally aggregated Aβ results in the activation of pro-inflammatory signaling pathways, furthering inflammation, oxidative stress, and neurodegeneration in AD (Lee and Landreth, 2010; Piirainen et al., 2017; Solito and Sastre, 2012). The following section aims at providing an overview of these various roles of microglia in AD, emphasizing the relationship to chronic stress as an environmental risk factor.

4.1. Loss of beneficial physiological functions

The classical complement pathway is normally utilized by microglia to eliminate apoptotic or damaged neurons, microbial load and cellular debris, as well as synaptic elements (Boulanger, 2009; Chung et al., 2015). The cascade involves tagging of the targeted elements by C1q, their opsonization and subsequent phagocytosis via C3b complement-CR3 microglial complement receptor (also known as CD11b) interaction. Its contribution to microglial pruning of synapses is now well accepted during normal physiological conditions (Sasaki et al., 2014; Schafer et al., 2012; Stevens et al., 2007) and was also proposed to underlie the pathological or traumatic remodeling of neuronal circuits during stress by 'dark' microglia, a newly-defined microglial phenotype discussed below (Bisht et al., 2016). Complement pathway-mediated microglial phagocytosis is a mechanism also recruited in diseases, implicated in AD and in a number of neurodegenerative disorders such as Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (Loeffler et al., 2006; Stevens et al., 2007). Zanjani et al. documented a progressive activation of complement proteins in human AD brain tissue, specifically of C1q, C3 and C4 around the plaques in both preclinical and clinical stages of the disease (Zanjani et al., 2005). This study revealed staining of NFTs and dystrophic neurites for the membrane attack complex C5b, which results from the cleavage of C5 upon binding of Cb3b to Aβ, in more advanced stages of pathology (Zanjani et al., 2005). Elevated C1q expression levels were also measured during aging in the human postmortem hippocampus, as well as in the hippocampus and frontal cortex of J20 and APP-PS1 mouse models of AD (see Fig. 1), showing co-localization with synapses before the plaques could be detected (Hong et al., 2016; Stephan et al., 2013). Synaptic loss was further prevented in the hippocampus of J20 and Tg2576 mice with either C1q neutralizing antibodies or knocking out of *C1q* (Fonseca et al., 2004; Hong et al., 2016). The knockout or inhibition of C3 similarly prevented synaptic loss in the hippocampus and cognitive decline in APPswe/PS1dE9 mice (see Fig. 1) still devoid of plaques, as well as during normal aging in wild-type mice (Shi et al., 2017). This detrimental role of microglial complement-mediated phagocytosis is supported by the fact that microglia are the main cellular source of complement C1q protein in the brain (Fonseca et al., 2017).

The exacerbated activity of microglial signaling through their CD33 receptors was also linked to their deleterious effects in AD. Sialic acid is an important glycan typically found on the outer membrane of most cell types. The interaction of sialylated residues on neurons with Siglec receptors on microglia is essential for a healthy neuron-microglial communication in the brain (Varki, 2008; Wielgat and Braszko, 2012). CD33 (or siglec-3), a sialic acid-binding transmembrane receptor protein, is largely expressed by microglia, and functions to inhibit autoimmune activation through its binding to sialylated self-association molecular patterns (Griciuc et al., 2013; Malik et al., 2013; Schwarz et al., 2015; Varki and Angata, 2006). A modest increase in *CD33* mRNA and protein levels detected in postmortem human AD frontal cortex was associated with a decrease in Aβ phagocytosis, and consequently, knockout mice lacking *CD33* showed a reduced Aβ burden (Griciuc et al., 2013). Sialic acid binding (from sialylated agents found in the vicinity of plaques, such as ApoE and ApoJ) to CD33 results in the activation of SHP1 and SHP2 phosphatases inhibiting the TREM2/DAP12 pathway. This mechanism was proposed to conceal the plaques from microglial immune surveillance and phagocytic clearance (Linnartz and Neumann, 2013). TREM2 binding to its ligands such as ApoE, clusterin (CLU, or ApoJ), and low density lipoproteins, allows its association with the plaques (Atagi et al., 2015; Bailey et al., 2015). TREM2-ApoE interaction is essential for the phagocytosis of apoptotic neurons and extracellular debris, from dying or dead neurons, as will be discussed below when presenting novel microglial phenotypes. It also prevents escalation of neuroinflammation in mice treated with cuprizone, a model of demyelination (Cantoni et al., 2015). TREM2 overexpression in mouse primary microglial cells results in their cytoskeletal reorganization through the activation of DAP12 and phosphorylation of extracellular signal-regulated kinases, and this step is crucial for the phagocytosis of microsphere beads *in vitro* (Takahashi et al., 2005). Furthermore, TREM2 is expressed by microglial processes in the immediate vicinity of the plaques. Plaque-associated microglia surround amyloid deposits in postmortem human AD brain tissue, as a mechanism proposed to compact the deposits and inhibit any additional deposition of Aβ peptides into the existing plaques, in order to prevent further neurotoxicity and axonal dystrophy (Yuan et al., 2016). This neuroprotective barrier was not observed in Trem2 knockout mice, or in human AD postmortem brain bearing the *TREM2* variant R47H, thus supporting the implication of TREM2 in mediating microglial ability to form neuroprotective barriers (Condello et al., 2017, 2015; Yuan et al., 2016).

4.2. Gain of detrimental inflammatory functions

A characteristic hallmark of stress, especially chronic, is the induction of pro-inflammatory mechanisms leading to oxidative stress (Hayashi, 2015; Miller and Sadeh, 2014), a condition resulting from the imbalance between antioxidant mechanisms and production of reactive oxygen species (such as H_2O_2, O_2^-, NO, $ONOO^-$/ONOOH), eventually triggering lipid peroxidation and DNA damage (Aschbacher et al., 2013; Bergamini et al., 2004; Epel, 2009). Oxidative stress induced neuronal damage is also a characteristic feature seen in Aβ and tau pathology, and often mediated by microglia and peripheral myeloid cells (Ghribi et al., 2003; Giraldo et al., 2014; Kempuraj et al., 2016; Martin et al., 2017). Microglia engaged in inflammation are considered a major source of reactive oxygen species in the brain (Block and Hong, 2007).

Aβ aggregates can mimic the damage-associated molecular patterns and stimulate Toll-like receptors (TLR; see Box 1) on microglia thereby mounting an inflammatory response by the NRLP3 (NACHT, LRR and PYD domains-containing protein 3) inflammasome complex (see Box 1) (Heneka et al., 2013). As a consequence of the inflammasome activation, caspase-1 is recruited to the inflammasome, and a number of pro-inflammatory mediators such as TNFα and IL-1β are released to induce further pro-inflammatory responses by microglia and other brain

immune cells like astrocytes (Heneka et al., 2013). Genetic deletion of NLRP3, caspase-1 and TLRs was shown to be neuroprotective by preventing the synaptic loss and cognitive decline, thereby confirming the pro-inflammatory contributions of CD11b-positive microglia in AD (Heneka et al., 2013). Also, microglia were demonstrated to increase the formation of Aβ oligomers and promote further their aggregation due to the ability of Aβ to rapidly bind to ASC specks (see Box 1) released by microglia, seeding further Aβ aggregation and spreading of Aβ pathology, as observed in APPSwePSEN1dE9 mice (see Fig. 1) given intra-hippocampal injection of ASC specks (Venegas et al., 2017). Similarly, co-application of an anti-ASC antibody did not exacerbate Aβ pathology, as was also the case in ASC-deficient APPSwePSEN1dE9 mice treated with brain homogenates derived from APPSwePSEN1dE9 mice (Venegas et al., 2017). These findings provide a direct evidence for the involvement of microglial inflammasome in the seeding and spreading of Aβ pathology in AD patients.

The pro-inflammatory C5a, which also results from the binding of C3b to Aβ, and is recognized by microglial CD88 receptors, leads to the production of various pro-inflammatory cytokines, reactive oxygen species (ROS), reactive nitrogen intermediates, and bioactive amines (Wilkinson and Landreth, 2006; Woodruff et al., 2010). Microglial ROS can be formed by the activities of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondrial respiratory chain, xanthine oxidase, microsomal enzymes, cycloxygenase and lipoxygenase (Wilkinson and Landreth, 2006). NADPH oxidase forms part of the integral innate phagocytic immune system that utilizes superoxide (O_2-) to mediate the destruction of invading microorganisms (Bergendi et al., 1999; Wilkinson and Landreth, 2006). Other sources of ROS include hydrogen peroxide, hydroxyl radical, peroxynitrite and other oxidants (Wilkinson and Landreth, 2006). In rat primary microglia, exposure to Aβ activates NADPH oxidase and causes the release of ROS, which can be terminated through the inhibition of upstream signaling partners such as the src-family tyrosine kinases or phosphatidylinositol-3 kinase (Bianca et al., 1999; McDonald et al., 1997). Aβ induced NADPH oxidase activation in the rat hippocampus results in the formation of peroxynitrite, a potent oxidant that oxidizes proteins, lipids, and DNA (Nam et al., 2012). Peroxynitrite mediated tyrosine nitration and nitrosylation of cysteines is extremely detrimental resulting in protein and enzyme dysfunction, leading ultimately to neuronal death *in vitro* (Bonfoco et al., 1995; Mander and Brown, 2005). The accumulation of peroxynitrite in AD is supported by the presence of elevated levels of nitrated proteins in postmortem AD brain tissue, particularly within regions containing NFTs (Castegna et al., 2003). Lipid peroxidation and DNA oxidative damage was also demonstrated in postmortem human AD brains (Matsuoka et al., 2001; Nunomura et al., 1999; Sayre et al., 1997; Wang et al., 2005). These findings indicate that pro-inflammatory microglial activities may be detrimental in AD due to the formation of reactive oxygen and nitrogen intermediates resulting in oxidative stress-induced neuronal damage, which could be further exacerbated by chronic stress.

5. Newly-described microglial phenotypes

The recent technical advancements, including in high-throughput gene expression analyses distinguishing microglia from bone marrow-derived myeloid cells, have allowed to start characterizing the diversity of microglial phenotypes in the CNS, especially in the context of altered brain homeostasis. Electron microscopy with immunostaining against these recently identified markers was also used by our group to describe 'dark' microglia, a newly-defined phenotype associated with both chronic stress and AD pathology.

5.1. Dark microglia

In 2016, we described the 'dark' microglia, which are strikingly distinct from typical IBA1-positive microglia in their ultrastructural details (Bisht et al., 2016). In electron microscopy, these cells showed a condensed, electron-dense cytoplasm and nucleoplasm, a characteristic giving them a 'dark' appearance. Dark microglia also displayed endoplasmic reticulum and Golgi apparatus dilation, as well as mitochondrial alterations, considered the best-characterized signs of oxidative stress at the ultrastructural level. These cells seemed to be extremely active at synapses, by means of their thin, elongated, ramified processes strongly expressing complement receptor CR3 when contacting synaptic clefts and encircling synaptic elements. In mouse hippocampus, dark microglia were highly prevalent in conditions where normal homeostasis is disturbed: chronic stress, aging, AD pathology (APP-PS1 mice; see Fig. 1), and where fractalkine signaling is disrupted (Cx3cr1 knockout mice; see Box 1). Especially in APP-PS1 mice, dark microglia were frequently encountered around the plaques, encircling dystrophic neurons, containing amyloid depositions in their processes, and showing a strong expression of TREM2, involved as discussed above in mediating microglial phagocytosis (Colonna and Wang, 2016; Numasawa et al., 2011; Painter et al., 2015; Zheng et al., 2017). Dark microglia showed a downregulated expression of homeostatic markers, CX_3CR1, IBA1 and P2RY12, but strongly expressed the microglia-specific 4D4 in their processes (Bisht et al., 2016). They were proposed to represent a subset of hyperactive microglia that become stressed as a result of their hyperactivity under adaptive pressure, leading to exacerbated interactions with synapses. The increased phagocytic activity of dark microglia also suggested that these cells might contribute to restricting the Aβ burden.

5.2. Disease associated microglia

Keren-Shaul et al. identified a unique microglial population, the disease associated microglia (DAM), using single-cell RNA-sequencing, by comparing microglia from wild-type *versus* 5xFAD mice (see Fig. 1) (Keren-Shaul et al., 2017). Using the immune marker $CD45^+$, myeloid cells were isolated from the brain and grouped into different clusters based on single-cell RNA-sequencing data. Three main microglial clusters emerged. Cluster I comprised cells expressing markers of homeostatic microglia, which were present in both control and AD pathology animals, while clusters II and III microglia were only observed in AD pathology. The clusters II and III microglia showed an upregulated expression of genes related to lipid metabolism, phagocytosis, and AD pathology, such as *CST7, APOE, LPL, CTSD, TYROBP*, and *TREM2*, and downregulated expression of homeostatic markers such as transmembrane protein 119 (TMEM119, selective to microglia) and CX_3CR1, without changes in expression of inflammatory cytokines. They differed in their expression levels of phagocytic markers, suggesting an intermediate phenotype between homeostatic and cluster III (DAM) microglia. This transition was proposed to proceed in two steps, with the complete transition into DAM requiring the expression of TREM2, highlighting again the importance of this receptor in mediating microglial response to AD pathology. The DAM phenotype was also described in human postmortem AD brains, where it was found to contain intracellular Aβ, suggesting a neuroprotective role for the DAM (Keren-Shaul et al., 2017).

5.3. Neurodegenerative microglial phenotype

The complexity of the roles played by microglia in homeostasis as well as diseased conditions is portrayed in another study by Krasemann et al. where the authors described regulatory mechanisms underlying the switch of microglia from a homeostatic to a neurodegenerative phenotype: MGnD (**m**icro**g**lia with a **n**euro**d**egenerative phenotype) (Krasemann et al., 2017). Microglia were isolated from the brain and spinal cord using a specific Fc receptor-like S scavenger receptor (FCRLS) antibody, in mouse models of AD (APP-PS1), multiple sclerosis (experimental autoimmune encephalomyelitis), and amyotrophic lateral sclerosis (SOD1-G93A). Under normal physiological conditions,

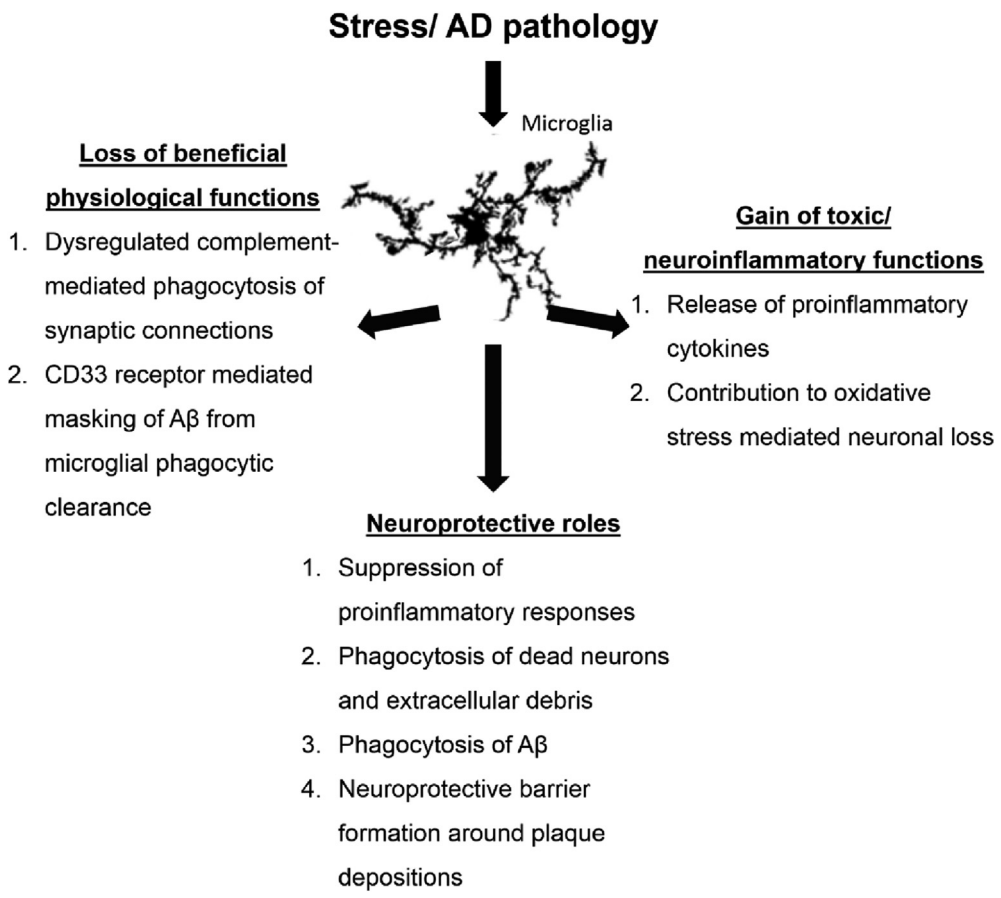

Fig. 2. Overview of microglial functions in response to stress and AD pathology.

homeostatic microglia expressed *Olfml3, P2ry12, Tmem119, Mef2a, Jun*, and *Sall1*, among other genes regulated by TGFβ, all of which were downregulated by the MGnD phenotype. Similarly, these cells showed an upregulated expression of *APOE, Axl*, and *Clec7a* genes. Microglial transformation into MGnD, identified by gene expression signature, was only observed in contexts where neuronal apoptosis occurred. In APP-PS1 mice, MGnD primarily encircled amyloid plaques and dystrophic neurites, blanketed by homeostatic microglia in the periphery. They also expressed TMEM119, providing support to their microglial origin. In APOE knockout mice, microglia still phagocytosed dying neurons, but did not show the expression patterns of MGnD, indicating the importance of APOE for maintaining this phenotype. Similar findings were observed in TREM2 knockout animals, proposing that an APOE-TREM2 switch mediates the transformation of homeostatic microglia into phagocytic MGnD during neurodegeneration.

The above three studies stress the importance of studying the variety of microglial phenotypes in the CNS. Brain resident microglia and peripheral macrophages should not be combined into one category, neither should the brain resident microglia considered as a single cell entity, since they appear to comprise heterogeneous populations having distinct gene expression signatures, functions, and morphologies depending on the homeostasis status. Future studies aiming to address the roles of microglia in stressed and pathological states should take these new findings into consideration.

6. Conclusion and perspective

The way the brain microglia react to homeostatic changes as in stress and neurodegeneration determines the overall outcome of the brain's capacity to respond to these alterations. These responses contribute to what is known as allostasis or the adaptive measures taken to adapt the organism to the adverse challenges. An imbalance or overload in the adaptive responses to conditions of prolonged stress especially by microglia may lead to altered physiological functions, becoming either maladaptive or pro-inflammatory, thus predisposing the brain to secondary insults in the form of trauma or disease. Hence, microglia were thus proposed to play an important role in linking the adverse effects of chronic stress with the onset and progression of AD (Piirainen et al., 2017). Therefore, a better understanding of the roles and underlying mechanisms by which microglia may contribute to regulating brain functions and behavior in response to changes in the environment under both homeostatic and altered states is required.

While microglia can exacerbate pathological damage during chronic stress and AD pathology via dysregulated complement-mediated phagocytosis, release of inflammatory cytokines, and their mediation of oxidative stress, they may also contribute positively to the restoration of neuronal homeostasis (see Fig. 2). The recent description of novel microglial phenotypes associated with chronic stress and neurodegenerative diseases further supports the view that microglia represent a heterogeneous cell population in which different phenotypes behave differently depending on the context. Through this review, we have attempted to highlight the importance of studying individual microglial phenotypes and their distinct contributions to brain homeostasis and disease, considering that their activities could be selectively targeted to promote neuroprotection in various neurological and neurodegenerative contexts.

Acknowledgements

We are grateful to Marie-Kim St-Pierre, Katherine Picard, and Mathilde S. Henry for their critical revision of the manuscript. This work was supported by a CIHR Foundation Scheme grant to MET and

an excellence scholarship from Fondation du CHU de Québec to KB. MET is a Canada Research Chair (Tier 2) in *Neuroimmune plasticity in health and therapy*.

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Box 1: Glossary

Aβ peptides: Proteolytic cleavage product of amyloid precursor protein or APP, formed as a result of sequential cleavage by β-secretase 1, and γ-secretase enzymes

Aβ40 and Aβ42: 40- and 42-residue long isoforms of Aβ respectively, derived from APP proteolysis, with Aβ42 forming a major component of amyloid plaques

Aβ42/Aβ40: This ratio plays a critical role in AD, with higher ratios often associated with greater neurotoxicity, and correlating with early-onset familial AD cases

APP carboxyl-terminal (APP-CTF) fragments: A 99 amino acid long C-terminal fragment generated by the cleavage of APP by the β-site APP cleaving enzyme, which on further cleavage by γ-secretase generates Aβ that gets deposited in AD

Toll-like receptors (TLRs): A class of protein receptors expressed on immune cells that recognize microbe derived structurally conserved molecules, and thus form an important part of the innate immune system

Inflammasome: A group of inducible, high molecular weight, cytosolic multiprotein complexes and an essential component of the innate immune response important for the clearance of pathogens or damaged cells

ASC Speck: Apoptosis-associated Speck-like protein containing Caspase Activation and Recruitment Domain. It functions as the adaptor protein in the inflammasome complex that after release in response to specific stimuli can form a discrete “speck,” within the activated cell. It functions to recruit caspase-1 to eventually result in the production of inflammatory cytokines, IL-1β and IL-18

Fractalkine signaling: Involves the interaction between fractalkine ligand CX_3CL1 expressed by neurons that interacts with its unique receptor, CX_3CR1, expressed by microglia and macrophages. It is essential for proper neuron-microglia communication in the brain across homeostatic and diseased conditions