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Healing the Chronic Wound in Alzheimer's Disease Brain: Early Targeting of Microglia as a Promising Strategy

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Abstract

Objectives: To outline the underlying pathophysiology and biochemistry in Alzheimer's disease (AD) development and progression, and then focus on microglial effect on AD microenvironment with exploitation of microglia as a promising approach to the development of effective therapeutic for AD.

Design: In this review, a search of the literature up to December 2020 in Scopus, Web of Science, Medline, and PubMed were included, using search terms that include Aβ peptide deposition, Aβ42 protofibril, senile plaque, hyper phosphorylated tau, neurofibrillary tangles, degenerated neurons, neurodegeneration, Microglia phenotype, microenvironments, physiological functions, phagocytosis, neuroinflammation, atrophy, frontal lobe, temporal lobes, proteolytic degradation, Biochemical imbalances, proinflammatory mediators, intracellular molecules, redox signalling molecules, Angiotensin 1 converting enzyme 1, single nucleotide polymorphisms, blood brain barrier, perivascular drainage, Low density lipoprotein receptor-related protein-1, interstitial fluid, P-glycoprotein, cerebral amyloid angiopathy, Ubiquitin-proteasome system.

Result: Success in developing an effective therapeutic approach of AD is limited due to incompleteness of our knowledge on the biochemical and physiological effects of the initial insult inflicted by Aβ peptide deposition and senile plaques in the extracellular space. Moreover, the complexity of AD is increased by the secondary insult caused by the spatiotemporal progression of intra-neuronal fibrillary tangles of hyper-phosphorylated tau. Taken together, these insults contribute greatly to neurodegeneration and cognitive malfunction.

Conclusion: There is no effective treatment and no known stimulus for effective repair of degenerated neurons, neuro-regeneration, or prevention of neuronal death. Microglia is the main innate immune cells of the brain and detects changes in the local microenvironments to maintain normal physiological functions. Changes in the microenvironment (e.g., infection, ischaemic injury, Aβ species, Aβ-plaque, tau proteins, proinflammatory mediators), soluble factors released from neurons and astrocytes, intracellular molecules, redox signalling molecules, and metabolic shift-mediated proteins negatively impact microglial clearing processes, such as change in phenotype, morphology, and proliferative responses. An imbalance in microglia phenotypes occurs in AD with AD progression and these results in increased microglia-derived neuroinflammatory activities.

Keywords: Chronic wound; Alzheimer's disease; Brain; Microglia

Introduction

Alzheimer's disease

AD is the most common form of dementia and is characterized by Aβ peptide deposition, which develops into senile plaque (SP) in the extracellular space, hyper phosphorylated tau, which develops into neurofibrillary tangles (NFTs) in the intracellular space and atrophy of the frontal and temporal lobes [1]. Conformational changes in Aβ peptides results in accumulative self-aggregation and tau protein hyper-phosphorylation leads to β-pleated sheet formation and subsequent NFTs [2]. Physiological homeostasis of excess neural Aβ occurs via various processes, including proteolytic degradation and clearance [3]. If these processes are dysfunctional, Aβ may become aggregated and contribute to NFT [4] and subsequent neuronal cell death and inflammation. Compounding this, the aggregated Aβ can induce the M1-dominated polarization of the microglia phenotype, which release proinflammatory mediators and free radicals that inhibit neuronal repair and regeneration [5]. The perturbed microenvironment becomes exacerbated by a cyclical process of inflammation and further plaque and tangle formation culminating in the development and progression of AD.

Effects of APP and Aβ in AD Development

Amyloid precursor protein (APP) is expressed in neurons in response to damaging agents. APP has a protective function to counter the damage; however, if APP protective function fails and neurons die, APP breakdown products misfold and lead to amyloid deposition [6]. Germline mutations in APP impair APP protective roles, and thereby lead to increase in neuronal loss in response to damage [6]. Beta secretase-1 (BASE-1) and γ-secretase are the main enzymes involved in the proteolytic production of Aβ from APP via the amyloidogenic and non-amyloidogenic pathways (Figure 1).

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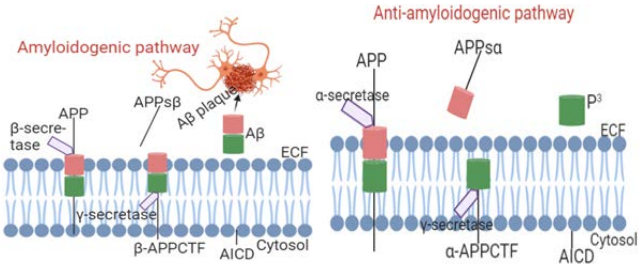

Figure 1: Proteolytic production of Aβ from APP. The N-terminus of APP lies within the extracellular fluid while the C terminus lies within the cytosol, a clear liquid portion of the cytoplasm (Figures 1A-B). APP proteolytic processing consists of 2 major pathways [amyloidogenic (abnormal), which generates Aβ and anti / non-amyloidogenic (normal), which prevents Aβ generation]. In amyloidogenic pathway, β-secretase cleaves a soluble large portion of ectodomain of APP (sAPPβ) from cells and retains membrane bound-C-terminal fragments (βAPPCTF). γ-secretase cleaves βAPPCTF within the hydrophobic regions of the cell membrane and liberates Aβ peptides between 38-43 residues into the ECF (plasma and CSF) where it slowly builds up to form amyloid plaques (figure 1A). In non-amyloidogenic pathway, γ-secretase cleaves APP in the middle of Aβ (removing sAPPα from cells) and this generates truncated αAPPCTF which lacks amino terminal portion of Aβ domain. γ-secretase cleaves αAPPCTF and this leads liberation of truncated Aβ (p3) which is pathologically irrelevant (figure 1B).

Aβ42 and Aβ40 are the main species in the proteolytic processes. Aβ42 is critical to deposition of Aβ and it is an initiator of AD pathogenesis. Aβ40 is neuroprotective against Aβ42 toxicity and oxidative damage (induced by metal) [6]. Presenilin 1 and 2 (PSEN1 and PSEN2) are vital components of γ-secretase complex. In all familiar Alzheimer's disease mutations, Aβ42 is increased while Aβ40 is decreased [6]. Study in PSEN mutated animal model has shown that Aβ42/Aβ40 ratio is elevated and microgliosis is decreased [7]. Thus, reducing the levels of toxic Aβ42 or Aβ42/Aβ40 ratio may be a therapeutic potential for AD. In clinical trials, many γ-secretase inhibitors have been designed, but none of them was succeeded [8,9]. Besides, level of Aβ42 and Aβ42/Aβ40 ratio could be reduced by converting Aβ42 to Aβ40 after Aβ production.

Degradation of naturally secreted Aβ by ACE: clinical implication of ACE inhibitors

Angiotensin 1 converting enzyme 1 (ACE1) is a peptidase. ACE inhibitors are used in the treatment of hypertension, heart failure, and chronic renal disease [10]. Hypertension is one of the vascular risk factors in AD. ACE cleaves dozens of different peptide substrates [11]. ACE has been reported to convert Aβ42 to Aβ40 in the human brain [6]. According to GWAS, patients with clinical late onset AD are reported to have ACE mutations [12]. Furthermore, single nucleotide polymorphisms rs4343 and rs4351 in ACE haplotype have a 45-fold higher risk of developing AD [13]. Replacement of CNS-microglia with ACE-overexpressing cells nearly results in complete elimination cerebral Aβ burden, astrocytosis, and full protection of cognitive functions in murine AD, like the levels seen in the wild-type mice [14,15]. Therefore, selective higher levels of ACE are potentially therapeutic [16]. ACE can destroy amyloidogenic peptides such as non-fibrillar and oligomeric Aβ structures (which can migrate into the brain) in peripheral inflammatory cells and strongly supports cognition [17]. Thus, this calls an attention to potential neuro-pathological consequences of ACE inhibitors. To date, the relationship between ACE and microglia is not elucidated.

In addition to degradation of naturally secreted Aβ, Neprilysin (NEP) has Aβ-degrading activity and reportedly degrades Aβ in blood. Higher level of NEP in the brain could have a therapeutic potential in AD treatment. However, NEP does not cross the BBB easily, its transport from the blood into murine and rat brains is facilitated by brain shuttle modules such as transferrin receptor (TfR) single chain Fab antibody and TfR monoclonal antibody OX26 [18,19]. It has been demonstrated in vivo that the amount of NEP in AD mice (APP/PSI, 8-month old) is significantly higher compared to the age-matched wild type mice [20]. Conversely, the levels of NEP may be negatively related to age or AD severity, with levels of NEP in APP/PS1 significantly decreased in the hippocampus after 6-month age compared to 3-month APP/PS1 or 6-month wild type [21]. Recently, Kai-Xin-San (KXS, a Chinese herbal extract used to treat deficit in memory, amnesia) has been revealed to increase NEP expression and thus enhance Aβ degradation in mice hippocampus [22]. Further research is required to establish the exact role that NEP plays in AD progression and APP clearance. Moreover, Insulin degrading enzyme (IDE) is a zinc endopeptidase in the cytosol, peroxisomes, mitochondria, and at the cell surface of neurons, astrocytes, microglia [23]. In APP/PS1 AD mice, IDE is significantly lower at 10-month age compared to 4-month age compared to the wild type mice [20]. This is similar to another study which reported a significantly lower level of IDE in APP/PS1 AD mice hippocampus compared to the wild type mice at 10 month and 18-months of age [24]. In contrary, in vivo and in vitro evidence has shown that growth differentiation factor-15 (GDF-15) increases IDE expression in microglia cells via TGFβ receptor type II (TGFβRII) [23].

Internalisation of intraneuronal Aβ from Interstitial fluid impacts cellular apoptosis

The physiological homeostasis of Aβ critically depends on Aβ clearance [25]. Neurons eliminate Aβ via cellular uptake by internalization and lysosomal degradation. Disturbances in the internalisation of neuronal Aβ leads to accumulation and aggregation of Aβ, which results in synaptic injury and eventually neuronal death. Low density lipoprotein receptor-related protein-1 (LRP-1) controls Aβ uptake and consequent degradation in their postsynaptic regions and cell bodies [26]. LRP-1 is in cells such as brain capillary endothelial cells, vascular cells, microglia, glia cells, and liver [27,28]. Liu et al. (2017) showed that LRP-1 deletion in astrocytes reduces Aβ uptake, downregulate key Aβ-degrading enzymes (such as IDE), decreases Aβ degradation, and thereby worsen Aβ accumulation in APP (KM670/671NL) and PS1 (ΔE9) mice [29]. Furthermore, deletion of LRP-1 in APP/PSI mice increases the half-life of Aβ in the interstitial fluid (ISF) in the cortex, aggravates Aβ pathology [29]. Dynamin is a protein, which is critical to endocytosis. It has been demonstrated in vivo and in vitro that, following internalisation, Aβ can be exocytosed via exomes to a neighboring neuron. Pharmacological inhibition of dynamin-mediated internalisation leads to accumulation of Aβ on cell surface and loss of transneuronal Aβ transmission [30]. Internalised Aβ can be degraded in the lysosome. However, Aβ aggregation can occur when lysosome-Aβ degradation capacity is saturated due to uncontrolled accumulation of Aβ and/or the degradation pathway is altered. Subsequently, intraneuronal Aβ aggregation and accelerate intraneuronal Aβ deposition occurs [31]. Spreading of intraneuronal Aβ aggregate may spread through neuronal connections and thus, contribute to propagation of Aβ aggregation and neuronal toxicity [26,30]. Protofibrils are elongated cluster of cells, which grows into fibril (Figure 2).

Intraneuronal aggregation of protofibrils in endosomes and lysosomes induces membrane leakage, which results in cytosolic acidification and apoptosis [32]. Soluble Aβ42 aggregate (such as Aβ42 protofibrils and

Aβ42 oligomers) in ISF activates microglia. Based on Aβ structure and degree of oligomerisation, microglia internalise Aβ42 (using receptors such as scavenger receptors, complement receptor, signal regulatory protein-β1 receptor, P2Y4 receptor, CD36, α6β1 integrin, and CD47) and transports it to the lysosome [33]. Microglia significantly internalise Aβ42 protofibril than Aβ42 monomers and Aβ42 fibril [34]. Microglia will rapidly internalise Aβ protofibrils in a process that depends on time, concentration of Aβ protofibrils in the ISF, and secretion of TNF-α. At a concentration of 2 μM of both AF488-Aβ protofibrils and AF488-Aβ monomers, primary microglia internalise, at 24 hours via pinocytosis, high level (>95%) of AF488-Aβ protofibrils compared to low level of AF488-Aβ monomers. As the concentration increases to 10 μM (but AF488 stoichiometry in Aβ monomers is 4X AF488 in Aβ protofibrils), primary murine microglia internalise higher AF488-Aβ protofibrils levels and lower AF488-Aβ monomers levels into their cytosols at 5 min, and also secretes TNF-α at the same period (5 min) [33-35]. Within the cytosol, Aβ protofibrils were dense and spread throughout the cytosols and only few Aβ protofibrils are transported to the lysosome. This means that Aβ protofibrils are not degraded and cleared after internalisation by primary murine microglia [33].

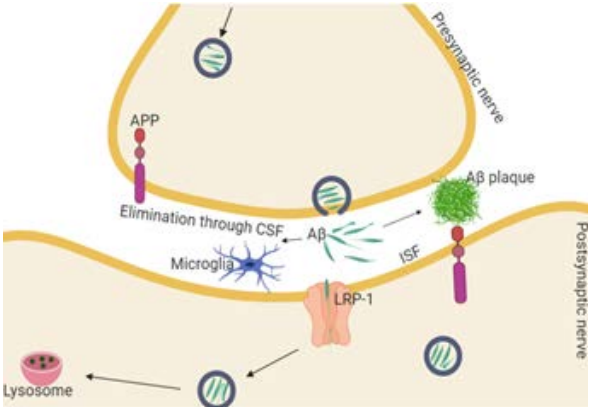

Figure 2: LRP1-mediated Aβ clearance pathways. Aβ is predominantly generated in neurons and secreted into ISF. Proteolytic degradation by endopeptidases (e.g., NEP and IDE) is a major Aβ clearance pathway. Cellular Aβ also plays a vital in eliminating Aβfrom the brain. LRP1 significantly controls Aβ endocytosis and subsequent lysosomal degradation. LRP1 is expressed in brain cells such as neurons, astrocytes, microglia, endothelial cells, vascular smooth muscles, and pericytes. In brain parenchyma, neurons, astrocytes, and microglia can take up and degrade Aβ mainly in lysosomes. ISF is drained along the cerebrovasculature, where Aβ is degraded by vascular cells. A portion of Aβmay be transported out of the brain through the BBB. Disturbances of these pathways induce Aβaggregation and deposition as Aβ plaques in brain parenchyma, perivascular regions as CAA and sometimes also inside neurons as intraneuronal Aβ .

Reduced Aβ clearance via the BBB into the plasma negatively impacts transporter profile of BBB and weakens the perivascular drainage

LRP-1 is negatively charged (receptor) and attracts (for) negatively charged ligands such as Aβ, α2-macroglobulin (α2M), ApoE in the presence of calcium ions [28]. α2M is a glycoprotein and an extracellular chaperone in plasma, CSF, and ISF: α2M traps proteases and thereby becomes activated to inhibits protein aggregation. When α2M is activated, it opens its receptor binding site for LRP-1 [36]. ApoE gene is the strongest genetic risk of late onset AD [37]. When Aβ binds with α2M or ApoE, α2M or ApoE undergo conformational change and binds with LRP-1 or LRP-2, which transport Aβ to the apical membrane of the endothelial cells, where transporters such as ANP-sensitive transporters, insulin-sensitive transporter, and ABC transporter (such as P-glycoprotein, P-gp) are located [38,39]. P-gp is a crucial protein and efflux transporter (in the plasma membrane of the brain capillary endothelial cells), which transports Aβ out of the brain across the BBB to the blood [38,40] (Figure 3).

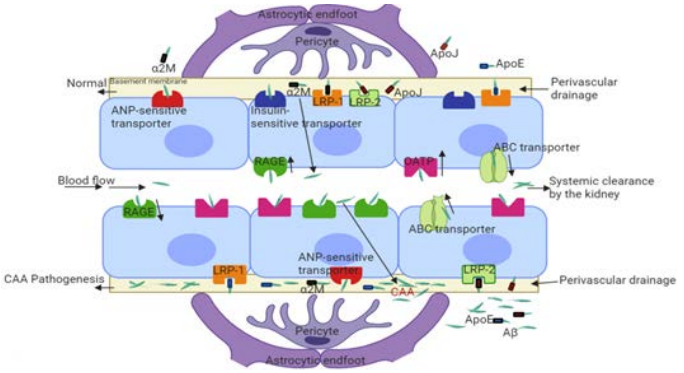

Figure 3: Aβ can be transported bi-directionally through BBB by receptors. In normal healthy conditions, efflux of Aβ is regulated by the receptors in the endothelium. After binding with ApoE or α2M, Aβ can be transported LRP1. If Aβ binds with ApoJ, Aβ is transported by LRP2. Other receptors that regulate efflux of Aβ include ABC transporter, insulin-sensitive transporter, and ANP-sensitive transporter. In addition, Aβ can be transported to the perivascular spaces and effluxed via perivascular drainage. During efflux of Aβ, little influx of Aβ is regulated by RAGE and OATP. In cerebral amyloid angiopathy (CAA) pathological condition, the transporter profile of the BBB is changed: the efflux receptors are decreasing, and the influx receptors are increasing. This decreases Aβ clearance and increases Aβ deposition on the vessel wall. Consequently, this creates changes in the cerebrovascular basement membrane and weakens the perivascular drainage. These result in aggregation of Aβ in the blood vessels, and thereby aggregating CAA.

Storck et al. (2016) reported a significant reduction in: efflux of Aβ42 out of the brain endothelial cells, plasma Aβ levels, and learning and memory by deleting LRP-1 in brain endothelium of C57BL/6 mice and 5xFAD mice compared to the control [41,42]. The mechanism of decline in learning and memory could be a proportional association between NMDAR and LRP-1. LRP-1 deletion leads to degradation of NMDAR. Although MEOX2 gene controls LRP-1 expression at the BBB, recent study in AD mouse model has shown that haploinsufficiency of MEOX2 gene does not affect Aβ plague deposition and glia activation, however, there are higher level of neuronal cell loss and significant decreased level of micro vessels in the brain region, which holds the Aβ plague [43]. Furthermore, LRP-1 might promote Aβ clearance via other Aβ-binding proteins such as heparan sulfate proteoglycans [44]. APOE-Aβ interaction regulates aggregation of Aβ. Therefore, low level ApoE directly impacts Aβ plaque development, CAA, and Tau pathology [37]. ApoE4 genotype is the most potent genetic risk factor of early onset of AD [45]. Lack of ApoE4 promotes Aβ oligomerisation. It has been demonstrated in vivo and in vitro that oligomers of Aβ and Tau are most neurotoxic species in AD and their level of toxicity is correlated with cognitive decline, compared to the burden of Aβ plague or NFT [46]. PS1 (E280A) mutation leads to Aβ aggregation, which typically causes clinical onset of mild cognitive impairment (MCI) and dementia in patients at the median ages of 44 and 49 years [47,48]. Interestingly, APOE3ch variant protein significantly reduces the development of

Aβ42 monomer into Aβ42 aggregate compared to a wild type APOE3 [37,47]. According to a study carried out in Columbia, a patient with PSI (E280A) mutation also has additional homozygous expression of the rare Christchurch APOE3 mutation, R154S (APOE3ch), which resist the effects of the PS1 mutation because the patient did not develop MCI until her seventies except slight tau pathology [47].

Impact of Aβ40 on P-gp reduction through ubiquitin-proteasome system at BBB in AD

Carrano et al. (2014) shows that Aβ deposit significantly reduced P-gp levels in the microvessels of AD human brain with CAA compared to healthy individual and AD patients without vascular Aβ deposit [49]. In mild and advanced AD patients, P-gp is reduced at the BBB of the brain region (such as hippocampus, frontal and posterior cingulate cortices, and parietotemporal) that are vital for memory formation. [50]. However, the mechanism by which P-gp is reduced at BBB in AD is unclear. Ubiquitin-proteasome system (UPS) is a primary degradation system in the nuclei and cytoplasm of eukaryotic cells. UPS offers fundamental molecular machinery for short-lived protein degradation, modulate vital cell functions (such as inflammation, differentiation, cell cycle, cell signalling during stress), and maintains a dynamic physiological homeostasis [51,52]. UPS facilitates removal of damaged proteins (soluble) and degradation of short-lived regulatory proteins via two basic stages, ubiquitination, and proteolytic degradation of ubiquitinated proteins [51]. Ubiquitination is an ATP dependent stage, which occurs when a polyubiquitin chain attaches (covalently) with a lysine residue of substrate (proteins). This represents a recognition signal for degradation of ubiquitinated proteins. Degradation of ubiquitinated proteins involves three enzymes viz: ubiquitin-activating enzymes (E1), ubiquitin-conjugative enzymes (E2), and ubiquitin ligases (E3). When ubiquitin enzymes assemble (minimum of four) on a substrate (protein), a polyubiquitinated substrate is formed. Proteasome recognise, unfold, degrade the polyubiquitinated substrate, and this subsequently results in generation of short peptides and amino acids. The short peptides and amino acids later recycle for new protein synthesis [53]. P-gp is a substrate for Ubiquitin ligase NEDD4-1. Ubiquitin ligase NEDD4-1 is elevated in the brain capillaries of hAPP (Tg2576) mice at 9-month-old: thus, Ubiquitin ligase NEDD4-1 may be responsible for decrease in P-gp [54]. Recently, Aβ40 has been found to mediate P-gp reduction at BBB through ubiquitin-proteasome system in AD. Aβ40 triggers ubiquitination, internalisation, and proteasomal degradation of P-gp at BBB in rat brain capillaries and in AD patients. These result in decreased P-gp expression and transport function [40,55].

Clearance of Aβ via bulk flow from ISF into the blood (Perivascular drainage) aggravate of CAA and neuronal death in AD

Moreover, Aβ could also be cleared from the brain ISF into the CSF via the perivascular Virchow-Robin arterial spaces by a physiological mechanism called bulk flow. Aβ is then drained into the blood across the arachnoid villi [56]. In the blood, Aβ is cleared by red blood cells and monocytes: Aβ also binds with soluble LRP-1 on the kidney and liver cells, which also clear Aβ [56]. Any alteration to these mechanisms could change the profiles of receptors in the BBB either by decreasing the efflux receptors and increasing the influx receptors, which all lead to a decrease in Aβ clearance and an increase in Aβ deposition on the vessel wall. These negatively impact cerebrovascular basement membrane and weaken perivascular drainage and results in aggregation of Aβ in blood vessels, which in turn is exacerbating CAA in AD [33,39]. Deposition of Aβ in the tunica media and adventitia of the arterioles and/or capillaries of the cerebral cortex and leptomeningeal contributes to cases of cerebral amyloid angiopathy (CAA) in AD [57,58]. Vascular wall of CAA consists of Aβ40 deposits [39]. The use of anti-Aβ immunotherapies in the treatment of AD has failed because the deposition of Aβ in the cerebrovascular pathway causes 221 further damage to blood vessels, and thereby exacerbates CAA [39]. Microglia activities in scavenging for Aβ still occur but chronic neuroinflammation due to increased neurotoxic chemicals (such as TNF-α) produced by microglia results in inevitably neuronal death [56].

Transport of Aβ from the blood into the brain

RAGE is a multiligand receptor (located at the BBB), whose level of expression is determined by the concentrations of its ligands. RAGE is involved in the influx (take up) of Aβ from the blood into the brain ISF across BBB [59]. That is, RAGE transport Aβ in an opposite direction to LRP1. Higher RAGE expressions in AD have been reported to enhance the activities of β-and/γ-secretases, and these processes result in pathogenesis of Aβ generation [60]. Thus, RAGE is identified as a key therapeutic target in AD [61]. Azeliragon (TTP488), a small molecule inhibitor of RAGE, has been shown to decrease Aβ plagues, total Aβ brain concentration (but increase plasma Aβ level), sAPPβ (but increase sAPPα) and level of inflammatory cytokines in preclinical animal models of AD (tgAPPSwedish/London) [62]. According to a phase 2b study in mild AD patients, Azeliragon (5 mg/day) delays time to cognitive decline [62]. Microglia is also activated following interaction of Aβ with RAGE [63].

Misfolded aggregated proteins alter microglia clearing potentials in AD

Glial cells are called neuroglia. Glial cells occupy about half of the space in the brain because they do not have extensive branching like neurons [64]. Glia cells do not conduct nerve electrical signals. They protect and nourish the neurons; determine the growth and effective synapses of neurons; maintain the composition of the fluid surrounding the neurons in the nervous system; support the neurons both physically and chemically through processes needed for cell survival. The glia cells in the CNS are astrocytes, oligodendrocytes, ependymal cells, and microglia.

Discussion

Microglia

Microglia is involved in the pathophysiology of AD, where microglia regulates Aβ pathology and Tau pathology [65]. Microglia play role in pruning surplus dendrites, clearing dead neuroblasts, and actively participates in adult hippocampal neurogenesis [66]. In healthy brain, microglia are not resting, microglia constantly survey their microenvironment to maintain normal physiological homeostasis [67].

Development and function of microglia

Microglia is a form of neuroglial cells located in the brain parenchyma [68]. According to Bar and Barak, 2019, microglia is the third element glia cells in the central nervous system (CNS) and exhibits physiological functions such as phagocytosis, synapse formation, myelination, plasticity, and cognition [69]. The CNS contains 5%-12% microglia cells. Microglia is resident immune cells of the brain and is made up of 10%-15% of the glial cells in adult brain [70]. During embryo development, microglia initially surround neuroepithelial cells (which form the wall of the closed neural tube), and later enters the neuroepithelial cells, where they spread non-uniformly throughout the brain parenchymal. At this stage (embryonic stage), microglia are located in the VS and SVS, where they regulate the size of the precursor cell pool [71]; in newly forming blood vessel for angiogenesis [66]; near dying cells in the choroid plexus and developing hippocampus for phagocytic activities [72] and; close to

developing axons to promote and develop axonal pruning and/or axonal growth and guidance mechanism [73]. Studies have shown that Yolk-sac derived microglia enter the brain at early embryonic stage in rodents [72] and humans [74]. Development of microglia involves three stages: early stage (E10.5-E14), pre-(E14-P9), and adult (4 weeks above).

During this development of microglia, microglia expresses different sets of genes (which relate to their specific stage activities in the brain) to perform three essential functions: nurturer functions, sentinel function, and warrior functions [75]. The nurturer functions are housekeeping functions, which include synaptic pruning and remodelling (vital for development of CNS, homeostasis such as microglia-astrocyte interaction homeostasis, and neurodegeneration) and migration for phagocytosis of dead or dying cells or debris. The genes encoding for synaptic pruning and remodelling C1q and Cx3cr1. TGFβr encodes for homeostasis, chemokine receptor encodes for migration, and Trem2 and scavenger receptors encode for removal of apoptotic neurons (Figure 4). The sentinel functions are sensing of the microglia microenvironment, using a sensome gene which encodes proteins that control microglia sensing activities (Figure 4). The warrior functions are basically defence against infectious pathogens and Aβ via microglia Fc receptors, TLRs, and antimicrobial peptide (Figure 4).

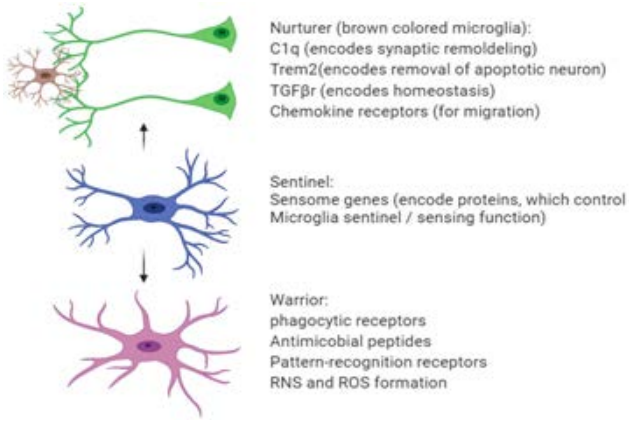

Figure 4: Developmental functional states of microglia. In healthy state, microglia in the nurture state are ramified and spread evenly in the brain parenchyma. They participate in synaptic pruning, remodelling, and migration via a specific receptors and receptor-linked pathways. In sentinel state, microglia is in constant motion, surveiling their microenvironments. Their sensing function is encoded by sensome genes, which controls sensing activities / function of microglia. In warrior state, the warrior (microglia) defends their microenvironments against infectious pathogens and injurious-self proteins such as Aβ via microglial Fc receptors, TLRs, and antimicrobial peptides.

Therefore, alteration in microglia environment can negatively affect the specific time of microglia development plans and thus disrupt brain development, which may cause neuropathology. Microglia enhances development of CNS and promotes neuronal survival (via microglial secretion nerve growth factors and fibroblast growth factors), and synaptogenesis. Trem2 is part of the microglia sensate [76] and has affinity for ligands such Aβ, dead neurons, damaged myelin, sphingomyelin, ApoE, and phosphatidylserine [77,78]. Trem2 is a cell surface receptor, which is found on microglia in the brain [79]. Trem2 gene translates an innate immunity receptor of the immunoglobulin family and it is located on chromosome 6 in humans and chromosome 17 in mouse [80]. According to GWAS, Trem2 is a major risk factors in late-onset AD. Trem2 mutation is associated with a 3.0-to 4.5 increased AD risk. Trem2 AD risk is as high as AD risk associated with ApoE4 [81]. Carriers of Trem2 variants have a faster rate of cognitive dysfunction and this suggest that Trem2 could influence progression of AD [82].

Microglia and neuroinflammation

Neuroinflammation or all form of inflammation is a physiologic immune response, which designated to protect the body from harm, coming from both endogenous and exogenous sources [67]. Initially, neuroinflammation is a protective response in the brain. Microglia cells regulate neuroinflammatory responses in connection to the conditions of the diseased brain [83]. Inflammatory cytokines are excessively expressed in proximity to Aβ plaques with NFT, exacerbate neuroinflammatory processes, and thereby cause cytotoxicity [84]. During the initial AD pathology, microglia and astrocytes are activated and this activation is beneficial because they are clearing Aβ [85]. However, as AD progresses, activated microglia generate abnormal high levels of proinflammatory cytokines (such as TNF-α), neurotoxic factors (such as ROS), and neurotoxic factors (such as ROS), which all block neuronal regeneration [86]: this also destroys tissues (neurodegeneration) in the surrounding brain regions [85,87]. This results in decrease microglial clearing potential. As Aβ accumulation increases due to decline microglial clearing activities, microglia releases more and more proinflammatory cytokines [85]. Destruction of nearby neurons creates astrogliosis (reactive astrocytes or abnormal increase in the number of astrocyte). Reactive astrocytes receive gain of toxic function and thereby undergo loss of neurotrophic functions with neurotoxic effects. Astrocyte dysfunction results in increased release of cytokines and inflammatory mediators, neurodegeneration, decrease glutamate uptake, loss of neuronal synapses, and eventually cognitive decline in AD [85]. Reactive gliosis, which surrounds Aβ plaques, is the characteristics of neuroinflammation. Uncontrolled long-term (chronic) glia activation and pro-inflammatory cytokine production enhances neurodegenerative processes such as cognitive dysfunction and AD.

M1 microglia phenotype and damages to neuronal cells

At basal level in the CNS, pathological conditions such as Aβ-plaques, infection, and brain trauma are considered as harmful stimuli to the microenvironment of brain cells. Microglia is the first responder to harmful stimuli. When microglia recognise (using their receptors such as toll-like receptors, TLRs, and nucleotide-binding oligomerisation domains, NODs) any of these harmful stimuli during their sensing and housekeeping physiological functions, microglia become activated [85,88]. Microglia then respond to the harmful stimuli by producing a high level of proinflammatory cytokines such as IL-1β, IL-6, IL-12, IL-23, STAT3, TNF-α, interferon-γ (IFN-γ) plus cytotoxic molecules such NO (produced from inducible nitric oxide, iNOS, in the presence of Arginine) and ROS in order to destroy invading harmful stimuli: this also damages neuronal cells in the microenvironment [67]. These activated microglias are scavengers and are called M1 microglia phenotype [89]. They denote the first line of defence because they secret proinflammatory cytokines and cytotoxic molecules, which destroy invading harmful stimuli. The production of proinflammatory cytokines is critical for M1 phenotype [85]. Other physiological mechanisms involved in the control of M1 phenotype are autocrine and paracrine of microglia. Once the harmful stimuli have been dealt with, this response is protective and downregulated. To restore homeostasis in brain cells and their microenvironment, an M2 phenotype, also called alternative phenotype (anti-inflammatory phase), needs to be consecutively activated. The M2 phenotype effect tissue repair and wound healing [67,89] and inhibit production of proinflammatory cytokines [85]. Otherwise, unregulated production of proinflammatory cytokines and cytotoxic molecules will

occur. This can result in progressive cell death and tissue damage. Therefore, it is vital that the cells can switch from proinflammatory M1 mode to M2 phenotype to ensure clearance of debris and extracellular debris deposition for tissue repair. In AD microglia M1 phenotype is pathogenic [90,91] (Figure 5).

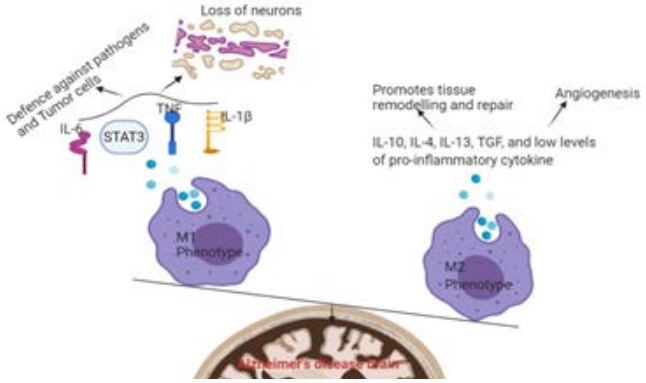

Figure 5: Pathogenicity of M1 phenotype results from physiological imbalances between M1 phenotypic activities and M2 phenotypic activities. The production of proinflammatory cytokines is critical for M1 phenotype. Other physiological mechanisms involved in the control of M1 phenotype are autocrine and paracrine of microglia. Once the harmful stimuli have been dealt with, this response is protective and downregulated. To restore homeostasis in brain cells and their microenvironment, an M2 phenotype, also called alternative phenotype (anti-inflammatory phase), needs to be consecutively activated. The M2 phenotype effect tissue repair and wound healing, and inhibit production of proinflammatory cytokines. Otherwise, unregulated production of proinflammatory cytokines and cytotoxic molecules will occur. This can result in progressive cell death and tissue damage.

M2 microglia phenotype and Aβ deposits

The M2 microglia phenotype is also called alternative M2 mode of microglia function. Microglia M2 mode of action has been associated with neurogenesis, angiogenesis, anti-inflammation and restoring homeostasis, degradation of Aβ deposits, wound repair, and debris clearance [92,93]. One of the best biomarkers of M2 microglia is arginase 1 (Arg1). Arg1 converts arginine to polyamine, proline, and ornithines, which are all extracellular matrix protecting proteins for wound healing and matrix deposition: Agr1 level is reduced in AD mouse model [94]. It is interesting to remember that the same, substrate (Arginine) is used in the conversion of iNOS to NO. Therefore, Agr1 can outcompete iNOS to downregulate NO production [67]. Therefore, iNOS and Agr1 are set of biomarkers, which can convert M1 phenotype to M2 phenotype. The M2 microglia phenotype also produce IL-10 to downregulate inflammatory cells, heparin-binding lectin (Ym1) with IL-10, IL-13, and TNF-β to repair wound, and higher level of receptors (such as scavenger receptors) for phagocytosis of cellular debris [92,93]. In both in vitro and animal model, overexpression of IL-4 and treatment with exogenous IL-4 enhance M2 phenotype, with a reduced Aβ deposit [94].

Three subtypes of M2 microglia have been suggested, including M2a (anti-inflammatory phenotype, which express CD206, Fizz-1, Arg1, and Ym1 and heal wound); M2b (inflammation modulatory phenotype, which express IL-10 and COX2) and; M2c (immunosuppressive phenotype, which express CD163) [95]. Moreover, mixed transitional phenotype of microglia (Mtran) has also been proposed. Mtran co-express M1 markers (iNOS and IL-12) and M2 markers (TGF-β and Arg1) [96]. It is difficult to differentiate between M1 or each M2 subtype in vivo and in vitro. Recently, technical advancement such as fluorescent analysis, cell sorting, and single-cell RNA-seq analysis have helped to establish microglia-specific genes compared to genes specific to macrophages and other glia [97]. M1 or M2 microglia phenotypes, however, do not exactly or absolutely match transcriptome microglia classification [98]. This is because M1/M2 polarisation is a view, which is derived from periphery, and this may not translate into CNS [99]. For instance, M1/M2 transcriptome microglia classification does not explain the function of proliferating microglia [100]. Recently, microglial heterogenicity has been reported in young mice: according to immunoregulatory and bioenergetics-related transcripts, there is greatest convergence between cerebellar and hippocampal microglia compared with cortex and striatum. Aging was associated with decreased differences between hippocampus compared with cortex or striatum [101]. The reasons or impact of these changes in microglial heterogeneity in space or time is unclear. Functional classification (use in this review for activated microglia) of microglia is either neurotoxic (M1) or neuroprotective (M2). This functional classification of microglia is useful for illustrating the pathophysiology of inflammatory and degenerative CNS disorder.

Microglia-Aβ interactions in AD

During sensing brain microenvironment, microglia sense Aβ, binds with Aβ via their pattern recognition receptors (PRRs) such as TLRs, SRs, and complementary receptor 3 (CR3), clears excess Aβ, and removes injurious agents [102,103]. Chronic activation of microglia M1 phenotype can exacerbate M1 mode of action because too much cytotoxic factors are produced [104]. This occurs when the pathological conditions are becoming more pronounced for a long period of time, probably due to mutation or loss of normal clearance (across the BBB) of the Aβ [105]. Thus, this consistent Aβ production induces chronic Aβ-microglia interaction, which results in more Aβ deposition. In this case, microglia produce a continuum of highly excess proinflammatory cytokines (IL-1β, IL-6, and TNF-α, interferon-γ (IFN-γ)) and neurotoxic factors (NO and ROS) [67], which all become accumulated and reduce the capacity of microglia to clear Aβ. This results in neuronal damage [106]. It has been reported that inhibition of NO prevents spatial memory dysfunction in AD animals [107]. In addition, Aβ fibrils activate leucine-rich repeat-and pyrin domain-containing 3 (NLRP3) inflammasome located in the microglia and astrocytes. NLRP3 recruits caspase-1 through interaction with homotypic caspase domain (CARD) during inflammasome assembly [108]. The CARD binds with Aβ and this causes Aβ aggregation, which results in Aβ seeding and consequently development of Aβ plague [109]. This triggers the maturation of proinflammatory cytokines such as IL-1β with TNF and produces neurotoxic reactive oxygen species (ROS). Higher level of proinflammatory cytokines bind to their receptors on neurons, glia cells, endothelial cells. Higher level of proinflammatory cytokines also induce other cytokine to initiate Th-cell signalling, thereby triggering a complex spectrum of signalling events, which result in exacerbation of inflammatory cascade responses within the brain and the spinal cord and early loss of synapse [110].

Microglia-Tau interactions in AD

In cognitively healthy individuals, NFTs are usually located in the medial temporal lobe. Tau tangle progresses into the limbic and neocortex with the existing Aβ plague exactly correspond with cognitive impairment [111]. It has been demonstrated that Aβ plaques drive the spread and formation of p-tau and AD progression by facilitating local tau seeding in dystrophic neurites in mice model [112, 113]. Microglia restrict

peri-plaques neuritic dystrophy [114]. In AD, M1 microglia sense and clear tau in their microenvironments to prevent tau toxicity [115,116]. When M1 microglia is activated, microglia produces proinflammatory cytokines, which increase tau phosphorylation [117]. This initiates the spread of tau pathology and a self-spreading loop, which reaches the highest level in severe AD [118]. Higher level of micro-vesicle Tau protein have been reported in the in the CSF and blood of AD patients [119,120]. Immunosuppressant drug, FK506, decreases the activation of proinflammatory microglia without any detrimental effect in lifespan of mice. These suggest that microglia can mediate tau toxicity. According to Nash et al. (2013) and Bemiller et al. (2017), dysregulation of fractalkine (Cx3cr1) and Trem2 pathways lead to dysregulation of microglia host-defense pathway in tau mouse models. This distorts neuroinflammatory response, and thereby results in neuronal damage and loss [121,122] (Figure 6).

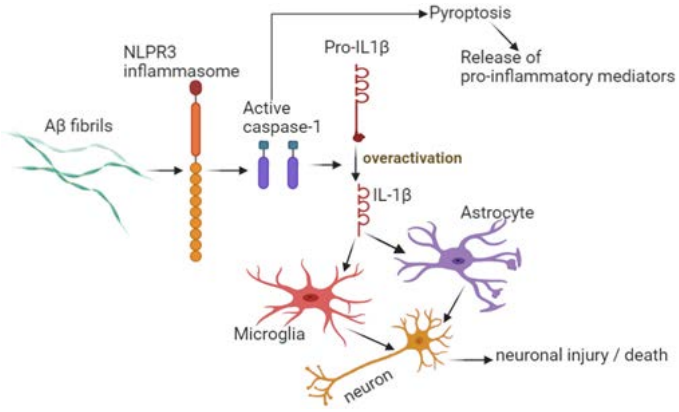

Figure 6: NLRP3 inflammasome activation-mediated neuroinflammation. Aβ fibrils activate NLRP3 located in the microglia and astrocyte. This triggers the maturation of IL-1β and induces pyroptotic cell death. Higher levels of IL-1β bind to their receptors on neurons and endothelial cells and induce other cytokines to initiate Th-cell signalling, thereby triggering a complex spectrum of signalling events, which result in exacerbation of inflammatory cascade responses within the brain and the spinal cord.

These studies suggest that reactive microglia is involved in the initiation and amplification of immune response, which eventually worsens the neurodegenerative conditions. Indisputably, an increased level of proinflammatory cytokines and chemokines has been observed in the brain and the cerebrospinal fluid of AD patients [123].

Microglia as neuronal killers

Several pathways are activated when ligands such as Aβ and infectious pathogens bind with microglia. In response to Aβ, microglia releases their proteases such as cathepsin, which causes apoptosis of neurons and metalloproteases which cause neuronal injury in hypoxia-ischemia. NADPH produces superoxide which is converted into hydrogen peroxide via extracellular superoxide dismutase or reacts NO to produce peroxynitrite. This leads to cell cellular necrosis or apoptosis [124]. Microglia also directly release glutamate or overexpress iNOS and thereby causing excitotoxic neuronal death [125]. Microglia could also damage neurons via indirect pathway which entails microglial release of TNF-α (which stimulate NMDA receptor), microglial reduction of nutritive BDNF and IGF [124] and microglial reduction in phagocytosis of debris dead cells and abnormally accumulated proteins [126] (Figure 7).

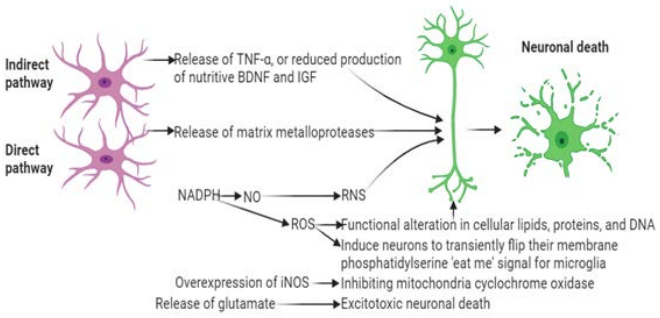

Figure 7: How microglia damage or kill neurons. When ligands such as Aβ and infectious pathogens bind with microglia, several pathways are activated. NADPH oxidase produces superoxide and derivative oxidants. iNOS produces nitric oxide and its derivatives. Glutamate, cathepsin B, and other proteases are released. Phagocytic killing of stressed neurons takes place. Oxidative lipid damage reduces membrane fluidity and membrane potential and increases ion permeability. These result in organelle swelling, loss of membrane depolarisation, and rupture of the plasma membrane, leading to necrosis. Microglia also utilise indirect means to kill and damage neurons via release of TNF-α, which stimulates NMDA receptor activity, or reduced production of nutritive BDNF and IGF. However, microglia killing is not continuous because they have many immunological checkpoints, which prevent their overreaction to external stimuli. These checkpoints include (a) Trem2 checkpoints, which mediates sensing, housekeeping, host defence microglial functions (b) Cx3cr1 checkpoints, which regulates sensing and housekeeping microglial functions (c) The progranulin checkpoints, which regulate housekeeping function. Trem2 deletion decreases: microglia phagocytosis, proliferation, survival and increases proinflammatory cytokines and reactive nitrogen species [127]. However, it is unclear how the actions of protective microglia and Trem2 variants (which interrupt microglia) contribute to AD risk and AD progression. In mouse and human models of AD with risk allele Trem2R47H, decrease level of Trem2 reduces microgliosis, which surrounds Aβ-plaques and thereby increases neuritic dystrophy around plaques [128-130]. Therefore, increased accumulation of dystrophic neurons in Trem2 mutant mice is due to decreased clearance of Aβ-plaques by microglia, not increased neuronal death. This is because microglia form a physical barrier to prevent plaque expansion and protect neurons [131]. TRem2 also affect tau seeding and spread. Study of Aβ and tau aggregation in mouse model reported decrease Trem2 and Trem2R47H variant levels. This increases predisposition of tau seeding and spread in dystrophic neurons that surround Aβ-plaques. Microglia and Trem2 are critical connection between Aβ and tau pathologies. Trem2 increases microgliosis to Aβ. This means that Trem2 probably contains toxic Aβ-42 species, which promotes microgliosis to Aβ and thus prevents early tau seeding events. Therefore, Trem2 function in microglia restricts Aβ-plaque-induced tau pathogenesis in AD. Disruption of Cx3cr1 checkpoint does not increase risk of developing AD, but alters AD courses in animal models. However, disruption of progranulin checkpoints increases the risk of AD. Disruption of any of these pathways results in initiation or exacerbation of neuro-degenerations.

Therapeutic approaches for modulating microglia phenotypes

At present, there are no treatment option to restore degenerated neurons, induce neuroregeneration, or prevent neuronal death in AD. Current drugs only limit the level of neuroinflammation in AD patients [132], reduce symptoms, and increase quality of life for AD patients. Gene

therapies such as viruses (which overexpress ABCA7, BDNF or IL4), recombinant proteins such as soluble TREM2 (STREM2), IL-4, IL-10, IL-13, and TGF-β, Etanercept (a TNF-α-antagonist fusion protein), and cell therapies (M2 microglia and macrophages) has been used as therapeutic measures.

Recent clinical trial has demonstrated the potential of gene therapy to treat AD [133]. For instance, the role and mechanism ATP-binding cassette transporter A7 (ABCA7) in AD development is unclear. Li et al. (2016) demonstrated that ABCA7 overexpression improves cognitive behaviour and neurotoxicity of AD mice, using a lentiviral vector mediating ABCA7 gene [134]. The latest gene therapy advances entail novel vectors (for better delivery of therapeutic material), which includes plasmid transfection, nanoparticles, engineered microRNA and in vivo CRISPR-based therapeutics [133]. The methods utilise viral vectors, which involve combining a therapeutic RNA and retrovirus RNA to create a recombinant RNA [133]. The recombinant RNA endosome enters the cell through endocytosis: the endosome breaks down and releases the recombinant RNA in the target cell. The RNA is converted into DNA (therapeutic DNA), which is incorporated into the genome to undergo transcription and translation, and eventually express protein of interest [133]. STREM2 decreases during AD progression. It is high at the early (asymptomatic) stages of AD [134]. STREM2 promotes microglia inflammatory responses and shield microglia from apoptosis. STREM2 could be an immunomodulatory neurodegenerative biomarker because concentrations of STREM2 in CSF correlate with neuronal injury markers such as total tau and phosphor-tau. Direct stereotaxic injection of recombinant STREM2 protein into 5Xfad mouse model reduces Aβ pathology, improves cognitive and synaptic function [135]. However, these therapeutic approaches are limited because of inefficacy to cross the BBB. Certain small-molecule compounds have been reported to control the phenotypic functions of microglia and exert neuroprotection against neurodegenerative diseases such as AD in animal models. Understanding the underlying mechanisms of action and identifying the target proteins of these compounds could be critical in designing better chemical modulators of microglia polarisation and effective neuroprotective drugs.

A balance in microglial M1/M2 phenotypes is implicated in AD and this results in increased microglial neuroinflammatory activities. Microglia phenotypes can be switched from one phenotype to another, using the following as mediators: (1) microglia microenvironment such infection, Aβ deposition, proinflammatory mediators such as TNF-α, nitric oxide, IL-β1 and ischaemic injury (2) soluble factors released from neurons and astrocytes (3) intracellular molecules such as nuclear receptors [peroxisome proliferator-activated receptor (PPARγ and PPARδ), retinoid X receptor (RXR)], redox signalling molecules [NOX_2, hypoxia-inducible factor (HIF)-1α], metabolic shift-mediated proteins, and NF-Kβ signalling molecules [136].

Nuclear receptor

Nuclear receptors (NRs) are a class of intracellular proteins (about 48), which convert an external signal, in form of a ligand, to a transcriptional output. NRs act as sensors for their respective ligands [137]. PPARs constitute a family of ligand-activated NRs, which belong to steroid superfamily is a nuclear hormone receptor [138]. PPAR is key regulator of M2 phenotype in microphage and microglia [139]. PPAR is neuroprotective because its activation increases phagocytic uptake Aβ plaques in AD mouse model [140]. Similarly, use of pioglitazone (PPARγ agonist) could switch proinflammatory M1 to anti-inflammatory M2 microglia. For instance, pioglitazone markedly decreases the levels of soluble and insoluble Aβ and reverses the cognitive deficits in 12-month-old APP/PS1 mice [141]. Besides, pioglitazone normalises higher phosphorylation of CRMP2 proteins and p35 proteins in the cerebellum [141]. According to Song et al., 2016, N-carbamolylated urethane compound (SNU-BP) is a novel PPARγ agonist, and it inhibits LPS-induced proinflammatory cytokine and nitric oxide production. In an LPS-injected mouse model, SNU-BP also exhibit anti-neuroinflammatory effects through M1/M2 switch [142]. Bexarotene is RXR agonist, and has an affinity for the RXR, which can cross the BBB and has FDA-approved safety profile [143]. When Bexarotene activates PPARγ/RXR and LXRs (liver receptors)/RXR, it induces ApoE expression, promotes microglia phagocytosis, and thereby enhances Aβ clearance [143]. Natural resveratrol oligomer, Malibator, is extracted from the leaves of the Chinese plants Hopes hainanensis. Malibator has been demonstrated to have an anti-inflammatory effect on LPS-stimulated microglia, decreases M1 (CD16, CD32, and CD86) expression, and increases M2 biomarkers (CD206 and YM-1) in the presence PPARγ [144].

Cyclic adenosine monophosphate (cAMP)-Dependent Pathways and their regulators

cAMP is intracellular signalling cascade, which prevents cellular reactivity and maintains physiological homeostasis. cAMP regulates microglia function and activation [144,145]. Higher levels of cAMP in microglia inhibit the production of proinflammatory molecules through adenylyl cyclase activator, synthetic cyclic AMP analogues or PDE inhibitors [146]. However, in disease state, cAMP level is compromised, and this results in lower level of cAMP and higher level of proinflammatory cytokines. This is supported in a study, where proinflammatory cytokines (TNF-α and IL-β1) swiftly reduce cAMP and increase PDE4 expression in microglia in vitro and following CNS injury [144]. cAMP has a protective effect on neural regeneration, and this has been supported in cerebral ischaemic-reperfusion injury models. Dibutyryl cAMP (db-cAMP) is a membrane-permeable derivative of cAMP. Administration of de-cAMP and IL-4 promotes microglia M2 phenotype in the leisons of SCI mouse model [145]. Therefore, based on these data, cAMP also critically determine M1-M2 microglia polarisation.

Phosphodiesterase 4 (PDE4) is an enzyme which hydrolysis cAMP in immune cells and brain cells, and thereby negatively impact regulation of cAMP signalling. To prevent this, PDE4 inhibitors such as rolipram exhibit precognitive, neuroprotective, and anti-inflammatory effects. PDE5 inhibitors have been suggested as potential therapeutic agents for neuroinflammatory, degenerative, or memory-loss diseases such as AD and other related dementia [147,148]. This is because they exert their neuroprotective effects through cGMP and cAMP signalling pathways and possess anti-inflammatory-related properties. For instance, study has demonstrated that PDE5 inhibitors decrease the production of TNF-α, nitric oxide, and IL-β1, and thus inhibit LPS-induced M1 polarisation [149].

Conclusion

In brain injury, microglia is disturbed and become activated. Microglia produce proinflammatory cytokines, which trigger a positive feedback loop of continual cytokine secretion and auto activation and thus amplify the death of neurons. Suppression of the microglia-mediated neuroinflammation is a potential therapeutic strategy to treat AD and other related neurodegenerative dementia. Proteins such as those regulating the cAMP pathway and other related proteins are potential therapeutic candidates for the effective treatment of AD and other neurodegenerative diseases. Moreover, an improved characterization of proteins functions will enable the design of novel pharmacological

compounds to modulate cytotoxic and/or neurotropic microglia phenotypes at specific stages of neurodegenerative diseases. This is because microglia activation in switching from one phenotype to another phenotype (i.e., in switching from neuroprotective to neurotoxic profiles) is time-dependent in chronic disease such as severe AD. Furthermore, studies are required to investigate the transcriptomes and epigenetic profiles in various disease (especially AD) states, understanding how aging and disease progression alter these profiles at single-cell-level, and correlate such changes with microglia behavior.

Acknowledgment

None

Conflict of Interest

The author's declared that they have no conflict of interest.

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