Review Article Open Access

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 neuro brillary 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 in ammation. Compounding this, the aggregated Aβ can induce the M1-dominated polarization of the microglia phenotype, which release proin ammatory mediators and free radicals that inhibit neuronal repair and regeneration [5]. e perturbed microenvironment becomes exacerbated by a cyclical process of in ammation and further plaque and tangle formation culminating in the development and progression of AD.

Akeem G Owoola, Department of Health and Biomedical Innovation, Queensland University of Technology, Australia, E-mail: owoolaag@

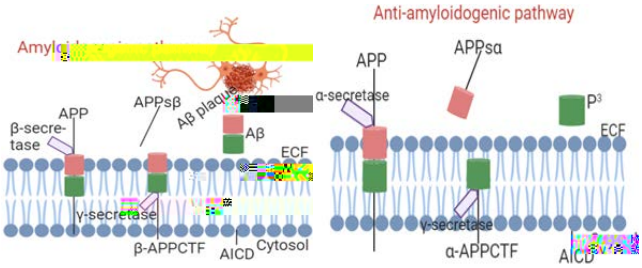

Figure 1: Proteolytic production of Aβ from APP. e N-terminus of APP lies within the extracellular uid while the C terminus lies within the cytosol, a clear liquid portion of the cytoplasm (Figures 1A-B). APP proteolytic processing consists of 2 major pathways [amyloidogenic (abnormal), which generates 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 (gure 1A). In non-amyloidogenic pathway, γ-secretase cleaves APP in the middle of Aβ (removing sAPP^{h} from cells) and this generates truncated ^{h}APPCTF which lacks amino terminal portion of Aβ domain. γ-secretase cleaves αAPPCTF and this leads liberation of truncated Aβ (p3) which is pathologically irrelevant (gure 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]. us, 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 a er 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 di erent 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

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 signi cantly internalise Aβ42 proto bril than Aβ42 monomers and Aβ42 bril [34]. Microglia will rapidly internalise Aβ proto brils in a process that depends on time, concentration of Aβ proto brils in the ISF, and secretion of TNF-α. At a concentration of 2 μM of both AF488-Aβ proto brils and AF488-Aβ monomers, primary microglia internalise, at 24 hours via pinocytosis, high level (>95%) of AF488-Aβ proto brils 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 proto brils), primary murine microglia internalise higher AF488-Aβ proto brils 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 proto brils were dense and spread throughout the cytosols and only few Aβ proto brils are transported to the lysosome. is means that Aβ proto brils are not degraded and cleared a er internalisation by primary murine microglia [33].

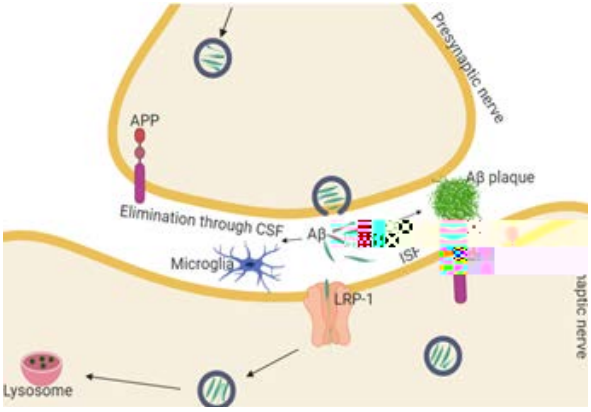

Figure 2: LRP1-mediated Aβ clearance pathways. Aβ is predominantly generated in neurons and secreted into ISF. Proteolytic degradation by endopeptidases (e.g., NEP and IDE) is a major Aβ clearance pathway. Cellular Aβ also plays a vital in eliminating Aβfrom the brain. LRP1 signi cantly controls Aβ endocytosis 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 pro le 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 e ux 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).

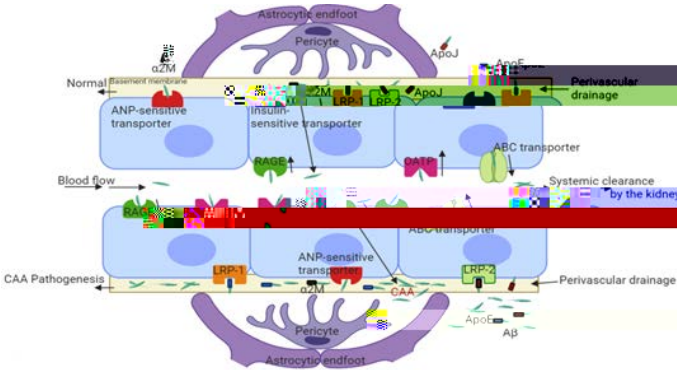

Figure 3: Aβ can be transported bi-directionally through BBB by receptors. In normal healthy conditions, e ux of Aβ is regulated by the receptors in the endothelium. A er binding with ApoE or α2M, Aβ can be transported LRP1. If Aβ binds with ApoJ, Aβ is transported by LRP2. Other receptors that regulate e ux of Aβ include ABC transporter, insulin-sensitive transporter, and ANP-sensitive transporter. In addition, Aβ can be transported to the perivascular spaces and e uxed via perivascular drainage. During e ux of Aβ, little in ux of Aβ is regulated by RAGE and OATP4 Tw cnera(l h)4.9 (r dm (y( )]y (l)7 2 (f Aid addSoceptene b4e3, euh4(o)12 (1.9 (6)3n1 (g w lo((io)1-D)-]TJ3)8o)12f Ai( )]TJ0

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:

occur. is can result in progressive cell death and tissue damage. erefore, it is vital that the cells can switch from proin ammatory 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).

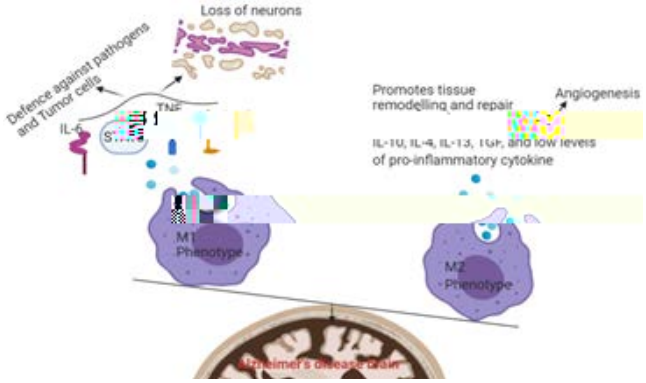

Figure 5: Pathogenicity of M1 phenotype results from physiological imbalances between M1 phenotypic activities and M2 phenotypic activities. e production of proin ammatory cytokines is critical for M1 phenotype. Other physiological mechanisms involved in the control of M1 phenotype are autocrine and 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

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 proin ammatory cytokines, which increase tau phosphorylation [117]. is 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

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]. e latest gene therapy advances entail novel vectors (for better delivery of therapeutic material), which

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

Acknowledgment

None

Con ict of Interest

e author's declared that they have no con ict of interest.

References

1. Tiwari S, Atluri V, Ajeet KA, Yndart A, Nair A (2019) Alzheimer's disease: Pathogenesis, diagnostics, and therapeutics. Int Nanomedicine 14: 5541-5554.
2. Viswanathan GK, Shwartz D, Losev Y, Arad E, Shemesh C, et al. (2020) Purpurin modulates Tau-derived VQIVYK brillization and ameliorates Alzheimer's disease-like symptoms in animal model. Cell Mol Life Sci 77(14): 2795-2813.
3. Maitrayee SS, Anna AS, Livia C, Camilla H, Larsson M, et al. (2018) Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers. Acta Neuropathol 136: 41–56.
4. Dregni AJ, Mandala VS, Haifan W, Matthew RE, Harrison KW, et al. (2019) In Vitro 0N4R tau brils contain a monomorphic β- sheet core enclosed by dynamically heterogeneous fuzzy coat segments. PNAS 166: 16357–16366.
5. Sarlus H, Heneka MT (2017) Microglia in Alzheimer's disease. J Clin Invest 127(9): 3240-3249.
6. Liu L , Ding L, Rovere M, Wolfe MS, Dennis JS (2019) A cellular complex of BACE1 and γ-secretase sequentially generates aβ from its full-length precursor. Cell Biol 218(2): 644-663.
7. William J, Meilandt HN, Gogineni A, Lalehzadeh G, Seung HL, et al. (2020) Trem2 deletion reduces lalex o

Front Aging Neurosci 6:93.

27.

94. Zhang F, Zhong R, Song L, Zhenfa F, Cheng C, et al. (2017) Acute hypoxia induced an imbalanced M1/M2 activation of microglia through NF-κB signaling in Alzheimer's disease mice and wild-type littermates. Front Aging Neurosci 9: 282.

95. Du L, Zhang Y, Chen Y, Zhu J, Yang Y, et al. (2016) Role of microglia in neurological disorders and their potentials as a therapeutic target. Mol Neurobiol 54(10): 7567-7584.

96. Kumar A, Alvarez CDM, Stoica BA, Faden AI, Loane DJ (2016) Microglial/macrophage polarization dynamics following traumatic brain injury. J Neurotrauma 33: 1732–1750.

97. Crotti A, Ransoho RM (2016) Microglial physiology and pathophysiology: Insights from genome-wide transcriptional pro ling. Immunity 44: 505–515.

98. Yamasaki R, Lu H, Butovsky O, Ohno N, Rietsch AM, et al. (2014) Di erential roles of microglia and monocytes in the in amed central nervous system. J Exp Med 211: 1533–1549.

99. Ransoho RM (2016) A polarizing question: Do M1 and M2 microglia exist? Nat Neurosci 19: 987-991.

100. Walker DG, Lue LF (2015) Immune phenotypes of microglia in human neurodegenerative disease: Calls(o)7 e (j)10 (ur)-29 (y gw 0 -1.2 Td[(4 0 0 9)-2.rTd[(4 0 0 J0 Tw0.005 (t)-5a)10 ( )]TJ0.056 Tw 0 -10 (ur)d[(I)16 (

126. Suzanne EH, Nathan DK, Toshiro KO, Mark LB, Li-chong W, et al. (2013) e microglial sensome revealed by direct RNA sequencing. Nat Neurosci 16(12): 1896-1905.

127. Wang Y, Ulland TK, Ulrich JD, Song W, Tzaferis JA, et al. (2016) TREM2-mediated early microglial response limits di usion and toxicity of amyloid plaques. J Exp Med 213(5): 667–675.

128. Samira P, omas A, Matthias B, Gernot K, Maximilian D, et al. (2019) Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. Nat Neurosci 22(2): 191-204.

129. Condello C, Yuan P, Schain A, Grutzendler J (2015) Microglia constitute a barrier that prevents neurotoxic proto brillar Aβ42 hotspots around plaques. Nat Commun 6: 6176..

130. Harald H, Filippo C, Claudio CA, Giuseppe C, Robert N, et al. (2020) A path toward precision medicine for neuroin ammatory mechanisms in Alzheimer's disease. Front Immunol 11: 456.

131. Stefanie AP, Rahul I, Rebecca SE, Nicole B, Jeenu M, et al. (2019) Gene therapy for neurological disorders: Challenges and recent advancements. J Drug Target 28(2): 111-128.

132. Mengqian L, Yefeng Y, Bo H, Lei W (2017) Study on lentivirus-mediated ABCA7 improves neurocognitive function and related mechanisms in the C57BL/6 mouse model of Alzheimer's disease. J Mol Neurosci 61: 489–497.

133. Zhong L, Chen XF, Wang T, Wang Z, Liao C, et al. (2017) Soluble TREM2 induces in ammatory responses and enhances microglial survival. J Exp Med 214: 597–607.

134. Suárez CM, Caballero MAA, Kleinberger G, Bateman R.J, Fagan AM, et al. (2016) Early changes in CSF sTREM2 in dominantly inherited Alzheimer's disease occur a er amyloid deposition and neuronal injury. Sci Transl Med 8: 369ra178.

135. John JF, Taavi KN (2019) Targeting nuclear receptors with PROTAC degraders. Mol Cel Endocrinol 493: 110452.

136. Bogna GG (2014) Peroxisome proliferator-activated receptors and their ligands: Nutritional and clinical implications--A review. Nutr J 13: 17.

137. D'Orio B, Anna F, Maria PC, Sandra M (2018) Targeting PPARalpha in Alzheimer's disease. Curr Alzheimer Res 15(4): 345-354.

138. Swati A, Anuradha Y, Rajnish KC (2017) Peroxisome proliferator-activated receptors (PPARs) as therapeutic target in neurodegenerative disorders. Biochem Biophys Res Commun 483(4): 1166-1177.

139. Toba J, Nikkuni M, Ishizeki M, Yoshii A, Watamura N, et al. (2016) PPARgamma agonist pioglitazone improves cerebellar dysfunction