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Manipulation of microglial activity as a therapy for Alzheimer's disease

Bobby Tan[1], Rachel Huiyi Choi[1], Tammy Jing Yee Chin[1], Charanjit Kaur[1], Eng-Ang Ling[1]

[1]Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 11759

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1. ABSTRACT

The review aims to elucidate the potential of microglia as a therapeutic target in alleviating Alzheimer's Disease (AD). Microglia are the resident immune cells in the brain which respond to the presence of the hallmarks of AD, amyloid-beta (A beta) plaques and neurofibrillary tangles (NFT). Activated microglia are able to phagocytose and secrete pro-inflammatory and anti-inflammatory cytokines. However, the eventual accumulation of excess A beta peptides and NFT in AD means that microglial clearance of pathogens has been impaired. Pro-inflammatory cytokines may also contribute to the neurodegeneration. Based on the amyloid cascade hypothesis, A beta-activated microglia can produce pro-inflammatory cytokines which may exacerbate the hyperphosporylation of tau proteins that forms NFT in AD pathology. Microglial activation can thus be manipulated to prevent neurodegeneration and promote neuroprotection through several therapeutic agents and methods. Further studies regarding comprehensive microglial response towards A beta and NFT are required to develop an effective treatment of AD involving microglia.

2. INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disorder characterised by poor recall of recent memories and preservation of remote memories. The cellular degeneration first occurs in the temporal and parietal lobes of the cerebral cortex and spreads to the subcortical regions of the brain, predominantly the hippocampus and the amygdala. Amyloid-beta (A beta) plaques or senile plaques, neurofibrillary tangles (NFT) containing hyperphosphorylated tau protein as well as neuritic plaques containing both A beta plaques and NFT are commonly found in the brain with AD. A beta plaques and NFT are subsequently identified to be the hallmarks of AD. However, the factors causing excess A beta and NFT deposition are yet to be determined.

Microglial cells constitute the innate immunity system in the brain. The highly motile processes of sessile ramified microglia suggest that they scan the brain environment and sense stimuli in their microenvironment (1). Microglia are activated by a wide array of changes in the brain such as the abnormal deposition of A beta and

NFT. Microglia subsequently change their conformation upon the detection of activating stimuli. Their initially ramified, branched morphology gradually changes into an amoeboid form with large body and short processes. A change in microglial activity marked by the change in morphology is thus dependent on the presence of stimuli in the brain.

Recent literature suggests that activated microglia are able to respond to stimuli via pro-inflammatory cytokines, anti-inflammatory cytokines and phagocytosis (2-4). Whereas the pro-inflammatory cytokines secreted by microglia may exacerbate the onset of AD, the anti-inflammatory cytokines and microglia's phagocytic ability have the potential to alleviate AD. To further complicate the relationship, microglia surrounding the A beta plaques were also found to proliferate in mouse models (5). Therapeutic agents have been developed on to manipulate microglial activity and activation level with reference to one of the hallmarks of AD. This review will focus on the treatment of AD in the light of both A beta and the NFT. Specifically, the various roles of microglia and their secretions relevant to each of the hallmarks of AD will be further explicated to enable the proposal, comparison and analysis of several therapeutic agents which have the potential to alleviate AD.

3. AMYLOID CASCADE HYPOTHESIS

Aggregates of A beta peptides are commonly found in senile plaques that signify one of the hallmarks in AD. The peptides are derived from amyloid precursor protein (APP), a large transmembrane protein (6) encoded by the *APP* gene. There are two types of amyloid beta plaques: senile plaques and diffuse plaques. Senile plaques consist of extracellular deposits of the A beta 42 and A beta 40 fibrils surrounded by dystrophic axons and dendrites, activated microglia and astrocytes (7). On the other hand, the diffuse plaques contain soluble non-fibrillar A beta deposits. However, it should be noted that soluble and insoluble A beta peptides are intermingled with each other. Diffuse plaques are believed to be more detrimental due to their ability to disrupt synaptic functions, thus contributing to the pathogenesis of AD.

The consideration of A beta aggregates as one of the hallmarks of AD is further supported by the amyloid cascade hypothesis. The abnormal processing of APP reverses the proportion of A beta 40 and A beta 42 produced - more A beta 42 is produced as compared to A beta 40. This pathway ultimately leads to insoluble protofibril species and plaque formation indicative of neurodegeneration. The amyloid cascade hypothesis proposes that AD is caused by toxic A beta 40 and A beta 42 peptide fragments produced by the proteolysis of APP. The increase in A beta production leads to a calamitous cascade which entails synaptic alterations, fibrillisation, microglial activation, abnormal phosphorylation of tau proteins to form oligomers and the paired helical filaments (PHF) of NFT, progressive synaptic loss of neurotransmitters and ultimately dementia (7). Accumulation of excess A beta in the brain due to the deposition outweighing the clearance is believed to be the one of the main factors that drives the pathogenesis of AD. The accumulation of A beta peptides is also directly related to the hyperphosphorylation of tau and the accumulation of NFT (8) signifying neurodegeneration in the brain. Thus, there is a need to consider the formation of NFT via amyloid cascade hypothesis to gain further insight regarding the onset of AD.

4. TAU HYPOTHESIS

Microtubules, which are a part of the cytoskeleton that helps in maintaining the shape of neurons, play a significant role in forming and developing the axons and dendrites. These microtubules are stabilised by microtubule-associated proteins (MAPs), including MAP tau (MAPT) which are mostly found in axons (9). In the brain, tau proteins play an important role in maintaining the neural transmission in axons by stabilising microtubules while suppressing microtubule dynamics (10). In addition, tau proteins can also regulate the axonal transport as their binding sites on the tubulin molecules located on microtubules also overlap with those for other proteins such as molecular motor kinesin (11). The binding of tau to the microtubules is thus directly related to the integrity and normal functioning of neurons.

Tau is believed to be associated with AD. Its hyperphosphorylated form is the main component of PHF, which subsequently forms NFT. One possible way in which tau forms NFT is through tau glycation, where sugar moiety is added onto the tau protein. The glycated tau isolated from the PHF suggested that glycation might be involved in the formation of NFT from PHF (12). At the same time, it is also suggested that tau glycation might play a role in transforming soluble tau into insoluble PHF (13). Additionally, tau is subjected to regulation by ubiquitin which tags proteins for recycling. Ubiquitinylated tau has been found in the aggregates located in PHF found in AD brain (14), which suggests that the altered tau proteins are attemptedly marked by neurons so that they can be degraded by proteosomes (7). However, the presence of NFT in the AD brain may imply that the attempt by the neurons to clear the altered tau proteins has failed.

5. MICROGLIA AS A MEDIATOR IN ALZHEIMER'S DISEASE

The role of microglia as the innate immune system in the brain elicits great interests in elucidating its role in the pathogenesis of AD. The amyloid plaques with A beta cores are commonly found to be surrounded by microglia and degenerating neurites (18). This involvement of microglia was thought to stem from the amyloid cascade hypothesis and the ensuing neurotoxic products from the activated microglia (19), contributing to the onset of neurodegeneration in AD. The link between microglia and tau is made based on the observation that microglia are also commonly found near the NFT from tauopathy in AD brain (20). Furthermore, tau is also linked to amyloid cascade hypothesis since A beta-activated microglia produce pro-inflammatory cytokines (21) which can induce

hyperphosphorylation of tau. Amidst the studies supporting the neurotoxicity of activated microglia, however, a study by Streit *et al*. (22) has shown that dystrophic microglia instead of activated microglia were found in amyloid plaques in AD brain, indicating that the onset of AD is marked by dysfunctional microglia. This view is supported by another study showing that microglia in AD are subjected to replicative senescence (23). This conflicting evidence nonetheless corroborates the hypothesis that microglia are associated with the two hallmarks indicating the pathogenesis of AD.

5.1. Role of microglia in amyloid cascade hypothesis

The role of microglia as mediators between A beta and AD was first considered because of microglial response towards A beta by several hypothesised mechanisms. Recently, some studies have found out that fibrillar A beta can activate microglia by binding to Toll-Like Receptors-2 (TLR2) and TLR4 expressed on microglia (24). The blocking of these receptors was shown to have reduced toxicity in the culture of microglia and A beta (24). In addition, microglia are known to sense A beta through receptor for advanced glycoxidation end-products (RAGE). An experiment blocking the interaction between A beta and RAGE resulted in transgenic mice retaining spatial memory and having lessened neuronal damage (25). The genetic factor of Apolipoprotein E *(APOE)* epsilon 4 allele and the production of apoE4 by microglia in the brain were also linked to the onset of AD. ApoE4 can form a complex with A beta peptides, but the complex has the lowest affinity towards low-density lipoprotein receptor-related protein 1 (LRP1) on microglia compared to the other ApoE isoforms in mouse models (26). Since the stimulation of LRP1 is linked to the activation of c-Jun N-terminal kinases and subsequently microglial activation (27), the expression of *APOE* epsilon 4 may potentially hamper microglial activation and the clearance of A beta through phagocytosis, contributing to the senile plaques seen in AD (26). These microglial activation pathways illustrate the role of microglia in bridging A beta and the pathogenesis of AD.

5.1.1. Microglial production of cytokines

The hypothesis of the contribution of A beta-activated microglia in AD is further supported by numerous *in vitro* studies which show the production of pro-inflammatory cytokines by microglia leading to neurodegeneration. Microglia were portrayed to be able to aggravate the pathogenesis of AD by facilitating neuronal loss and cognitive deficits through the production of neurotoxic pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumour necrosis factor-alpha (TNF-alpha) (28). The production of IL-1 may induce the processing of APP by beta-secretase, as shown *in vitro* (29). IL-1 can also increase the production of reactive oxygen species (ROS) (6) and TNF-alpha (30) which are neurotoxic and may exacerbate the neurodegeneration in AD. The production of TNF-alpha by A beta-activated microglia was also shown to promote inducible nitric oxide synthase (iNOS) expression in neurons resulting in cumulative neuronal apoptosis (31). IL-1, IL-6 and TNF-alpha production may further increase AD burden through promoting the hyperphosphorylation of tau (21, 32, 33). In this case, there is a positive feedback loop, whereby the pro-inflammatory cytokines activate more microglia to produce even more pro-inflammatory cytokines (6). The empirical evidence to date suggests that A beta-activated microglia may mediate the neurodegeneration in AD.

However, there are studies which show that microglia can also produce anti-inflammatory cytokines, including IL-4 and transforming growth factor-beta (TGF-beta). IL-4 was shown to attenuate the production of ROS and nitric oxides by activated microglia in culture, leading to lesser neuronal death (34). IL-4, IL-10 and TGF-beta production modulates the secretions of pro-inflammatory cytokines by activated microglia (2, 35). Nevertheless, the secretion of both pro-inflammatory and anti-inflammatory products when activated renders microglia a potential mediator in AD as well as a strategic target for therapeutic mechanisms.

5.1.2. Microglial phagocytosis

The phagocytic ability of microglia further shows their potential as a mediator between A beta and AD. Microglia were shown to be able to clear soluble form of A beta peptides by pinocytosis and were capable of taking up fibrillar A beta peptides through phagocytosis (4). This hypothesis is supported by an experiment conducted using two-photon microscopy to follow single plaques over a period of time, demonstrating the internalisation and delivery of A beta fragments into the lysosomes of microglia (36). Microglia were activated when they recognise fibrillar A beta via a receptor complex, initiating an intracellular signaling cascade to start phagocytosis (37).

However, in another experiment using two-photon microscopy, microglia were recruited to newly formed senile plaques within 1-2 days of their appearance without the clearance of these plaques (38). One study further supports the reduction of A beta clearance by demonstrating how interferon-gamma and TNF-alpha stimulation inhibit the phagocytosis of A beta by microglia; wild-type microglia could take up and degrade A beta but lost their capacity following the cytokine stimulation (39). To explain the disagreement between the hypothesis of microglial A beta phagocytosis and the experimental findings, one study suggests that microglia may take up and degrade A beta plaques but the rate is slow and microglia may be overwhelmed by the amount of A beta plaque present. *In vitro* experiments show that following the internalisation of the peptide into the microglial endolysosomal system, the peptides could still remain undegraded for over 72 hours (40) or the undegraded peptides were resecreted into the culture medium (41). Therefore, there is currently no clear evidence proving the modulation of A beta plaques formation through microglial phagocytosis.

5.1.3. Factors affecting microglial activity

The two aspects of A beta-activated microglia in AD highlighted – the production of neurotoxic products causing neurodegeneration and the impaired phagocytosis of A beta peptides leading to plaque formation – seem to be

in contrast to their role as supportive immune cells in the brain. This contradiction is exacerbated by the research findings which show anti-inflammatory cytokines produced by activated microglia as well as microglial phagocytosis of A beta peptides *in vitro* are manifested poorly in AD brain as evidenced by the ensuing neurodegeneration and accumulation of amyloid plaques.

There are a few possible explanations to this seeming contradiction in microglial contribution towards the AD pathogenesis. One of the reasons is the experimental design itself – the limitations of the experiments conducted to explore the role of microglia in AD. Firstly, the activation of microglia *in vitro* is not equivalent to *in vivo* microglial activation. The assumption that cultured microglia are representative of resting microglia in AD brain is inaccurate and extrapolations made from many *in vitro* data may be irrelevant (42). *In vivo* study of IL-1 production shows that microglia produce virtually undetectable levels of IL-1 compared to cultured microglia (43). The identification of activated microglia in AD brain by the expression of major histocompatibility complex class II (MHCII) (44) was also potentially misleading, as MHCII expression occurs in resting microglia in normal human and animal brain albeit limited to the white matter (45). However, another study by Xu and Ling (46) maintained that the level of MHCII expression in resting microglia was virtually undetectable. Similar to the MHC antigen, many pro-inflammatory cytokines are also expressed in non-AD brains due to the presence of peripheral infections (42). Equating microglial activation *in vivo* and the onset of AD thus can be misleading since non-AD inflammation such as sepsis may also activate microglia *in vivo* (22). The presence of A beta peptides clearance identified is also dependent on the duration and conditions during which the activity of microglia was observed. In APP/presenilin-1 transgenic mice, the presence of microglia did not affect the amount of amyloid plaque formed in three weeks whereas decreased A beta deposits were observed in 4 months with regular administration of macrophage colony-stimulating factor (26). In sum, the roles of activated microglia in AD which were elucidated experimentally are still insufficient in explaining the true roles of microglia in the brain of AD patients.

The inability of microglia to clear A beta plaques may also be attributed to the novel finding of senescent microglia around the senile plaques with amyloid cores. A study by Streit *et al.* (22) revealed the presence of ostensibly activated microglia around the senile plaques. However, the microglial cells were found to be highly abnormal, with the cytoplasm fragmented into small pieces (cytorrhexis). The same study contends that the neurodegenerative changes in AD were associated with microglial fragmentation instead of activated microglia. However, the dynamic structure of the amyloid plaques may have activated or overactivated microglia at some point during the onset of AD, which may eventually cause the cytorrhexis and cell death (22). Post-mortem observations on human brains with AD have shown that the microglia, which were thought to be activated, showed signs of cell death and cytoplasmic degeneration (47). Thus, microglial degeneration may precede the neurodegeneration seen in AD caused by impaired microglial phagocytosis.

Post-mortem *in vivo* analysis with microglia in the human brain also showed that individuals with AD pathology possessed larger quantities of shorter microglial telomeres compared to nondemented subjects. This may be caused by A beta-induced microglial proliferation and replicative senescence (23), especially since microglia around A beta plaques are found to proliferate via RAGE pathway in mouse models (5). As a result of high rate of proliferation due to the activation in AD, microglia may become senescent and less able to phagocytose amyloid plaques. This deterioration of microglial cell function possibly contributes to the neurodegeneration and aggregation of A beta peptides as aging and amyloid act synergistically (23). Microglial overactivation also acts hand-in-hand with telomere shortening to produce the pro-inflammatory cytokines and oxidative species, causing neurodegeneration as well as impaired clearance of A beta peptides leading to senile plaque formation. Therefore, microglial senescence is a possible hypothesis to clarify the role of microglia in mediating the onset of AD.

Amyloid cascade hypothesis is a potential link which bridges A beta plaques and tau pathology, the two hallmarks of AD. In addition, post-mortem analysis of brain tissue of AD patients showed correlation between tau burden and microglial burden (48). Therefore, there is a need to consider the roles of microglia in tau pathology to get a holistic picture of microglial roles in AD.

5.2. Role of microglia in tau hypothesis

Neurodegeneration found in AD is concerned with the death of neurons surrounding activated microglia. A study shows that one signaling pathway facilitating communication between microglia and neurons is chemokine (C-X3-C motif) ligand 1 expressed in neurons and its cognate receptor, CX3C chemokine receptor 1 (CX3CR1), which is expressed solely in microglia (49). CX3CR1-deficient mice have been shown to have lesser regulation of microglial activation and pro-inflammatory cytokines secretions. The inadequate regulation potentially results in the enhanced MAPT hyperphosphorylation and aggregation via p38 mitogen-activated protein kinases microglial activation pathway observed in the experiment (50). More importantly, pro-inflammatory cytokines produced by microglia also potentially exacerbate hyperphosphorylation (21). IL-1, IL-6 and TNF-alpha were also shown to be triggers for tau hyperphosphorylation which leads to subsequent NFT formation. IL-6 was shown to increase the levels of intracellular p35 which also lead to tau hyperphosphorylation (21) while IL-1 was shown to induce tau hyperphosphorylation by the activation of p38-MAPK in murine models (32). One *in vitro* experiment showed that TNF-alpha signaling also induced tau aggregation in neurites (33). Microglial activation thus potentially modulates tau pathology via enhancing tau hyperphosphorylation and aggregation, leading to NFT and neuritic plaques evidencing neurodegeneration in AD.

Experimental observations to date suggest tau pathology is linked to A beta in the onset of AD. One study suggests that hyperphosphorylated tau is found within neuritic plaques and the presence of A beta plaques correlate with greater NFT burden (51). Furthermore, in both early and later onsets of sporadic AD, individuals with *APOE* epsilon 4 allele were shown to have greater amount of hyperphosphorylated tau deposited in the frontal cortex than the individuals without *APOE* epsilon 4 allele (52). Recent studies have shown that double mutant transgenic mice with *APP* mutation and injection of A beta fibrils were found to have A beta deposition and robust NFT formation (53). The confirmation of link between A beta peptides and tau pathology subsequently reaffirms the potential role of microglia as the mediator between the two hallmarks of AD via its activation, in addition to its role as a mediator between each of the two hallmarks of AD and the onset of AD itself.

The role of microglia in mediating the A beta plaques, tau pathology and the onset of AD has been highlighted. Due to microglial role as the only cell in the CNS capable of eliciting immune responses as well as the strategic positioning of microglia in the development of AD, there is a potential for treatment of AD by modulating the immune response of microglia. This possible modulation of microglial immune response towards insoluble A beta peptides and A beta plaques will be explored based on microglial phagocytic ability as well as the reduction of pro-inflammatory cytokines secretions.

6. THERAPEUTIC STRATEGIES INVOLVING MICROGLIA

According to the amyloid cascade hypothesis, the accumulation of A beta peptides drives the progression of AD and results in a pro-inflammatory response that entails the activation of microglia. Thus, many therapeutic interventions have been developed to target at the removal of A beta peptides, encompassing immunotherapy, pharmacological agonists for receptors on microglia as well as foreign molecules introduced to manipulate microglial activity, especially their neurotoxicity. These strategies and agents aim to modulate microglial phagocytosis and production of pro-inflammatory cytokines – the two main responses of microglia towards A beta deposition – in order to treat AD.

To date, immunotherapy seems to hold promise for the treatment of AD. A study shows that immunisation with A beta 42 in PDAPP transgenic mouse reduced diffuse and senile A beta deposits (54). Passive immunisation with anti-A beta antibodies was also shown to reduce A beta levels (55). The exact mechanism by which immunotherapy facilitates the clearance of A beta peptides remains to be elucidated. Suggested mechanisms include the disaggregation of amyloid deposits (56) by the peripheral sink hypothesis, which postulates the removal of A beta from the brain by the binding of circulating plasma A beta with anti-A beta antibodies leading to a concentration gradient from brain to plasma and microglia-mediated phagocytosis of A beta (57). Hence, there is a possibility to harness the inevitable microglial activation and their phagocytic ability to remove A beta and alleviate AD.

Immunisation studies done by Wilcock *et al.* showed that there was a rapid microglial activation-independent removal of diffuse amyloid deposits in APP transgenic mice after intracranial anti-A beta antibody injections (58). However, in the same study, the removal of senile A beta plaques was shown to be dependent on microglial activation. The removal of diffuse A beta deposits was completed within 20 hours after the diffusion of antibodies throughout the hippocampus, and no microglial activation was detected using markers such as MHC-II and cluster of differentiation-45 (CD45). The removal of senile A beta plaques stained with thioflavine-S was observed after 68 hours with microglial activation detected by immunohistochemistry. One week after the injection of anti-A beta antibodies, the injection site remained devoid of most forms of amyloid and the injected antibodies were mostly cleared from the area. Next, the authors inhibited the activation of microglia 68 hours after the diffusion of antibodies throughout the hippocampus by injecting the glucocorticosteroid dexamethasone (56). Although the clearance of diffuse plaques was not affected, the removal of senile plaques by the antibodies and microglial activation was arrested. This manipulation indicates that the inhibition of microglial activation is associated with the inability of antibodies to remove senile plaques – suggesting that microglia may be involved in the removal of senile plaques.

A follow-up immunotherapy study by the Wilcock *et al.* by systemically injecting anti-A beta antibodies into Tg2576 APP transgenic mice weekly across the duration of three months showed that microglial activation was regulated in accordance with amyloid plaque clearance (56). Fragment, crystallisable gamma (Fc gamma) receptor expression on microglia increased after a month and CD45 was increased after 2 months of treatment, with the reduction in both diffuse and senile plaques. The increase in Fc gamma receptor expression on microglia suggests that microglia phagocytose the anti-A beta antibodies-opsonised amyloid plaques via an Fc gamma receptor-mediated mechanism (58). After 3 months, the levels of amyloid plaques remained reduced and there was an improvement in behavioral performances of the mice indicated by the increase in alternation in the Y-maze as well as the number of arm entries. Similarly, the levels of microglial immunohistochemistry staining were also reduced to control levels, suggesting that microglial activation was regulated. This experiment indicates that the clearance of most amyloid plaques could possibly be attributed to the regulation of microglial activation (55). This regulation is important to prevent bystander damages through release of pro-inflammatory cytokines and oxidative species responsible in neurodegeneration in AD.

A study done by Wang *et al.* has shown that suppressing A beta synthesis by treating amyloid-bearing tet-off APP mice with doxycycline before giving the mice combination therapy has increased the effectiveness of the passive immunization (59). Throughout the treatment with

weekly injections of anti-A beta antibodies, the amyloid load in the mice was found to be reduced significantly. This reduction might be due to the easing of microglial A beta clearance since the amyloid burden remained unchanged throughout the treatment. Moreover, it was found that many months after the final injection, the anti-A beta antibodies were still associated with a subset of amyloid deposits. Hence, it is suggested that suppressing Aβ production during treatment is one of the feasible ways for therapeutic strategy for AD.

Cannabinoid is also found to inhibit microglial activation by activating cannabinoid receptors both *in vivo* and *in vitro*. A study done by Martín-Moreno *et al.* has shown that cannabidiol (CBD), one of the cannabinoids, could enhance the movement of microglia, which is essential for the microglia to phagocytose aggregated A beta peptides (60). In the same study, it was also found that NO production is inhibited by cannabinoids by preventing NO synthases from being stimulated by LPS. The modulation of microglial activity by cannabinoid hence potentially helps to alleviate the neurodegeneration in AD.

The role of ApoE4 in the AD pathogenesis via its weak binding to the A beta peptides also suggests a connection between cholesterol metabolism and AD. Liver X receptors (LXRs), which exist in two forms: LXR alpha and LXR beta, are involved in cholesterol metabolism through the induction of genes that encode proteins responsible for cholesterol export such as ApoE and ATP-binding cassette transporter (ABCA1). In a study carried out by Terwel *et al.*, amyloid plaque-bearing APP23 mice were treated with LXR agonist TO901317 (61). Treatment with TO901317 resulted in a 40% and 80% reduction of both soluble and insoluble A beta 40 and A beta 42 levels respectively, possibly through microglial phagocytosis of A beta. While direct treatment of microglial cells with TO901317 did not enhance A beta phagocytosis, there was a significant increase in microglial phagocytosis of A beta in astrocytic-derived medium exposed to TO901317. Results from the study suggest that stimulation of microglial phagocytosis of A beta is dependent on astrocytic ApoE and LXR alpha. Even though the treatment with TO901317 ameliorated amyloid pathology in mice through microglial phagocytosis of A beta, it only improves spatial memory performance mildly, indicating that neurodegeneration that occurred is nearly irreversible.

Microglial phagocytosis to clear A beta peptides is also found to be regulated by the scavenger receptors (SR) on microglia, including scavenger receptor type-A (SR-A), scavenger receptor type-B1 (SR-B1) and CD36 (62). In a study done by Yang *et al.*, the specific subtypes of SRs that mediate microglial A beta internalisation were identified by using small interfering RNAs (siRNAs), which target SR-A, SR-B1 and CD36, and subtype-specific neutralising antibodies (63). SR-A was found to mediate the internalisation of insoluble A beta peptides but not CD36. Furthermore, the A beta degradation mechanism was also studied by using inhibitors of lysosomal proteases and proteasome. It was found that lysosomal cathepsin B (CatB) is involved in mediating the internalisation of insoluble A beta peptides. Thus, the study shows that SR-A and CatB are involved in clearing A beta peptides.

Microglial production of pro-inflammatory cytokines is also a target for modulation to alleviate the burden of AD. Burguillos and colleagues (64) demonstrated that caspase-3/7-dependent D(OMe)E(OMe)VD(OMe)-ase (DEVD-ase) regulates LPS-activated microglial activation. The inhibition of the caspase-3/7 pathway further hinders microglial activation. Caspases are cysteinyl-aspartate-specific proteases which upon activation will inevitably lead to apoptotic cell death (65). Transfection of BV2 microglial cells with siRNA targeting specifically either caspase-3 or caspase-7 did not induce iNOS, ROS formation and production of pro-inflammatory cytokine such as IL-1β and TNF-alpha, which collectively results in neuronal loss often seen in AD. The same study also shows that treatment with caspase inhibitor DEVD-fmk alleviates LPS-induced microglial production of pro-inflammatory cytokines including iNOS, TNF-alpha and IL-1 beta. Furthermore, caspase-8 was shown to be able to activate caspase-3/7 (66). Activated caspases and microglial marker CD68 are mainly co-localised in post-mortem AD brain samples, indicating that caspase-8 and -3 are activated mainly in microglia in AD. The authors' findings have opened up the possibility of delivering caspase inhibitors as therapeutic agents to treat AD.

Another method of regulating microglial expression and production pro-inflammatory cytokines which are potentially neurotoxic is via lipoxin A_4 (LXA_4). LXA_4 is a metabolic product of arachidonic acid which signals the discontinuation of inflammation endogenously and has anti-inflammatory properties (67). *In vitro* and *in vivo* findings have shown that LXA_4 can suppress the expression of IL-1 beta and TNF-alpha by interfering with the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- kappa B) signal pathway (68). The NF- kappa B signal pathway is believed to play a key role in the progression of inflammation in AD as NFT and A beta deposits are closely associated with the activation of NF-kappa B (69). In addition, due to its anti-inflammatory properties, LXA_4 is considered as a potential anti-inflammatory regulator that could preserve the balance between crucial, beneficial pro-inflammatory processes and neurotoxic, persistent inflammation (70). However, NF-kappa B signal pathway is only one of the many signal pathways involved in the pathogenesis of AD and the functions of LXA_4 via other pathways and its implication on other pro-inflammatory genes are not exhaustive.

The therapeutic strategies involving the promotion of microglial phagocytosis of A beta peptides and the prevention of excessive pro-inflammatory cytokines secretion, as suggested by present literature, are still insufficient. Recently, one study emphasises that the main factor causing neurodegeneration in AD is tau burden; amyloid plaques without neurofibrillary tangles do not cause dementia (71). A two-pronged approach to address both the hallmarks of AD may be required for a more wholesome treatment of AD. Here, the role of microglia as

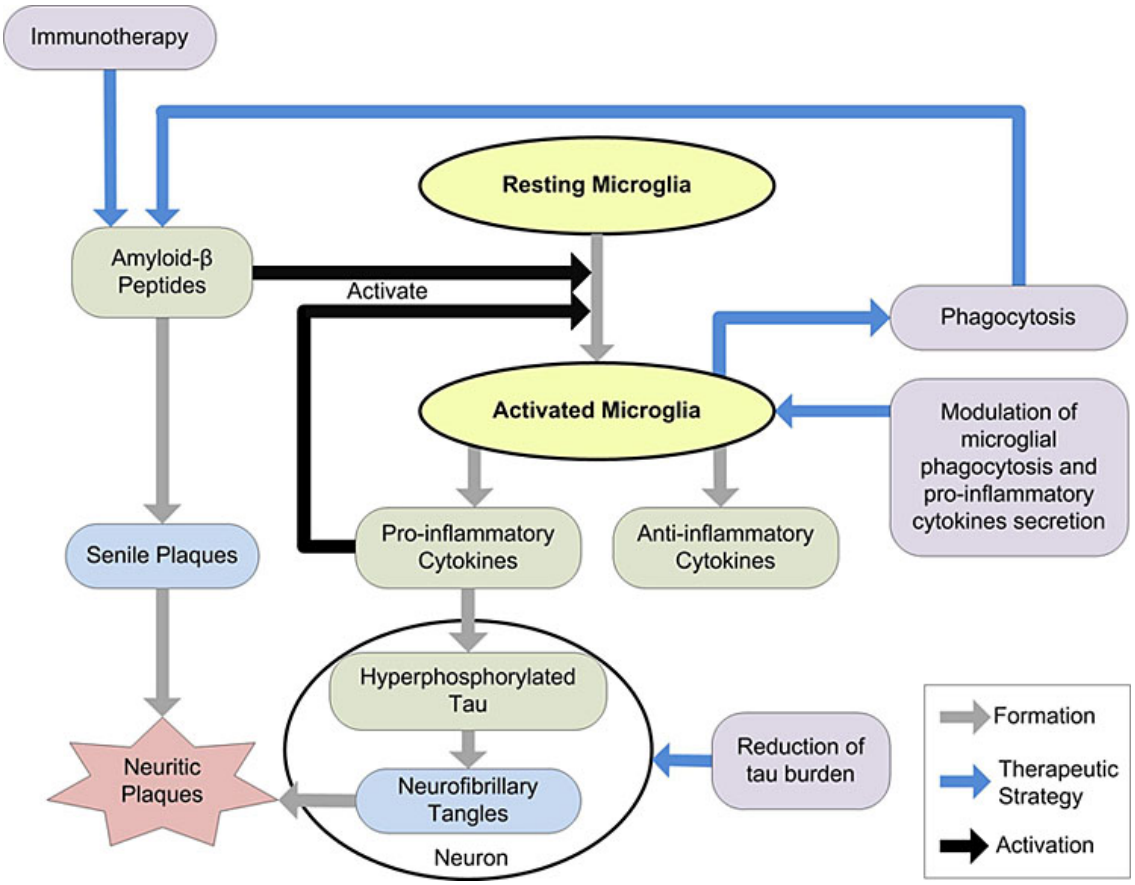

Figure 1. Schematic diagram showing the interrelationships between microglia and the hallmarks of AD as well as potential therapeutic strategies to alleviate AD.

the mediator between the hallmarks of AD can be utilised in the development of therapeutic strategies. The heavy focus on A beta is further ladened with complications, especially regarding microglial activity. The eventual deposition of A beta plaques may indicate that overworked and senescent microglia cannot effectively clear the peptides. There may be a need to focus on the proliferation of microglia *in vivo*, which may subsequently aid in the process of plaque clearance. The emphasis on preventing microglial activation may also result in greater dilemma; phagocytosis of A beta peptides and secretion of anti-inflammatory cytokines may be hampered. The patients' peripheral infections may also require microglial activation – the treatment of real-life AD cases should not be in isolation of other symptoms. Future studies may need to further clarify the link between microglia and AD, especially the intracellular and intercellular signaling involved as well as the cytokines in the light of the whole brain physiology. Looking deeper, there should also be a clear distinction between general microglial activation and microglial production of pro-inflammatory cytokines, i.e. the degrees of microglial activation. Microglial activation may be essential to alleviate the burden of AD and thus excessive suppression may further exacerbate the pathogenesis. Also, different stimuli may result in different microglial activity and secretions, even though activated microglia may look similar morphologically. The interactions between microglia and other glial cells also need to be considered to further illuminate microglial responses against the presence of excess A beta plaques and NFT. More studies are still required to develop a successful therapeutic strategy for AD based on microglial activity manipulation.

7. CONCLUSION AND PERSPECTIVE

This review has maintained that microglia as the resident immune system in the brain plays an active role in the pathogenesis of AD. Current literature suggests that microglial detection and activation of A beta peptides is the cue for microglial response in AD. In their activated state, microglia have been shown to phagocytose and secrete pro-inflammatory and anti-inflammatory cytokines. Whereas phagocytosis and anti-inflammatory cytokines may be potentially beneficial in alleviating AD burden, pro-inflammatory cytokines have been shown to exacerbate neurodegeneration based on the amyloid cascade hypothesis. The microglia-mediated cascade thus has the potential to give rise to the two hallmarks signifying the burden of AD, A beta plaques and NFT. However, there is also evidence that the excess deposition of A beta plaques may be caused by senescent microglia whose activity is

impaired. Recent studies regarding therapies for AD which involve microglia focus on the microglial phagocytic ability towards A beta peptides and the minimisation of pro-inflammatory cytokines secretion. A schematic diagram which highlights the interrelationships between microglia and the hallmarks of AD as well as the potential therapeutic mechanisms is shown in Figure 1. These treatments, however, are still inadequate. Studies elucidating the reduction of tau burden, the exact mechanism of microglial response in AD as well as the comprehensive physiology of the disease beyond focusing on the relationship between microglia and the hallmarks of AD should be more emphasised in the future. When the roles of microglia in the pathogenesis AD are more clearly defined, more effective therapeutic strategies that address both the disease and the normal functioning of the body can be developed.

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Abbreviations: A beta: Amyloid-beta, ABCA: ATP-binding cassette transporter, AD: Alzheimer's disease, APOE: Apolipoprotein, APP: Amyloid precursor protein, CatB: cathepsin B, CBD: Cannabidiol, CD: Cluster of Differentiation, CX3CR1: CX3C chemokine receptor 1, DEVD-ase: D(OMe)E(OMe)VD(OMe)-ase, Fc gamma: Fragment, crystallisable gamma, IL: Interleukin, iNOS: Inducible nitric oxide synthase, LPS: Lipopolysaccharide, LRP: Low density lipoprotein receptor-related protein, LXA_4: Lipoxin A_4, LXRs: Liver X receptors, MAPs: Microtubule-associated proteins, MAPT: Map tau, MHC II – Major histocompatibility complex class II, NF- kappa B: Nuclear factor kappa-light-chain-enhancer of activated B cells, NFT: Neurofibrillary tangles, PHF: Paired helical filaments, RAGE: Receptor for advanced glycoxidation end-products, ROS: Reactive oxygen species, SR: scavenger receptors, siRNAs: small interfering RNAs, TGF-beta: Transforming growth factor beta, TLR: Toll-like receptors, TNF-alpha: Tumour necrosis factor-alpha

Key Words: Microglia, Alzheimer's disease, Therapeutic strategies, Amyloid-beta, Tau, Amyloid plaques, Neuritic plaques, Neurofibrillary tangles, Amyloid cascade hypothesis, Review

Send correspondence to: Eng-Ang Ling, Department of Anatomy, Yong Loo Lin School of Medicine, MD10, 4 Medical Drive, 04-01, Singapore, 117597, Tel: 65-65163203, Fax: 65-67787643, E-mail: eng_ang_ling@nuhs.edu.sg