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REVIEW

Inflammatory Cytokines and Alzheimer's Disease: A Review from the Perspective of Genetic Polymorphisms

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Abstract Neuroinflammatory processes are a central feature of Alzheimer's disease (AD) in which microglia are over-activated, resulting in the increased production of pro-inflammatory cytokines. Moreover, deficiencies in the anti-inflammatory system may also contribute to neuroinflammation. Recently, advanced methods for the analysis of genetic polymorphisms have further supported the relationship between neuroinflammatory factors and AD risk because a series of polymorphisms in inflammation-related genes have been shown to be associated with AD. In this review, we summarize the polymorphisms of both pro- and anti-inflammatory cytokines related to AD, primarily interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha, IL-4, IL-10, and transforming growth factor beta, as well as their functional activity in AD pathology. Exploration of the relationship between inflammatory cytokine polymorphisms and AD risk may facilitate our understanding of AD pathogenesis and contribute to improved treatment strategies.

Keywords Alzheimer's disease · Neuroinflammation · Cytokine · Genetic polymorphism

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Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease characterized by progressive declines in cognitive and functional abilities. Amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) are its main pathological hallmarks. Aβ aggregates seem to initiate the pathogenesis of AD, while NFTs may be more involved in its progression [1]. However, the exact mechanisms by which AD occurs and develops remain ill-defined, and effective methods to cure the disease or halt the associated cognitive decline remain undiscovered. Nevertheless, neuroinflammation and oxidative stress have received increasing attention as accumulating evidence suggests their involvement in its development [2, 3]. Activation of microglia, the brain-specific macrophages, has been reported in both AD patients and animal models [4], accompanied by an activated complement system [5] and increased levels of chemokines and cytokines [6, 7]. In addition, the protective effects of non-steroidal anti-inflammatory drugs against AD risk [8] further support the neuroinflammation hypothesis of AD.

Moreover, AD is a multifactorial disease with a hereditary component, and advanced technologies for the analysis of genetic polymorphisms have identified numerous genetic loci that affect AD. Recent genome-wide association studies (GWASs) strongly support the interaction of inflammation and AD because several inflammation-related genes, such as *CR1* (complement receptor 1), *MS4A* (membrane-spanning 4-domains subfamily A), *TREM2* (triggering receptor expressed on myeloid cells 2), and *CD33* [9], have been identified as AD risk modifiers in Caucasians. The association has been further supported in other populations. For instance, variants of immune-related genes, including complement factor H [10], *MS4A* [11], *CR1* [12], and *CD33* [13] are associated with AD susceptibility in Han Chinese.

Moreover, based on the findings that the levels of cytokines are altered in AD patients and that cytokines are key components of neuroinflammation, numerous case-control studies have explored the association between AD risk and genetic polymorphisms of inflammatory cytokines, primarily interleukin-1 (IL-1), IL-4, IL-6, IL-10, tumor necrosis factor alpha (TNFα), and transforming growth factor beta (TGFβ). However, the results have been inconsistent. Thus, a series of meta-analyses was conducted, and conclusions with high reliability were obtained. However, because genetic polymorphism analyses are increasingly used in different populations, the data in this field are continually updated.

Accordingly, in the current review, we comprehensively summarize the key genetic polymorphisms of inflammatory cytokines associated with AD, including the latest evidence (summarized in Table 1). In addition, progress in the exploration of the functional activity of these polymorphisms and the mechanisms by which they modify AD susceptibility are illustrated.

Pro-inflammatory Cytokines

IL-1

Increased expression of IL-1 has been reported in AD brains [48]. Subsequent investigations suggest that the overexpressed IL-1 restrains the function of cholinergic systems [49] and favors the formation of Aβ plaques and accumulation of NFTs [50, 51], supporting the important role of IL-1 in AD development. This concept has been further supported by gene association analysis, as several variants located in the genes of IL-1A and IL-1B have been found to influence AD risk.

The relationship between AD risk and the *IL1A* −889 C/T polymorphism has been tested in numerous experiments that include different ethnic groups from different regions, and the results vary because a polymorphism in the 5' regulatory region was shown to either increase the AD risk [52, 53] or failed to influence it [54, 55]. Two recent meta-analyses have consistently found significant associations in Caucasians but not in Asians [14, 15]. Hayes and colleagues showed that microglial activation is greater in the brains of AD patients with the T allele, particularly those with the apolipoprotein E (*APOE*) ε4 allele [16]. Moreover, the functional significance of this polymorphism may be attributable to its promotional effect on *IL1A* gene transcription and IL-1α protein synthesis, as has been shown in both a human pancreatic tumor cell line and an astrocyte cell line [56, 57]. Overall, the T allele of *IL1A* −889 C/T diminishes AD progression *via* the promotion of microglial activation and an increase of *IL1A* gene transcription, causing overexpression of pro-inflammatory cytokines, which can facilitate neuroinflammatory processes and AD pathology. However, the causes of the differing results in Caucasians and Asians remain unclear. Furthermore and paradoxically, patients who are homozygous for the C allele exhibit an accelerated rate of cognitive decline [58]. Therefore, further work, especially *in vivo* investigations, are needed to explore the mechanisms by which this polymorphism influences AD-related phenotypes.

Several polymorphisms of the *IL1B* gene have been suggested to increase AD risk [59, 60], while negative associations are also frequently reported. Meta-analysis by Di Bona *et al.* [18] revealed that the *IL1B* +3953 TT genotype is associated with an increased AD risk and that the *IL1B* −511 TT genotype might be a risk factor for AD only in Caucasians, supporting an association between *IL1B* genetic polymorphisms and AD. However, according to the latest meta-analysis, the *IL1B* −511 single nucleotide polymorphism (SNP) has no significant relationship with overall AD risk while the CC genotype is a risk factor for AD in non-Europeans [17]. The inconsistency concerning *IL1B* −511 partially results from the inclusion criteria that involve subgroup analysis, because a significant effect could be obtained only when the investigators analyzed the four studies of Caucasians with the highest statistical power [18]. Thus, studies with larger sample sizes are needed to confirm or refute these conclusions. The significance of the *IL1B* −511 SNP is under investigation, and the findings that monocytes from healthy carriers of the T allele and lymphocytes from patients with epilepsy carrying the T allele have a slight but non-significant elevated capacity to produce IL-1β *in vitro* [61, 62], indicating that the SNP in the promoter region may have a promotional effect on IL-1β production. In addition, *IL1B* −511 may influence IL-1β in coordination with other genetic loci, such as *IL1B* +3953, as suggested by Santtila *et al* [62]. Furthermore, the findings that the *IL1B* −511 T allele is related to both increased Aβ42 in the cerebrospinal fluid (CSF) and decreased homocysteine in the plasma suggest that this SNP is associated with AD risk factors other than neuroinflammation [19, 20]. Regarding *IL1B* +3953, AD patients carrying the T allele have a significantly earlier onset, particularly those who carry the *IL1A* −889 TT genotype [21]. However, the T allele is also associated with a delayed age at AD onset in patients without the *APOE* ε4 allele and is accompanied by reduced amyloid plaques and NFTs [22]. These findings suggest that gene-gene interactions are involved in AD progression, and analyses of haplotypes should be considered in further studies. Similarly, Payão *et al.* suggested that the haplotypes of *IL1B* −511C, *IL1B* −31T, and an IL1 receptor antagonist (*VNTR2*) have protective effects against AD [63]. Moreover, the *IL1B* −31 TT genotype seems to be a risk factor for AD in Caucasians [23], but fails to influence the risk in the Chinese population [64]; therefore, additional studies with larger populations are needed to confirm or deny this association.

Table 1 Genetic polymorphisms of cytokines associated with AD.

Gene	Variant	rs number	Functional consequence	Association with AD	Ethnicity	Key ref.
IL1A	−889 C/T	rs1800587	5′ UTR variant	Increased risk	Caucasian	[14, 15]
				Increased microglial activity	Caucasian	[16]
IL1B	−511C/T	rs16944	Upstream variant	Decreased risk	Non-European	[17]
				Possible increased risk	Caucasian	[18]
				Increased Aβ42 in CSF	German	[19]
				Decreased plasma homocysteine	Italian	[20]
	+3953 C/T	rs1143634	Synonymous codon	Increased risk	Caucasian	[18]
				Earlier onset	Italian	[21]
				Delayed onset	American Caucasian	[22]
				Reduced NP		
				Reduced NFT		
	−31 T/C	rs1143627	Upstream variant	Decreased risk	Italian	[23]
IL-6	−174 G/C	rs1800795	Intron variant	Reduced risk	Asian, Caucasian	[23–25]
				Increased IL-6 in blood and brain	Italian	[26]
	−572 C/G	rs1800796	Intron variant	Reduced risk	Han Chinese	[27, 28]
TNFA	−850 C/T	rs1799724	Upstream variant	Increased risk	Australian Caucasian, European	[29]
	−308 G/A	rs1800629	Upstream variant	Increased risk	East Asian	[30]
				Earlier onset	Italian	[31]
VEGF	−2578 C/A	rs699947	Upstream variant	Increased risk in APOE ε4 (-)	Caucasian, Asian	[32]
	−1154 G/A	rs1570360	Upstream variant	Decreased risk in APOE ε4 (-)	Caucasian, Asian	[32]
IL-18	−607 C/A	rs1946518	Upstream variant	Decreased risk	Han Chinese, Italian Caucasian	[33–35]
				Decreased IL-18 production	Italian Caucasian	[35]
	−137 G/C	rs187238	Upstream variant	Decreased risk	Han Chinese	[34]
				Faster cognitive decline	Italian Caucasia	[33]
IL-33	rs7044343	rs7044343	Intron variant	Decreased risk	Caucasian	[36]
	rs1157505	rs1157505	Intron variant	Decreased CAA		
	rs11792633	rs11792633	Intron variant			
IL-12A	rs568408	rs568408	Intron variant	Decreased risk	Han Chinese	[37]
IL-12B	rs3212227	rs3212227	3′ UTR variant	Decreased risk	Han Chinese	[37]
IL-4	−590 C/T	rs2243250	Upstream variant	Decreased risk	Caucasian, Han Chinese	[38, 39]
	−1098 T/G	rs2243248	Upstream variant	Decreased risk	Caucasian	[38]
				Increased risk	Han Chinese	[39]
IL-10	−1082G/A	rs1800896	Intron variant	Increased risk	European	[40, 41]
				Decreased risk	Brazilian	[42]
TGFB1	+10 T/C	rs1800470	Missense mutation	Increased risk	Caucasian	[43, 44]
				Decreased CAA	Japanese-American, Japanese	[45, 46]
				Increased neocortical plaques		
	−509 C/T	rs1800469	Upstream variant	Increased risk	Caucasian	[47]

CAA cerebral amyloid angiopathy; *NFT* neurofibrillary tangle; *NP* neuritic amyloid plaque

IL-6

Associations between AD and IL-6 have also been identified, as AD patients show increased IL-6 expression in both the periphery [65] and the CNS [66]. An *in vitro* study suggested that overexpressed IL-6 influences the cdk5/p53 pathway to induce the phosphorylation of tau, increasing the AD risk [67]. Regarding genetic polymorphisms of the IL-6 gene, the protective role of *IL-6* −174 in AD development has been highlighted [68, 69]. However, inconsistent results have also been reported [70]. Several meta-analyses have suggested that the CC genotype is likely a protective factor for AD [24, 71]. Moreover, the latest study involving 1,246 individuals in Italy revealed that the frequency of the GG genotype in AD patients is significantly higher than that in controls [23]. This finding further

supports a protective effect of the −174 C allele on AD risk. Based on findings that the G allele is associated with both increased IL-6 secretion *in vitro* and increased levels of plasma IL-6 [72], it has been assumed that the SNP in the IL-6 gene promoter region may modify the risk of AD by influencing IL-6 protein release in the brain, playing an important role in the neuroinflammatory cascade and the AD process. However, the association between this genotype and IL-6 plasma level has been queried, and negative results have been reported [73]. Furthermore, a study by Licastro and colleagues provided results that further confuse the association because they reported increased levels of IL-6 in the blood and brain of AD patients with the CC genotype. Similarly, the same study showed that the C allele also increased AD risk [26]. Very recently, this SNP was shown to influence the CSF level of clusterin protein, which is significantly associated with AD risk and the tau/Aβ ratio in CSF [74]. These contradictory results may arise from the different genetic backgrounds, but they also strongly imply multifaceted roles of *IL-6* −174 in AD. The G allele of the *IL-6* −572 C/G polymorphism also has protective effects against AD risk in Han Chinese populations [27, 28], whereas contrary results have been reported in other populations [65, 75, 76]. Moreover, protective effects of the *IL-6* −174G and *IL-6* −597A haplotypes have been found [76], further suggesting gene-gene interactions and the complicated effects of genetic polymorphisms on AD.

TNFA

The role of TNF-α seems to be multifunctional. In animal models of AD, increased TNF-α is a key element in inflammatory cascade and increases the Aβ and tau pathology [77]. Moreover, short-term anti-TNF-α treatment improves cognition in AD patients [78], probably by relieving the Aβ pathology [79]. However, neuroprotective roles of TNF-α have also been reported, as long-term and non-specific inhibition of TNF-α signaling worsens the AD-related pathology in the brains of AD transgenic mice [80]. Correspondingly, TNF-α mediates the microglial phagocytosis of Aβ [80]. Two types of TNF-α receptors (TNF-RI and TNF-RII) have been identified, and they activate different downstream pathways to mediate distinct biological effects. In AD brains, TNF-RI is over-activated, while TNF-RII is inhibited [81]. Furthermore, activation of TNF-RI promotes the deposition of Aβ and Aβ-induced neuronal death [82, 83], while TNF-RII seems to counteract the TNF-RI-mediated injury [84]. The interactions between the two receptors, at least partially, lead to the diverse effects of TNF-α on AD. Concerning genetic polymorphisms, several SNPs have been reported to influence the risk of AD. A meta-analysis conducted in 2009 by De Bona *et al.* [29] supported the −850 T allele as a risk factor for AD susceptibility, particularly in individuals who carry the *APOE* ε4 allele. Although no further studies on this SNP and AD risk have been published, the conclusion is credible because no evidence of heterogeneity between studies was found. However, as noted by Bona *et al.*, larger samples are needed to confirm the association because only five medium-sized studies have been performed thus far. Correlations of AD risk with other *TNFA* SNPs (−238, −308, −863, and −1031) have also been included in meta-analyses, and negative results have been reported [29]; however, significant between-study heterogeneities may have influenced the reliability of these conclusions. Subsequently, several studies concerning the association between the *TNFA* −308 G/A polymorphism and AD risk involving different ethnic groups have been performed. Negative results were obtained in the majority of these investigations [23, 38, 85], strongly suggesting that the *TNFA* −308 polymorphism alone does not significantly influence AD susceptibility. As reported by Vural *et al.* [86], the AA haplotype *TNF* –308 and IL-10 –1082 and the AC haplotype *TNFA* –308 and IL-6 –174 significantly increase the risk of AD, suggesting that *TNFA* –308 exerts its function *via* gene-gene interaction. However, inconsistent results have also been reported [87–89], and the latest meta-analysis by Lee *et al.* [30] implied that the *TNFA* −308 polymorphism may influence the AD risk in certain ethnic groups. Moreover, Lio *et al.* [31] reported an association of *TNFA* −308 A with the earlier onset of AD among Italians. Thus, TNF −308 G/A might be a disease-modifying polymorphism in AD patients of certain ethnic groups or in coordination with other polymorphisms; however, this interaction needs further examination. Little progress has been made on the interactions between AD risk and the other three SNPs of the TNF gene noted above, with the exception of a negative result reported for the *TNFA* −863 polymorphism in an Azeri Turk population [88]. Therefore, the *TNFA* −308 and −850 genetic polymorphisms may be associated with AD susceptibility, and they have been hypothesized to act by influencing *TNFA* gene transcription. Some *in vitro* experiments have provided support for this hypothesis [90], but no direct evidence is available [91].

Other Pro-inflammatory Cytokines

Changes in the expression of vascular endothelial growth factor (VEGF) have been reported in AD patients; a cross-sectional study showed that it significantly increased in the early stage of AD while decreasing as the disease progressed [92]. In AD brains, VEGF immunoreactivity is mainly located in reactive astrocytes [93], and oxidative stress can regulate its expression [94]. Two functional

SNPs (−2578C/A and −1154G/A) located in the promoter region of *VEGF* have been suggested to influence AD risk, but the results in this area are ambiguous. Previous meta-analysis has suggested that the AA genotype of −2578C/A is a risk factor for AD development in Europeans [95], but further studies with larger sample sizes seem to have negated this association [32, 96]. However, in the subgroup of *APOE* ε4 non-carriers, −2578C/A increases AD risk while −1154G/A plays a protective role [32]. These results seem puzzling, as both of these SNPs have been shown to reduce VEGF expression *via* controlling the activity and responsiveness of the gene promoter [97]. Therefore, it will be of interest to investigate the functional role of VEGF in AD. Initially defined as an endothelium-specific vascular permeability factor, VEGF has neuroprotective effects, as it promotes adult neurogenesis and associated memory and learning [98]. Meanwhile, it may also be neurotoxic, as a high dose has been demonstrated to reduce neuronal survival and promote neuronal apoptosis *in vitro* [94]. Therefore, the inconsistency concerning the associations of AD risk with −2578C/A and −1154G/A may be attributable to the complex roles of VEGF in AD.

IL-18 is a member of the IL-1 family. In addition to its pro-inflammatory activity, IL-18 is involved in aging and neurodegeneration [99]. Elevated expression of IL-18 has been detected in AD brains [100], and peripheral cells from AD patients show increased production of IL-18 upon stimulation [35]. Gene association analysis further supports the involvement of IL-18 in AD development. Two SNPs in the promoter region of its gene have been reported to influence AD, −137 G/C and −607 C/A. The C allele of *IL-18* −137 G/C has a negative correlation with AD risk in Han Chinese [34], but the CC genotype is strongly associated with accelerated cognitive decline in Caucasians [33]. Meanwhile, the C allele of *IL-18* −607 and the CC genotype are associated with increased AD risk in Han Chinese and Italian Caucasian populations, respectively [33, 34]. Functional analyses have revealed that the *IL-18* −607 CC genotype results in significantly elevated IL-18 production by blood mononuclear cells in AD patients [35], implying that this polymorphism exacerbates AD processes *via* the promotion of IL-18 secretion. However, negative interactions have also been found in Italian Caucasians by Segat *et al.* [101], implying that this interaction needs to be confirmed in further studies with larger numbers of AD patients.

IL-33 also belongs to the IL-1 family. Decreased expression of IL-33 has been reported in the brains of AD patients [36]. In a cellular model, overexpressed IL-33 was reported to promote the production of Aβ [36]. A study by Chapuis *et al.* initially identified the association between IL-33 polymorphisms and AD risk in Caucasian populations. They found protective effects of rare alleles of three intronic SNPs (rs7044343, rs1157505, and rs11792633) and the associated haplotypes [36]. In addition, functional analyses have revealed interactions between these protective allele and decreased cerebral amyloid angiopathy in the brains of non-APOE ε4 individuals with AD [36]. Subsequently, consistent results for rs11792633 were obtained in a Han Chinese population; however, rs7044343 failed to affect AD risk, and the rs1157505 polymorphism was not observed [102]. These data suggest that IL-33 polymorphism modifies AD risk by influencing Aβ metabolism, but this needs further confirmation.

IL-12, another member of the IL-1 family, has recently been implicated in the AD process. Elevated levels of the p40 subunit of IL-12 have been detected in AD brains [103]. In AD animal models, inhibition of p40 alleviates the cognitive impairments and AD-related pathology [103, 104]. Rs568408 and rs3212227, which are located in *IL-12A* and *IL-12B*, respectively, have recently been reported to influence AD risk in the Han Chinese population [37]. Based on previous research, these SNPs may influence the levels of IL-12 mRNA and protein, which may account for their functional activity [105, 106]. However, associations of these two SNPs with AD risk require further validation in other ethnic groups.

Anti-Inflammatory Cytokines

IL-4

IL-4 is an anti-inflammatory cytokine and plays a role in neutralizing the neuroinflammatory process in AD brains. A previous study found that peripheral mononuclear cells from AD patients showed reduced IL-4 production upon stimulation [107]. *In vitro*, IL-4 induces the microglial clearance of Aβ *via* promoting the expression of CD36 and Aβ-degrading enzymes (neprilysin and insulin-degrading enzyme) [108]. Moreover, *in vivo* treatment with IL-4 reduces the accumulation of Aβ and alleviates the cognitive impairments in AD animal models [109]. Two SNPs in the promoter region of *IL-4* (−590 C/T and −1098 T/G) have been reported to influence AD risk in a study of Han Chinese and another study of Caucasians [38, 39]. The −590 T allele had protective effects against AD in both studies, but the results varied for the −1098 T/G allele. In Caucasians, the −1098 T allele appears to be a risk factor [38], but the −1098 G allele may increase the susceptibility to AD in Han Chinese [39]. This discrepancy may be due to ethnic characteristics, but it should be noted that the study by Ribizzi *et al.* was conducted with only 39 individuals (19 patients and 20 controls); therefore, further studies with larger samples are needed to confirm or deny this interaction. The significance of the SNPs might be related to the

control of IL-4 gene transcription or IL-4 protein expression [110, 111]; this would result in an imbalance between pro- and anti-inflammatory cytokines and ultimately accelerate the AD process. The +33 T/C polymorphism of *IL-4* has been identified and was assumed to affect AD risk, but negative results have been obtained in all three relevant studies conducted with Asians [39, 112, 113].

IL-10

IL-10 plays a neuroprotective role in the CNS, as it is anti-inflammatory, anti-apoptotic, and promotes cellular survival [114], but its implications for AD are complex. IL-10 expression mediated by adeno-associated virus (AAV) in the brains of AD animal models was reported to enhance neurogenesis and cognition [115]. Unexpectedly, further investigation opposed these findings, as AAV-mediated IL-10 expression increased the Aβ burden and worsened cognitive impairment in AD animal models [116]. Exploring the interactions between AD-related phenotypes and polymorphisms of *IL-10* will help understand its roles in AD. The −1082G/A polymorphism has been extensively investigated, and the GG genotype has been suggested to decrease [86, 117], increase [38], or have no influence on AD risk [118]. According to the two recent meta-analyses, *IL-10* −1082G may be associated with reduced AD risk, particularly among Europeans [40, 41]. However, negative results were reported in two studies conducted in Asia [112, 119]. Moreover, contradictory conclusions have been drawn by Moraes *et al.*, who very recently found a significant association between the *IL-10* −1082 AA genotype and decreased AD risk in a large sample in Brazil [42]. These data query the relationship between the *IL-10* −1082 genetic polymorphism and AD risk and strongly imply differences between ethnic groups. Moreover, in a recent investigation by Medway *et al.*, association of the *IL-10* −1082 genetic polymorphism with AD was only found in women [120], suggesting a sex-specific effect of this SNP. It has been reported that this SNP alters IL-10 gene transcription and plasma IL-10 concentrations [119, 121], which may account for the functional activity. Moreover, interactions between the other two SNPs in the promoter regions of *IL-10* (*IL-10* −819 and *IL-10* −592) and AD risk have also been investigated, and strong or even complete linkage disequilibrium (−592C and −819C) has been reported in most studies [117, 119, 122]. The GG genotype has been reported to promote [119], decrease [117], or have no effect [122] on AD risk, and the meta-analysis by Bona *et al.* [41] suggested that neither individual SNPs nor haplotypes were associated with AD risk. The differences between individual experiments may have resulted from ethnic characteristics, and further clarification of this association requires additional studies involving larger numbers of participants from various regions.

TGFB1

TGF-β signaling has been reported to be insufficient in the brains of AD patients [123]. This deficiency has been shown to cause more Aβ deposition and neurodegeneration [123], while treatment with TGF-β prevents Aβ-induced neurotoxicity [124]. All these results suggest a neuroprotective effect of TGF-β in the AD process. Both the +10 T/C and −509 C/T polymorphisms have been suggested to influence TGFB1 gene transcription and TGF-β1 protein expression [47, 125], and a series of studies has explored their interactions with AD risk. The +10 T/C polymorphism was associated with increased AD risk in studies by Arosio *et al.* and Caraci *et al.* [43, 44], and the −509 C/T polymorphism exhibited the same association in a study by Luedecking *et al* [47]. Moreover, patients with mild cognitive impairment carrying the +10 C allele had an increased risk of developing AD over a 4-year follow-up conducted by Arosio *et al.* [43]. Furthermore, the +10 CC genotype has been shown to be associated with increased neocortical plaques in Japanese-Americans [46], but the T allele of the +10 T/C polymorphism exhibited a positive correlation with the severity of cerebral amyloid angiopathy in another Japanese sample [45]. These data indicate the involvement of *TGFB1* polymorphisms in AD development and AD-related pathology. However, inconsistent results have been reported in the majority of studies conducted in various populations [126], and a negative association has been further supported by a recent meta-analysis [126]. No positive results have been obtained for the other SNPs in *TGFB1* [43, 44, 46, 73, 127–129], so it remains controversial whether *TGFB1* polymorphisms influence AD risk.

Conclusions and Perspectives

In the current review, we have summarized the key findings on genetic polymorphisms of the inflammatory cytokines associated with AD (Table 1). These discoveries highlight the importance of cytokines in AD pathology and support the neuroinflammatory hypothesis of AD. Moreover, the majority of loci identified thus far are located in the promoter regions of cytokine genes, suggesting that the polymorphic loci function primarily by influencing the expression of cytokines in AD. This may partially account for the microglial priming in AD because the polymorphism-induced increases in gene transcriptional activity could lead to excessive pro-inflammatory cytokine release by microglia upon stimulation [130, 131].

Accumulating evidence has demonstrated the involvement of microglia in AD [132], and cytokines are key components that mediate microglial function (Fig. 1). Pro-

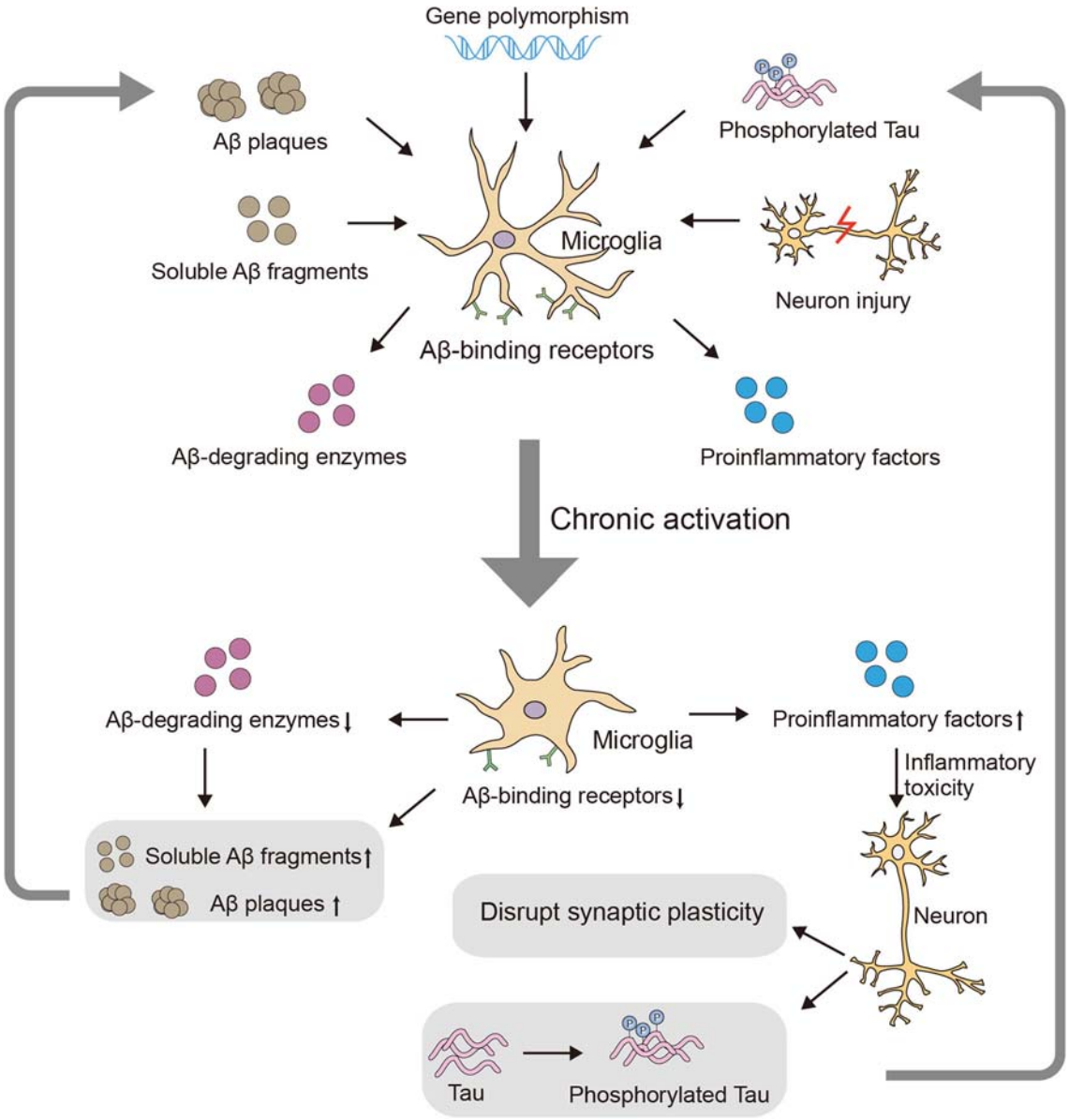

Fig. 1 Involvement of microglia in AD development. AD-related pathology induces chronic activation of microglia, exacerbating neuroinflammation and inhibiting the clearance of Aβ, in turn leading to AD-related deterioration.

inflammatory cytokines acutely benefit the CNS and play major roles in immune attack when pathogens invade the brain. However, due to their non-specific nature, these cytokines can simultaneously damage surrounding healthy tissue [133] *via* "by-stander" injury. Thus, the chronic increase in pro-inflammatory cytokines in the AD brain [134, 135] could induce sustained inflammatory-toxicity, causing neuronal dysfunction and ultimately the deterioration observed in AD progression. Furthermore, as noted above, cytokines can also influence AD-related pathology, including Aβ and tau [67, 79, 136, 137]. Moreover, indoleamine 2, 3-dioxygenase, which is activated by cytokines, may be an additional candidate mechanism of cytokine-induced AD pathology and could lead to increased levels of the neurotoxic factor, quinolinic acid [138], and promote tau hyperphosphorylation [139]. In summary, chronic overexpression of pro-inflammatory cytokines exacerbates AD, and the influence of anti-inflammatory cytokines in the process of AD also merits attention. The functional significance of anti-inflammatory cytokines is to down-regulate the pro-inflammatory process and initiate tissue reconstruction [140]. Therefore, it can be hypothesized that anti-inflammatory cytokines have protective effects against AD by neutralizing the harmful effects of pro-inflammatory cytokines, and their deficiency may also promote the risk of AD. In addition, TGF-β is protective against Aβ-

induced cytotoxicity both *in vivo* and *in vitro* [124]. Deficiency of TGF-β1 promotes not only Aβ accumulation but also NFT formation [141], directly highlighting the importance of TGF-β in AD pathology. However, no direct evidence has been obtained concerning the beneficial effects of other anti-inflammatory cytokines in AD, and further work is needed. In conclusion, dysfunction of the cytokine system, which is an important component of neuroinflammation, may be involved in AD pathology.

However, it must be noted that a recent GWAS did not highlight the SNPs discussed here in AD development (apart from *IL-6* 572 C/G and *TNFA* −308 G/A, all the SNPs were included in the GWAS analysis, but none reached genome-wide significance) [142]. It may be that the effect size of each individual SNP was too small. In addition, the influence of the same SNP on AD risk varies among populations. The population-based differences arise, at least partially, from natural selection during evolution, causing the minor allele frequency to shift over time. Furthermore, other factors such as diet, infection (cytokines play crucial roles in immune defense against pathogens), and the environment can also contribute to ethnic diversity. Therefore, further research on the interactions between AD and cytokine polymorphisms is needed in additional independent samples that include different ethnic groups, and validation of the functional activity of these loci deserve high priority. Moreover, several other cytokines, such as IL-17, have been shown to have interactions with AD [143], but no studies seem to have investigated the association of polymorphisms of these cytokines with AD. More importantly, gene-gene interactions merit more attention, and studies of such interactions could provide a more comprehensive understanding of heredity in AD. Therefore, the genetic polymorphisms of inflammatory cytokines are promising targets for exploring the etiology of AD, and extensive work remains to be done.

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