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REVIEW ARTICLE

Interleukin-17A in Alzheimer's Disease: Recent Advances and Controversies

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease that mainly affects older adults. Although the global burden of AD is increasing year by year, the causes of AD remain largely unknown. Numerous basic and clinical studies have shown that interleukin-17A (IL-17A) may play a significant role in the pathogenesis of AD. A comprehensive assessment of the role of IL-17A in AD would benefit the diagnosis, understanding of etiology and treatment. However, over the past decade, controversies remain regarding the expression level and role of IL-17A in AD. We have incorporated newly published researches and point out that IL-17A expression levels may vary along with the development of AD, exercising different roles at different stages of AD, although much more work remains to be done to support the potential role of IL-17A in AD-related pathology. Here, it is our intention to review the underlying mechanisms of IL-17A in AD and address the current controversies in an effort to clarify the results of existing research and suggest future studies.

Keywords: Interleukin-17A, Alzheimer's disease, Aβ accumulation, Tau hyperphosphorylation, neuronal, synaptic plasticity, biomarker.

1. INTRODUCTION

AD is the most common neurodegenerative and inflammatory neurological disease with insidious onset and slow progression. Different from other neurodegenerative diseases and inflammatory neurological diseases, AD affects the greatest number and has become the fifth leading cause of death globally [1]. Early diagnosing and intervention may help reduce morbidity and mortality, but that remains a challenge.

Accumulating evidence supports that IL-17A-producing (Th17) cells and their effector cytokine interleukin-17A (IL-17A, also called IL-17), are implicated in AD. Specifically, the evidence from epidemiological studies showed that in the serum and brain of AD patients, the protein level of IL-17A increases to about 3 fold of age-matched controls [2]. Correspondingly, a comparable increase of IL-17A was found in the brain and serum of AD mouse models [3]. Based on these results, IL-17A is supported to be a good biomarker for distinguishing AD from cognitively healthy control [4, 5], and a potential contributor to the progression of AD. However, the level changes and specific role of IL-17A in AD remains controversial.

In this review, we intend to address these controversies, initiate discussions to overcome the limitations of existing research and suggest future studies.

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2. BIOLOGICAL FUNCTIONS OF IL-17A

IL-17A (originally called CTLA-8), cloned in 1993 [6, 7], is a novel type of cytokine that is different from other known cytokine families. The human IL-17A gene (mapped to the chromosome location 6p12) product is a protein of 150 amino acids with a molecular weight of 15 kDa, and is secreted as a disulfide-linked homodimer of 30–35 kDa glycoprotein [8, 9]. The cluster of differentiation 4^+ ($CD4^+$) T helper 17 (Th17) cells was initially considered to be the cellular source of IL-17A [10, 11]. However, with in-depth research, it has been shown that various cell types can produce IL-17A, including $CD8^+$ cells (termed "Tc17"), γδ-T cells, $CD3^+$ invariant Natural Killer T (iNKT) cells, Lymphoid-Tissue inducer (LTi)-like cells, Natural Killer (NK) cells and myeloid cells [12, 13]. In addition to immune cells, glial cells residing in the Central Nervous System (CNS) also express IL-17A under physiological conditions [7, 14].

IL-17A is a typical cytokine of the IL-17 family, which contains six structurally related inflammatory cytokines, including IL-17A, IL-17B, IL17C, IL-17D, IL-17E (IL-25) and IL-17F [15]. These cytokines adopt a monomer folding of typical cystine knot growth factors, analogous to Nerve Growth Factor (NGF) and Platelet-Derived Growth Factor (PDGF) [7].

IL-17 functions through attaching to the high-affinity ligand-receptor IL-17R [16]. The IL-17R is located on different cell types of the CNS, including neurons, astrocytes, and microglia [17]. The first reported IL-17-binding receptor (IL-

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17RA) is a single-pass transmembrane protein of approximately 130 kDa [9]. It contains a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a long 525 amino acid cytoplasmic tail [18]. In accordance with IL-17, IL-17R family also comprises of five subunits, IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE, which share a cytoplasmic motif named ''SEFIR''. It is far related to the "Toll/IL-1R" (TIR) domain [15]. The SEFIR domain plays a crucial role in IL-17 signal transduction. This domain is also present in Act1,which is a unique cytoplasmic adaptor required to activate IL-17-dependent signaling pathways [19]. Hence, Act1 (also known as CIKS, connected to IκB kinase and stress-activated kinase) interacts with IL-17RA and IL-17RC through homotypic SEFIR interactions to initiate signal transduction. Act1 additionally contains a TRAF-binding site, which can associate with TRAF family proteins to complete IL-17-driven signaling pathways [19]. Firstly, Act1 binds to TRAF6 to drive the activation of the classical Nuclear Factor of activated B-cells (NF-κB) pathway through IκB kinases (IKK) activation and IκBα degradation [19]. Subsequently, NF-κB involves in the physiological inflammatory processes of AD by regulating the production of inflammatory cytokines [20]. On the other hand, TRAF6 also promotes the activation of MAPK pathways, which are involved in the pathology of a variety of human diseases, such as AD [21].

In addition, IL-17RA has a non-conserved region at extending ~100 residues beyond the SEFIR. SEFIR and SEFEX regions together comprise a single composite structural motif. SEFIR/SEFEX is needed for IL-17-dependent signaling [22]. The cytoplasmic tail of IL-17RA also contains a remote domain called "C/EBPβ activation domain" (CBAD), whose function is related to negative regulation of signals [19]. C/EBP family members are part of the synergistic activation of IL-17A and TNF-α, and these alternative translations and phosphorylation of C/EBPβ are mediated by the IL-17RA CBAD domain, linking C/EBPβ to negative regulation of IL-17 [23].

Many studies have suggested that IL-17A plays an important role in inflammatory diseases. More and more evidence has indicated that there is a strong link between IL-17A and AD.

3. PHYSIOLOGICAL ROLE OF IL-17 IN BRAIN

IL-17A plays protective roles in host defense against extracellular bacterial and fungal infections [24]. In addition to its role in immunity, IL-17A also participates in supporting short-term learning. A new study from Ribeiro *et al.* pointed out that IL-17A has an important physiological role in brain rather than a simply pro-inflammatory factor. IL-17 produced by the unique population of meningeal-resident γδ T cells can up-regulate Brain-Derived Neurotrophic Factor (BDNF) levels and support short-term learning [25].

4. IL-17A IN ALZHEIMER'S DISEASE

Although IL-17A serves an important role in host defense and short-term learning, it can also elicit pathophysiological roles (Fig. **1**). IL-17A gradually increases in the aging process and is accompanied by an increase in the proportion of IL-17-producing cells [26, 27]. Th17 cells (IL-17-producing T cell) were significantly elevated in AD patients [28]. The serum IL-17A levels in patients with AD (median 0.2 and interquartile range (0.5-4.7) pg/mL) were also significantly (P=0.028) higher than those of control (median 0.7 and interquartile range (0.2-1.7) pg/mL) [2]. Furthermore, the level of IL-17A in cerebrospinal fluid (CSF) in AD patients was elevated [4, 29]. A significantly increased expression of IL-17A in AD mouse model brain (3.29 pg/100 μg protein) was also observed [30]. In old mice, a specific subset of γδ T cells strongly expanded in lymph nodes and these T cells promoted the production of the pro-inflammatory cytokine IL-17A [31]. The levels of IL-17A in hippocampus, CSF, and serum of AD rats were also markedly elevated [7, 32]. Taken together, the protein levels of IL-17A in the serum, brain and CSF of AD patients and mouse models were upregulated (Fig. **1A**).

On the other hand, reduced IL-17A level in AD patients has also been reported in two distinct human cohort studies [5, 33] (Fig. **1B-1G**). The conflicting results may be due to the small size of the study group, different pharmacological treatments, and lack of clinical dementia rating. To date, there is no definitive evidence on how IL-17A altered in AD. Further studies on the association between IL-17A level and stages of AD are needed in the future.

In spite of the indefinite IL-17A alteration in AD, increasing evidence has shown that IL-17A plays a role in the neuronal degeneration of AD. IL-17A is related to olfactory sensory impairments, cognitive dysfunction, Aβ accumulation, Tau hyperphosphorylation, Blood-Brain Barrier (BBB) disruption, neuroinflammation, neuronal loss, neural differentiation inhibition, and synaptic plasticity, which can accelerate neurodegeneration in AD (Fig. **2**).

4.1. IL-17A and Olfactory Sensory Impairments

Olfactory dysfunction has been identified as one of the earliest clinical symptoms of AD [34]. The exact pathophysiological mechanism of olfactory impairment in AD was not yet elucidated. Current research suggests that IL-17A-producing cells, Th17 lymphocytes, can drive the physiological deficits of the olfactory circuit *via* reducing the excitatory synapses of the Olfactory Bulb (OB) [35]. Moreover, the olfactory function can be partially restored in mice lacking Th17 lymphocytes [35]. Similarly, the neutralization of IL-17A substantially alleviates olfactory impairment in AD mouse model [36].

4.2. IL-17A and Cognitive Dysfunction

Cognitive impairment is prominent in AD [37]. The patients with this devastating disorder lose their ability to encode new memories, which are first trivial and then important details of life. As time goes on, both declarative and non-declarative memory becomes profoundly impaired, and the capacities for reasoning, abstraction, and language slip away.

Disordered IL-17A production promotes cognitive impairment. Tian *et al.* reported that the enhanced IL-17A level in the hippocampus contributed to Aβ accumulation and thus declined the cognitive function [38]. Faraco *et al.* pointed out that IL-17A impaired cognitive function through the induction of neurovascular disorders and tau phosphorylation

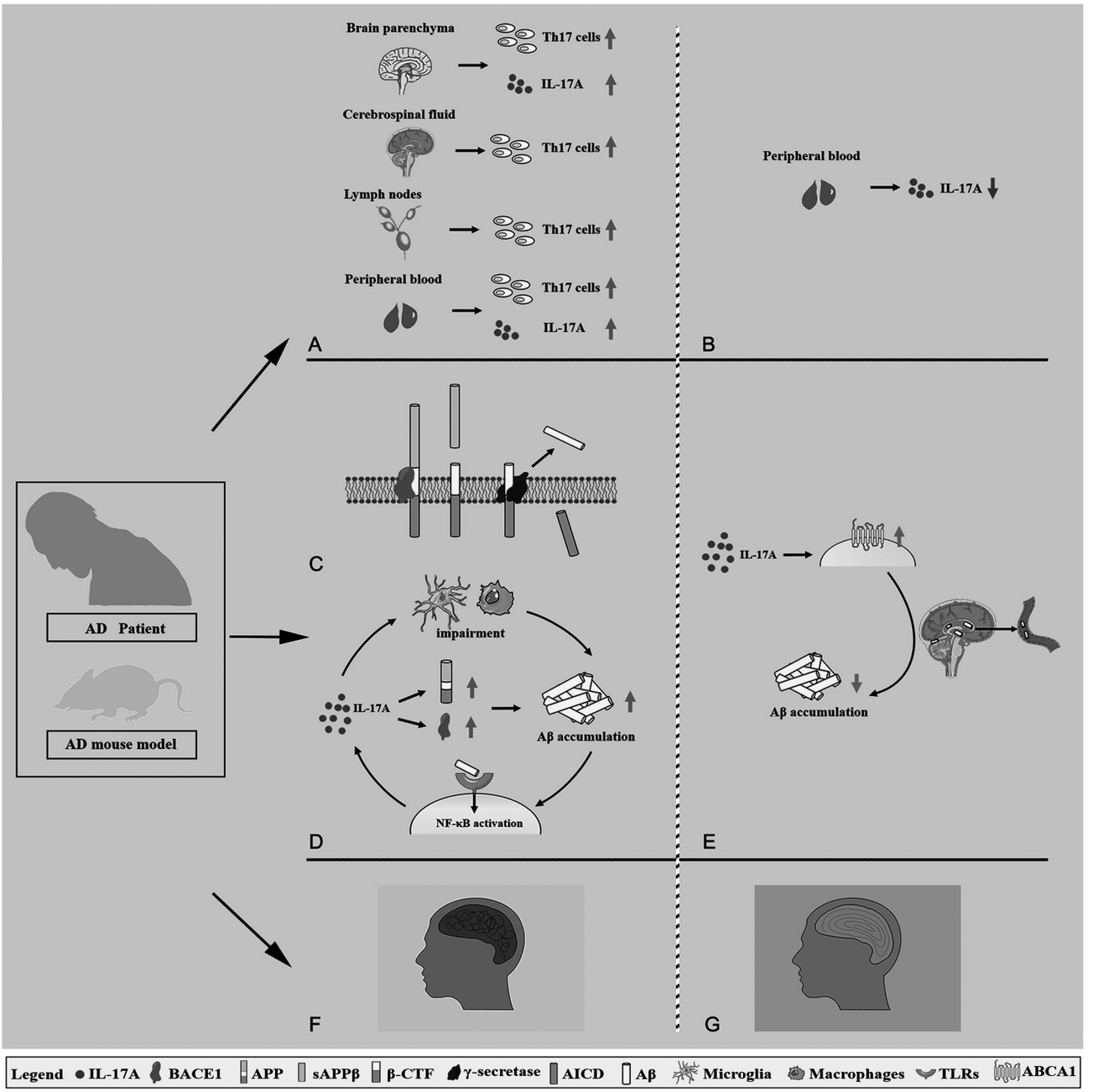
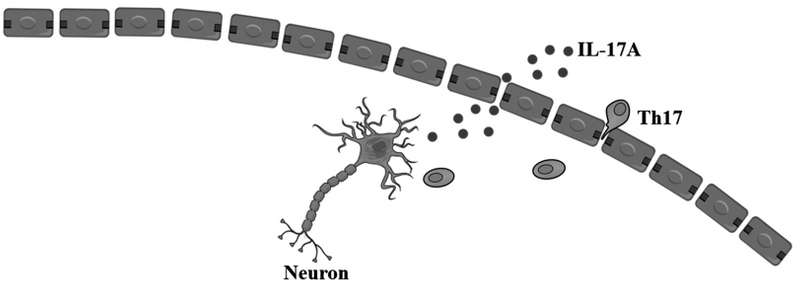


Fig. (1). The controversial issues on IL-17A in Alzheimer's disease. (**A**, **B**). Evidence shows that IL-17A and IL-17A-producing Th17 cells are elevated in AD patients' brain parenchyma, cerebrospinal fluid, lymph nodes and peripheral blood (A). However, the contrary evidence exists that IL-17A level is decreased in AD patients' peripheral blood (B). (**C**). A diagram of Amyloid Precursor Protein (APP) processing pathway. APP is first cleaved by β-secretase β-site APP cleaving enzyme1 (BACE1) to liberate the soluble ectodomain of APP—soluble APPβ (s APPβ), and the intracellular domain C-Terminal Fragment (CTF) of APP (β-CTF). β-CTF is further processed by γ-secretase to release the APP intracellular domain (AICD) and Aβ peptides. (**D**). IL-17A induces Aβ accumulation by promoting Aβ production and impairing Aβ removal, which are through reducing the ability of microglia and macrophages to remove Aβ accumulation, and upregulating the APP and BACE1 expression level. Moreover, the Aβ peptides could bind to Toll-like receptors and activate NF-κB, which further promote IL-17A production and ultimately aggravate Aβ accumulation. (**E**). The contrary evidence shows that Il-17A could upregulate ATP-binding cassette subfamily A member 1 (ABCA1) expression to facilitate Aβ transportation from brain into the blood circulation, thus reducing Aβ accumulation. **(F**, **G)**. IL-17A deteriorates cognitive function (**F**) whereas the controversial evidence support that IL-17A promotes cognition (**G**). *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*



Mechanism	Evidence	Controversial Evidence
Olfactory function	Reduce olfactory bulb excitatory synapses	—
Cognitive function	Impair cognitive function	Improve learning deficits
Aβ	Mediate Aβ accumulation and impair Aβ clearance	Facilitate Aβ transportation from brain into the blood circulation
Tau	Induce Tau hyperphosphorylation	—
BBB	Disrupt BBB integrity	—
Neuroinflammation	Upregulate neuroinflammation	—
Neurons	Cause neuronal injury	—
Neurogenesis and neural differentiation	Inhibit neurogenesis and neural differentiation	—
synaptic function	Impair basal synaptic transmission	—

Fig. (2). Recent understanding of the molecular mechanisms of IL-17A in Alzheimer's disease and the controversial evidence. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

[39, 40]. In addition, neutralization of IL-17A resulted in substantial functional recovery of Aβ-induced memory impairment [36] (Fig. **1F**). In contrast, Yang *et al.* reported that the mice overexpressed IL-17A showed a significant improvement in learning deficits but not long-term memory [25] (Fig. **1G**).

4.3. IL-17A Related Aβ Accumulation and Tau Hyperphosphorylation

The main pathological characteristics of AD are the presence of extracellular Aβ deposition and intracellular hyperphosphorylated tau accumulation in the affected areas of the brain [41]. The abnormal Aβ deposition is mainly due to excessive production and impaired clearance. Aβ is a 36-43 amino acid peptide generated by the amyloidogenic process of Amyloid Precursor Protein (APP) [42]. Multiple alternate pathways exist for APP proteolysis, but the most canonical processing pathways are non-amyloidogenic pathway and amyloidogenic pathway. The amyloidogenic pathway leads to the generation of Aβ peptide, but the non-amyloidogenic pathway does not. In amyloidogenic pathway, APP is first cleaved by β-secretase β-site APP cleaving enzyme1 (BACE1) to release soluble ectodomain of APP-soluble APPβ (s APPβ), and the intracellular domain C-Terminal Fragment (CTF) of APP consisting of 99 amino acids (C99 or β-CTF)[43]. β-CTF is further processed by γ-secretase to release the APP intracellular domain (AICD) and Aβ peptides [44] (Fig. **1C**). The reason for the Aβ overload can be the overproduction and the clearance failure.

IL-17A signals dominantly mediate $A\beta_{1\text{-}42}$ accumulation in AD mouse model. Tian *et al.* reported that an enhanced level of IL-17A in the hippocampus led to the load of neocortical Aβ by promoting APP synthesis [38]. Conversely, IL-17A antibody treatment effectively reduced Aβ accumulation [36, 45], and the possible mechanism is that IL-17A antibody-induced BACE1 and inhibited APP expression [45]. Studies also revealed that Aβ could be recognized by immune receptors such as Toll-Like Receptor 4 (TLR4) and Toll-Like Receptor 2 (TLR2), and the interactions led to activation of IL-17A-related transcription factors, such as NF-κB, which lead to upregulation of IL-17A in AD patients [46-48]. Consequently, high amounts of IL-17A promote Aβ deposition. Thus, the vicious circle *in vivo* will further aggravate the pathological process of AD (Fig. **1D**).

In addition to mediating Aβ production, more and more evidence shows that IL-17A can impair Aβ clearance. The key mechanisms of Aβ clearance include removal of Aβ into the peripheral blood and lymphatic systems and Aβ degradation within the CNS tissues. Recent reports suggest that IL-17A decreases Aβ clearance in a dose-dependent manner through impairing the amyloid clearing capacity of macrophage and microglia, and this effect can be blocked by IL-17 antibody [49] (Fig. **1D**). In contrast, Yang *et al.* reported that overexpressed IL-17A in AD model mice reduced soluble Aβ levels in the hippocampus and cerebrospinal fluid by upregulating of ATP-binding cassette subfamily A member 1 (ABCA1), which facilitate Aβ transportation from brain into the blood circulation [50] (Fig. **1E**).

The accumulation of hyperphosphorylated Tau is also implicated in the development of AD [51]. The mechanism of how the abnormal IL-17A affects Tau phosphorylation and mislocalization in AD has not been elucidated, but clinical data showed that the IL-17A expression level in CSF is significantly positively correlated with Tau, which can be

used for the identification of tau pathology [4]. In addition, a new study proposed that IL-17A might contribute to tau phosphorylation by increasing calpain and Cyclin-Dependent Kinase 5 (CDK5) activity, promoting p35 cleavage, and these reactions may derive from the IL-17A induced reduction of nitric oxide production and neuronal calpain nitrosylation [40]. Remarkably, IL-17A has also been proved to play a critical role in MAPK (p38, ERK and JNK) activation, which are key kinases for tau phosphorylation [6, 52]. However, further studies are needed to confirm the relation between IL-17A and Tau hyperphosphorylation.

In summary, the dual role of IL-17A in the regulation of Aβ and Tau might be closely associated with the stage and processes of AD. In the initial stage of AD, the elevated IL-17A may induce moderate glia activation, thereby promoting the clearance of Aβ and Tau aggregation. Along with the disease development, the infiltrated neutrophils and over-activated glia secret excessive IL-17A in brain and CSF, which aggravate the production but disrupt the clearance of Aβ and Tau, leading to neuronal loss and further episodes. However, more studies regarding how IL-17A regulates Aβ and Tau in AD patients are needed.

4.4. IL-17A and Blood Brain Barrier Disruption

BBB is a highly selective semipermeable structural barrier, which is composed of brain microvascular endothelial cells, pericytes, and astrocytes. Tight Junctions (TJ) are large multiprotein complexes that form a continuous, circumferential, and belt-like structure at the end of the lumen of the intercellular space to limit the paracellular flux of solutes [53], thereby maintaining homeostasis and environment for the neurons. A dysfunctional BBB has been implicated in the pathogenesis of AD. Recent neuroimaging studies have revealed that patients with Mild Cognitive Impairment (MCI) and early AD have significant BBB breakdown in the hippocampus and several gray and white matter regions [54-56]. Correspondingly, transgenic mouse AD models have also been shown to have BBB TJ loss [57]. IL-17A can disrupt BBB integrity in both human brain endothelial cells and murine brain endothelial cell lines [58, 59]. According to reports, the endothelial cells of BBB (BBB-ECs) express IL-17A receptors, and the binding of IL-17A to the receptors causes the disruption of BBB tight junctions [60]. Blockade of IL-17A by genetic deletion or neutralization can reduce the BBB disruption [59, 61, 62]. The underlying mechanisms implicated may be related to TJ molecules reduction and oxidant-antioxidant imbalance [59]. IL-17A can down-regulate the level of TJ molecules (occluding, claudin-5, and zonula occludens-1) to break BBB integrity [59], whereas blocking IL-17A can reverse the decrease of occluding and claudin-5 [61]. In addition, studies have also shown that IL-17A disrupts BBB by directly disrupt the oxidant-antioxidant balance by stimulating NO, reactive oxygen and nitrogen species (ROS/RNS) formation in endothelial cells of BBB, which primarily *via* activating ROS-producing enzymes (NAD(P)H and xanthine oxidase), and phosphorylating endothelial NO synthase at Ser1177 site [59, 63].

Once the BBB integrity is disrupted, more Th17 cells and neutrophils will migrate into brain parenchyma, which produce more IL-17A and induce irreversible neuronal dysfunction [64, 65]. This synergy between the peripheral and central systems aggravates neuroinflammation and exacerbates neurodegeneration of AD (Fig. **3**).

4.5. IL-17A and Neuroinflammation

AD is a highly complex neurodegenerative disease, and its etiology is also complicated, but it is clear that neuroinflammation plays a significant role in the progress of AD [66]. Studies have shown that IL-17A supports the development of AD by increasing and spreading pro-inflammatory responses.

IL-17A up-regulates neuroinflammation by inducing and maintaining the expression of inflammatory genes or triggering the migration of neutrophils through the BBB. The unbalanced production of IL-17A promotes the expression of various cytokines through activating NF-κB, Mitogen-Activated Protein Kinases (MAPK), janus kinases (JAKs), and activators of transcription (STATs) [67-69]. Similarly, phosphorylated Act1 and IL-17A can recruit TRAF2, TRAF5, HuR, and Arid5a, and then the complex promotes the pathway of post-transcriptional mRNA stabilization and up-regulates the expression of inflammatory genes [70]. Other than that, the synergistic effect of IL-17A and TNF-α also can maintain mRNA stabilization [71].

In addition, the chronic production of IL-17A facilitates BBB dysfunction and initiates neutrophils into the CNS, which further promotes AD-like pathology and cognitive decline in AD mouse model [65]. The infiltrated neutrophils in the cortex and hippocampus produced IL-17A [65] and induce the cytokine crosstalk between microglia and astrocytes through peripheral immune cells [72, 73]. Then the stimulated microglia and astrocytes produce pro-inflammatory cytokines and chemokines, thereby amplifying the infiltration of neutrophils, which lead to neurodegeneration in AD by enhancing neuroinflammatory response and detrimental neurotoxic effects [74, 75]. Moreover, a biochemical investigation also revealed that IL-17Ab attenuated the production of S100B, which is a component of the neuroinflammatory cycle that drives the pathogenesis of AD [36, 76].

4.6. IL-17A and Neuronal Loss

Neuronal loss is another critical pathological change in AD brain. Several studies have shown that IL-17A or Th17 cells accumulated in AD neuronal loss [17]. Studies have suggested that IL-17A/$CD4^+$ Th17 cells have a direct effect on CNS-resident cells, especially neurons [77]. IL-17A can induce direct cytotoxicity on neurons through an IL-17-IL-17R combination [78], which leads to further neuronal injury *via* NF-κB activation [79], excessive autophagy and cell cycle dysregulation [80]. Besides, the $CD4^+$ Th17 cells can also induce neuronal cell death by directly contacting with neurons. Studies have shown that Th17 cells formed immune synapse-like contacts with neurons and resulted in increased Ca^{2+} concentration, which precedes neuronal damage through excitotoxicity [64, 81]. Th17 cells can also interact with neurons through repulsive guidance molecule (RGMa)-mediated direct contact and Fas/Fas ligand (FasL) interaction [32]. Th17 cells strongly express RGMa, and the binding of RGMa to neogenin receptor on neurons induces neurodegeneration through the dephosphorylation of Akt [82]. Depletion of RGMa rescues neural degeneration [82]. In AD

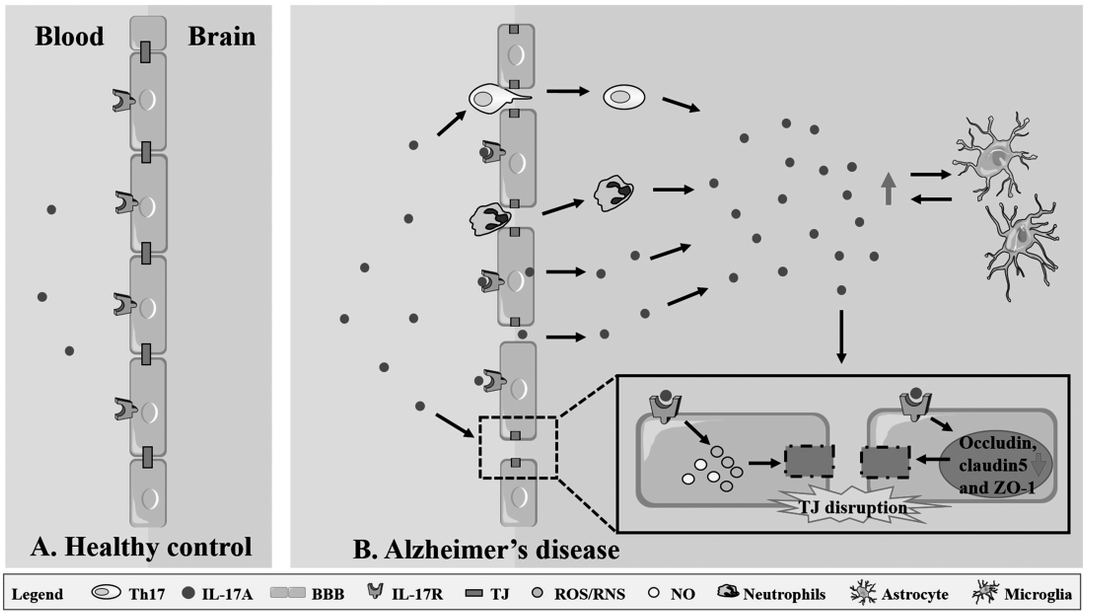


Fig. (3). Possible mechanisms of IL-17A on blood-brain barrier (BBB) disruption. (**A**). The circulating IL-17A in healthy individual is not able to disrupt BBB. (**B**). The elevated circulating IL-17A in Alzheimer's patients binds to the receptor on the surface of endothelial cells, then provokes BBB disruption by evoking ROS/RNS/NO and reducing TJ molecules. The breakdown of BBB facilitates migration of neutrophils and Th17 cells into the brain, as well as IL-17A. Moreover, the IL-17A-activated astrocytes and microglia, and the migrated neutrophils and Th17 cells would amplify the BBB disruption by secreting more IL-17A. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

hippocampus, neurons expressed increased Fas and Th17 cells expressed FasL, the occupancy of Fas receptor by the ligand FasL induces apoptosis of neurons (Fig. **4A**) [32]. In addition, IL-17A is sufficient to exert an indirect effect on neurons through mediating neuroinflammation, ROS production, microglia activation, and oxygen-glucose deprivation. The inflammatory responses heavily contribute to neuronal death, and IL-17A has been shown to exacerbate neuroinflammation through triggering lymphocytes infiltration and cytokines secretion. Similarly, ROS production and microglia activation can aggravate the toxic effects on neurons. In addition, neurons are extremely susceptible to changes in oxygen or blood flow. Studies have shown that IL-17A is able to elicit neurovascular dysfunction, thus producing neuronal impairment (Fig. **4B**) [39]. Studying the detailed mechanism of IL-17 in neuron loss will shed more light onto the AD pathology and may have major implications on potential therapeutic intervention.

4.7. Neurogenesis and Neural Differentiation Inhibition

Adult hippocampal neurogenesis is the process in which newly generated functional neurons incorporate into the adult Dentate Gyrus (DG) of the hippocampus. This progress contributes to learning and memory [83]. However, neurogenesis declines sharply in AD patients [84].

Several studies have shown that IL-17A acts as a negative modulator on adult hippocampal neurogenesis and neuronal differentiation [85, 86]. Genetic deletion of IL-17A increases both adult-born immature and mature neurons in the DG of hippocampus, and further promotes synaptic function [85], and the underlying mechanism appears to have two different aspects. First, IL-17-KO ameliorates the detrimental environment for neurogenesis in the DG tissue by altering the production of cytokines. Second, IL-17-KO reduces the differentiation of Neural Stem Cells (NSCs) into glia through elevating the expression of pro-neural genes and inhibiting the expression of glial fate genes [87]. Similarly, studies showed that IL-17A neutralization relieved the inhibition of directional differentiation into astrocytes rather than neurons [87].

In addition, the Th17 cells have been shown to impair neurogenesis. Repulsive Guidance Molecule-a（RGMa） participates in the collapse of axonal growth cones by interacting with the neogenin receptor in CNS and contributes to the regeneration failure of degenerated axons in AD [88], which is associated with impaired neurogenesis [89]. Studies have found that there is an intense RGMa in the amyloid plaques and glial scar in AD brains [88], and Th17 cells have been identified to strongly express RGMa. Therefore, the neuronal network regeneration inhibition and neurogenesis impairment of AD may be partly related to Th17 cells [90].

4.8. IL-17A and Synaptic Function

Many neurochemical analyses of AD brain tissue revealed that AD represents, at least initially, as an attack on synapses [91]. A quantitative morphological study of temporal and frontal cortex biopsies was performed in an average of 2 to 4 years after the onset of clinical AD. The results revealed that the number density of synapses in the biopsy AD cortex was reduced by about 25% to 35% (uncountable in electron micrographs), and the number of synapses per cortical neuron was reduced by about 15% to 35% [92]. As mentioned above, synapses may be the initial targets in AD, and synaptic degeneration and synapse loss are early events

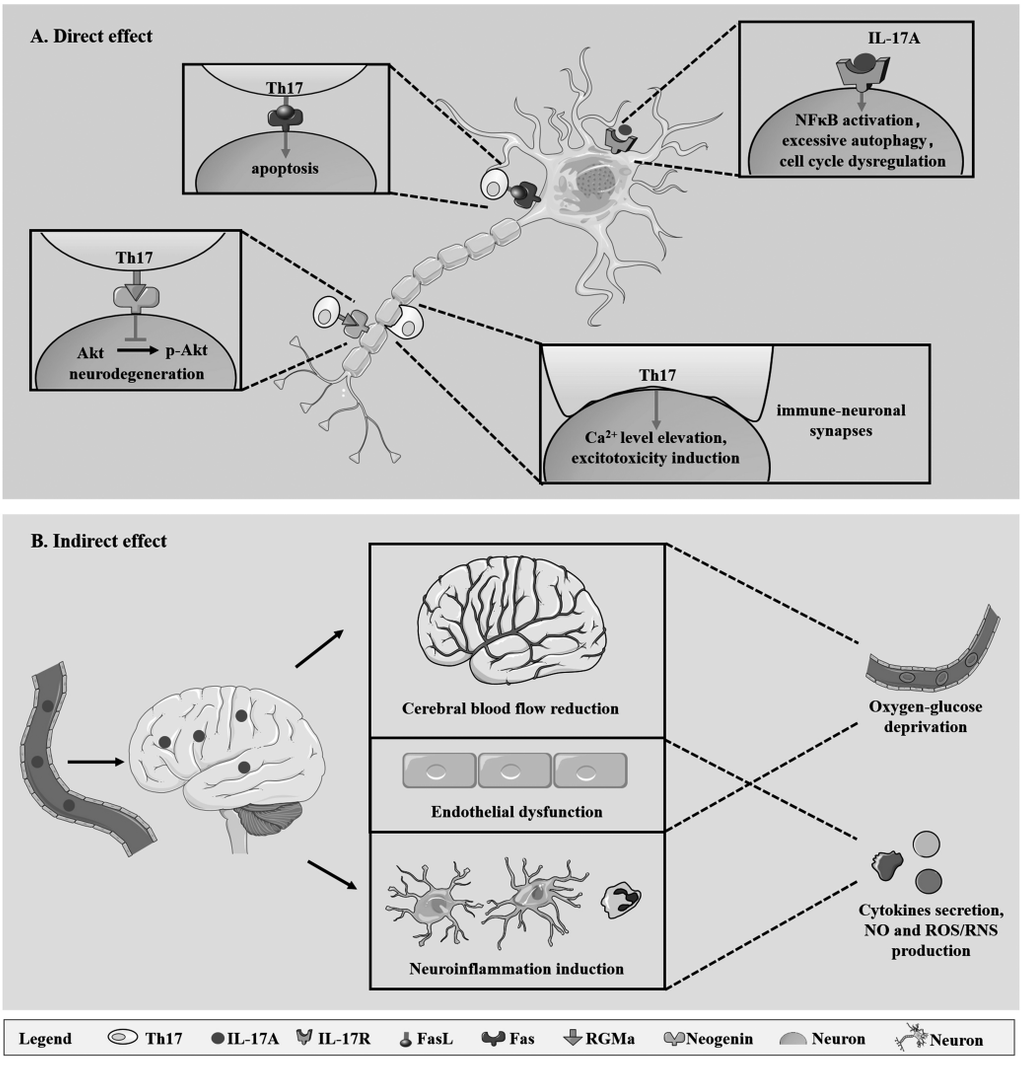


Fig. (4). Mechanisms underlying IL-17A-mediated neuronal damage in Alzheimer's disease. **(A)**. IL-17A induces neuronal damage directly *via* binding to IL-17RA which express on the neuron. The IL-17A/IL-17RA interaction induces neuronal damage through NFκB activation, expressive autophagy and cell cycle dysregulation. Additionally, the IL-17A-producing Th17 cells are able to induce neurodegeneration *via* Fas/FasL, RGMa/Neogenin interaction and immune-neuronal synapses formation. (**B**). The circulating IL-17A deprives oxygen-glucose supply *via* reducing cerebral blood flow and insulting endothelial function, which indirectly induces neuronal damage. Additionally, the injury of endothelial cells, activation of microglial cells and astrocytes, infiltration of neutrophils would amplify the neuronal damage processes *via* producing cytokines and ROS/RNS/NO. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

in the pathogenesis of patients with early AD and MCI. In addition, research on Long-Term Potentiation (LTP) has shown that it is functional, not structural synaptic changes, which are responsible for the cognitive deficits [93].

However, little is known about the effects of IL-17A on synapse. Several studies pointed out that deficiency of IL-17A is associated with synaptic function. In Liu's study, they examined baseline synaptic transmission, short synaptic and LTP in the DG of hippocampus in both IL-17 KO and WT mice and found that the basic synaptic transmission was significantly enhanced in the DG of IL-17 KO mice [85].

CONCLUSION

In this review, we focus on the relationship between IL-17A and AD from many aspects, such as olfactory impairments, cognitive dysfunction, Aβ accumulation, Tau hyperphosphorylation, BBB leakage, neuronal loss, neurogenesis and neural differentiation inhibition, synaptic plasticity injury. Although data from basic studies and clinical trials have shown that there is a close link between IL-17A and AD, many questions remain unanswered.

Although accumulating evidence suggests that IL-17A has the potential to serve as a biomarker for AD, the IL-17A level detected in AD patients is inconsistent among different population-based cohort studies. Some results support that IL-17A level is significantly higher in AD than those of control [2, 94, 95], but the other reported a reduced IL-17A level in AD patients [5]. The conflicting results may be due to a lack of clinical dementia rating as the immune events may change during the disease course. Therefore, the relation

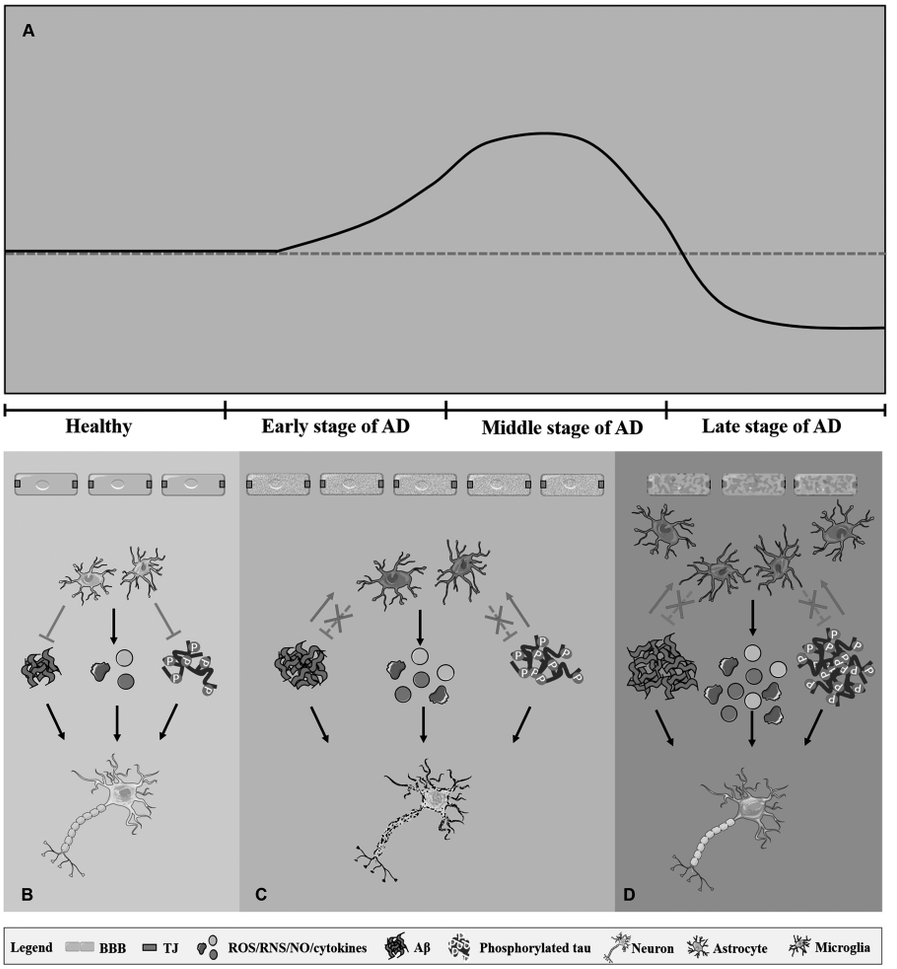


Fig. (5). A schematic diagram of IL-17A level changes and action mechanisms at different stages of AD. (**A**). The IL-17A level in healthy control and different stages of AD are indicated by the curves, and the red dotted line stands for the IL-17A level in healthy control. (**B**). At the early stage of AD, circulating IL-17A and IL-17A-producing cells infiltrate into brain through the disrupted BBB. The brain IL-17A level increases within a controllable range and lead to moderate activation of glia, which facilitate Aβ toxic proteins and phosphorylated tau protein removal and relieve neuronal impairment. The level of ROS/RNS/NO/cytokines release from glia is insufficient to induce neuronal impairment. (**C**). At the middle stage of AD, the BBB is destroyed seriously, and more IL-17A and IL-17A-producing cells infiltrate into brain, coupled with the IL-17A from glia and other CNS resident cells, the IL-17A level increased abnormally in AD brain. Subsequently, the glia is over activated by IL-17A, which leads to failure of glia to phagocytose Aβ and hyperphosphorylated tau, and high release of ROS/RNS/NO/cytokines, jointly contribute to neurodegeneration. Additionally, the accumulation of Aβ and tau would further activate the glia, which forms a vicious circle. (**D**). At the late stage of AD, BBB breakdowns and peripheral immune system badly disorders lead to the impairment of IL-17A-producing cells and reduction of IL-17A secretion, the overall level of IL-17A declines, including brain parenchyma. The persistent activated glia failed to clear the accumulated Aβ and tau protein, contemporaneously, the toxic protein deposit stimulates the proliferation of glia and secretion of ROS/RNS/NO/cytokines, which accelerate the neuronal death. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

between IL-17A level and AD clinical stages is worthy of further study.

Based on the previous results, we provide a rational explanation for the controversial issues about the level and role of IL-17A in AD (Fig. **5**). In the early stage of AD, circulating CD3+CD8−IL-17A+IFNγ-Th17 cells are increased [28], and IL-17A level increases within a controllable range and leads to moderate activation of glia, which facilitates the degradation of Aβ toxic proteins and relieves cognitive impairment. In the middle stage of AD, IL-17A increases abnormally in vicious cycles, which accelerates neuronal failure and speeds the degeneration of AD. IL-17A decreases at the late stage of AD [96], the persistently activated glia failed to clear the toxic protein deposit and continuously released ROS/RNS/NO/cytokines, the neuronal damage exacerbates.

In summary, IL-17A is undoubtedly dysregulated in AD. We believe that IL-17A level may vary along with the development of AD and exert different roles in different stages of AD, but much more work remains to be done to support the potential role of IL-17A to AD-related pathology. Uncovering the definitive relationship between IL-17A and AD would have the potential to be used in AD early diagnosing and intervention, such as IL-17A inhibitors.

AUTHORS' CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Hodson, R. Alzheimer's disease. *Nature,* **2018**, *559*(7715), S1. http://dx.doi.org/10.1038/d41586-018-05717-6 PMID: 30046078

[2] Chen, J.M.; Jiang, G.X.; Li, Q.W.; Zhou, Z.M.; Cheng, Q. Increased serum levels of interleukin-18, -23 and -17 in Chinese patients with Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.,* **2014**, *38*(5-6), 321-329. http://dx.doi.org/10.1159/000360606 PMID: 25138786

[3] St-Amour, I.; Bosoi, C.R.; Paré, I.; Ignatius Arokia Doss, P.M.; Rangachari, M.; Hébert, S.S.; Bazin, R.; Calon, F. Peripheral adaptive immunity of the triple transgenic mouse model of Alzheimer's disease. *J. Neuroinflammation,* **2019**, *16*(1), 3. http://dx.doi.org/10.1186/s12974-018-1380-5 PMID: 30611289

[4] Hu, W.T.; Chen-Plotkin, A.; Grossman, M.; Arnold, S.E.; Clark, C.M.; Shaw, L.M.; McCluskey, L.; Elman, L.; Hurtig, H.I.; Siderowf, A.; Lee, V.M.; Soares, H.; Trojanowski, J.Q. Novel CSF biomarkers for frontotemporal lobar degenerations. *Neurology,* **2010**, *75*(23), 2079-2086. http://dx.doi.org/10.1212/WNL.0b013e318200d78d PMID: 21048198

[5] Doecke, J.D.; Laws, S.M.; Faux, N.G.; Wilson, W.; Burnham, S.C.; Lam, C.P.; Mondal, A.; Bedo, J.; Bush, A.I.; Brown, B.; De Ruyck, K.; Ellis, K.A.; Fowler, C.; Gupta, V.B.; Head, R.; Macaulay, S.L.; Pertile, K.; Rowe, C.C.; Rembach, A.; Rodrigues, M.; Rumble, R.; Szoeke, C.; Taddei, K.; Taddei, T.; Trounson, B.; Ames, D.; Masters, C.L.; Martins, R.N. Blood-based protein biomarkers for diagnosis of Alzheimer disease. *Arch. Neurol.,* **2012**, *69*(10), 1318-1325. http://dx.doi.org/10.1001/archneurol.2012.1282 PMID: 22801742

[6] Amatya, N.; Garg, A.V.; Gaffen, S.L. IL-17 Signaling: the yin and the yang. *Trends Immunol.,* **2017**, *38*(5), 310-322. http://dx.doi.org/10.1016/j.it.2017.01.006 PMID: 28254169

[7] Chen, J.; Liu, X.; Zhong, Y. Interleukin-17A: The key cytokine in neurodegenerative diseases. *Front. Aging Neurosci.,* **2020**, *12*, 566922. http://dx.doi.org/10.3389/fnagi.2020.566922 PMID: 33132897

[8] Fossiez, F.; Djossou, O.; Chomarat, P.; Flores-Romo, L.; Ait-Yahia, S.; Maat, C.; Pin, J.J.; Garrone, P.; Garcia, E.; Saeland, S.; Blanchard, D.; Gaillard, C.; Das Mahapatra, B.; Rouvier, E.; Golstein, P.; Banchereau, J.; Lebecque, S. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J. Exp. Med.,* **1996**, *183*(6), 2593-2603. http://dx.doi.org/10.1084/jem.183.6.2593 PMID: 8676080

[9] Moseley, T.A.; Haudenschild, D.R.; Rose, L.; Reddi, A.H. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev.,* **2003**, *14*(2), 155-174. http://dx.doi.org/10.1016/S1359-6101(03)00002-9 PMID: 12651226

[10] Harrington, L.E.; Hatton, R.D.; Mangan, P.R.; Turner, H.; Murphy, T.L.; Murphy, K.M.; Weaver, C.T. Interleukin 17-producing CD4+ effector T cells develop *via* a lineage distinct from the T helper type 1 and 2 lineages. *Nat. Immunol.,* **2005**, *6*(11), 1123-1132. http://dx.doi.org/10.1038/ni1254 PMID: 16200070

[11] Park, H.; Li, Z.; Yang, X.O.; Chang, S.H.; Nurieva, R.; Wang, Y.H.; Wang, Y.; Hood, L.; Zhu, Z.; Tian, Q.; Dong, C. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat. Immunol.,* **2005**, *6*(11), 1133-1141. http://dx.doi.org/10.1038/ni1261 PMID: 16200068

[12] Milovanovic, J.; Arsenijevic, A.; Stojanovic, B.; Kanjevac, T.; Arsenijevic, D.; Radosavljevic, G.; Milovanovic, M.; Arsenijevic, N. Interleukin-17 in chronic inflammatory neurological diseases. *Front. Immunol.,* **2020**, *11*, 947. http://dx.doi.org/10.3389/fimmu.2020.00947 PMID: 32582147

[13] Miossec, P. Local and systemic effects of IL-17 in joint inflammation: A historical perspective from discovery to targeting. *Cell. Mol. Immunol.,* **2021**, *18*(4), 860-865. http://dx.doi.org/10.1038/s41423-021-00644-5 PMID: 33692481

[14] Cua, D.J.; Tato, C.M. Innate IL-17-producing cells: the sentinels of the immune system. *Nat. Rev. Immunol.,* **2010**, *10*(7), 479-489. http://dx.doi.org/10.1038/nri2800 PMID: 20559326

[15] Brevi, A.; Cogrossi, L.L.; Grazia, G.; Masciovecchio, D.; Impellizzieri, D.; Lacanfora, L.; Grioni, M.; Bellone, M. Much More Than IL-17A: Cytokines of the IL-17 family between microbiota and cancer. *Front. Immunol.,* **2020**, *11*, 565470. http://dx.doi.org/10.3389/fimmu.2020.565470 PMID: 33244315

[16] McGeachy, M.J.; Cua, D.J.; Gaffen, S.L. The IL-17 Family of Cytokines in Health and Disease. *Immunity,* **2019**, *50*(4), 892-906. http://dx.doi.org/10.1016/j.immuni.2019.03.021 PMID: 30995505

[17] Cipollini, V.; Anrather, J.; Orzi, F.; Iadecola, C. Th17 and cognitive impairment: possible mechanisms of action. *Front. Neuroanat.,* **2019**, *13*, 95. http://dx.doi.org/10.3389/fnana.2019.00095 PMID: 31803028

[18] Yao, Z.; Fanslow, W.C.; Seldin, M.F.; Rousseau, A.M.; Painter, S.L.; Comeau, M.R.; Cohen, J.I.; Spriggs, M.K. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity,* **1995**, *3*(6), 811-821. http://dx.doi.org/10.1016/1074-7613(95)90070-5 PMID: 8777726

[19] Li, X.; Bechara, R.; Zhao, J.; McGeachy, M.J.; Gaffen, S.L. IL-17 receptor-based signaling and implications for disease. *Nat. Immunol.,* **2019**, *20*(12), 1594-1602. http://dx.doi.org/10.1038/s41590-019-0514-y PMID: 31745337

[20] Seo, E.J.; Fischer, N.; Efferth, T. Phytochemicals as inhibitors of NF-κB for treatment of Alzheimer's disease. *Pharmacol. Res.,* **2018**, *129*, 262-273. http://dx.doi.org/10.1016/j.phrs.2017.11.030 PMID: 29179999

[21] Kim, E.K.; Choi, E.J. Compromised MAPK signaling in human diseases: An update. *Arch. Toxicol.,* **2015**, *89*(6), 867-882. http://dx.doi.org/10.1007/s00204-015-1472-2 PMID: 25690731

[22] Onishi, R.M.; Park, S.J.; Hanel, W.; Ho, A.W.; Maitra, A.; Gaffen, S.L. SEF/IL-17R (SEFIR) is not enough: An extended SEFIR domain is required for il-17RA-mediated signal transduction. *J. Biol. Chem.,* **2010**, *285*(43), 32751-32759. http://dx.doi.org/10.1074/jbc.M110.121418 PMID: 20729198

[23] Ruddy, M.J.; Wong, G.C.; Liu, X.K.; Yamamoto, H.; Kasayama, S.; Kirkwood, K.L.; Gaffen, S.L. Functional cooperation between interleukin-17 and tumor necrosis factor-alpha is mediated by CCAAT/enhancer-binding protein family members. *J. Biol. Chem.,* **2004**, *279*(4), 2559-2567. http://dx.doi.org/10.1074/jbc.M308809200 PMID: 14600152

[24] Beringer, A.; Noack, M.; Miossec, P. il-17 in chronic inflammation: from discovery to targeting. *Trends Mol. Med.,* **2016**, *22*(3), 230-241.

http://dx.doi.org/10.1016/j.molmed.2016.01.001 PMID: 26837266

[25] Ribeiro, M.; Brigas, H.C.; Temido-Ferreira, M.; Pousinha, P.A.; Regen, T.; Santa, C.; Coelho, J.E.; Marques-Morgado, I.; Valente, C.A.; Omenetti, S.; Stockinger, B.; Waisman, A.; Manadas, B.; Lopes, L.V.; Silva-Santos, B.; Ribot, J.C. Meningeal γδ T cell-derived IL-17 controls synaptic plasticity and short-term memory. *Sci. Immunol.,* **2019**, *4*(40), eaay5199. http://dx.doi.org/10.1126/sciimmunol.aay5199 PMID: 31604844

[26] De Angulo, A.; Faris, R.; Daniel, B.; Jolly, C.; deGraffenried, L. Age-related increase in IL-17 activates pro-inflammatory signaling in prostate cells. *Prostate,* **2015**, *75*(5), 449-462. http://dx.doi.org/10.1002/pros.22931 PMID: 25560177

[27] Lim, M.A.; Lee, J.; Park, J.S.; Jhun, J.Y.; Moon, Y.M.; Cho, M.L.; Kim, H.Y. Increased Th17 differentiation in aged mice is significantly associated with high IL-1β level and low IL-2 expression. *Exp. Gerontol.,* **2014**, *49*, 55-62. http://dx.doi.org/10.1016/j.exger.2013.10.006 PMID: 24140620

[28] Oberstein, T.J.; Taha, L.; Spitzer, P.; Hellstern, J.; Herrmann, M.; Kornhuber, J.; Maler, J.M. Imbalance of circulating T_h17 and Regulatory T Cells in Alzheimer's Disease: A Case Control Study. *Front. Immunol.,* **2018**, *9*, 1213. http://dx.doi.org/10.3389/fimmu.2018.01213 PMID: 29915582

[29] Sun, L.; Ju, T.; Wang, T.; Zhang, L.; Ding, F.; Zhang, Y.; An, R.; Sun, Y.; Li, Y.; Lu, Y.; Zhang, X.; Chi, L. Decreased Netrin-1 and Correlated Th17/Tregs balance disorder in $A\beta_{1-42}$ induced Alzheimer's Disease Model Rats. *Front. Aging Neurosci.,* **2019**, *11*, 124. http://dx.doi.org/10.3389/fnagi.2019.00124 PMID: 31191297

[30] Fragoulis, A.; Siegl, S.; Fendt, M.; Jansen, S.; Soppa, U.; Brandenburg, L.O.; Pufe, T.; Weis, J.; Wruck, C.J. Oral administration of methysticin improves cognitive deficits in a mouse model of Alzheimer's disease. *Redox Biol.,* **2017**, *12*, 843-853. http://dx.doi.org/10.1016/j.redox.2017.04.024 PMID: 28448946

[31] Prinz, I.; Sandrock, I. Dangerous γδ T cells in aged mice. *EMBO Rep.,* **2019**, *20*(8), e48678. http://dx.doi.org/10.15252/embr.201948678 PMID: 31286651

[32] Zhang, J.; Ke, K.F.; Liu, Z.; Qiu, Y.H.; Peng, Y.P. Th17 cell-mediated neuroinflammation is involved in neurodegeneration of aβ1-42-induced Alzheimer's disease model rats. *PLoS One,* **2013**, *8*(10), e75786. http://dx.doi.org/10.1371/journal.pone.0075786 PMID: 24124514

[33] Hu, W.T.; Watts, K.; Grossman, M.; Glass, J.; Lah, J.J.; Hales, C.; Shelnutt, M.; Van Deerlin, V.; Trojanowski, J.Q.; Levey, A.I. Reduced CSF p-Tau181 to Tau ratio is a biomarker for FTLD-TDP. *Neurology,* **2013**, *81*(22), 1945-1952. http://dx.doi.org/10.1212/01.wnl.0000436625.63650.27 PMID: 24174584

[34] Devanand, D.P.; Michaels-Marston, K.S.; Liu, X.; Pelton, G.H.; Padilla, M.; Marder, K.; Bell, K.; Stern, Y.; Mayeux, R. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am. J. Psychiatry,* **2000**, *157*(9), 1399-1405. http://dx.doi.org/10.1176/appi.ajp.157.9.1399 PMID: 10964854

[35] Platt, M.P.; Bolding, K.A.; Wayne, C.R.; Chaudhry, S.; Cutforth, T.; Franks, K.M.; Agalliu, D. Th17 lymphocytes drive vascular and neuronal deficits in a mouse model of postinfectious autoimmune encephalitis. *Proc. Natl. Acad. Sci. USA,* **2020**, *117*(12), 6708-6716. http://dx.doi.org/10.1073/pnas.1911097117 PMID: 32161123

[36] Cristiano, C.; Volpicelli, F.; Lippiello, P.; Buono, B.; Raucci, F.; Piccolo, M.; Iqbal, A.J.; Irace, C.; Miniaci, M.C.; Perrone, C, C.; Calignano, A.; Mascolo, N.; Maione, F. Neutralization of IL-17 rescues amyloid-β-induced neuroinflammation and memory impairment. *Br. J. Pharmacol.,* **2019**, *176*(18), 3544-3557. http://dx.doi.org/10.1111/bph.14586 PMID: 30673121

[37] Serrano-Pozo, A.; Das, S.; Hyman, B.T. APOE and Alzheimer's disease: Advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol.,* **2021**, *20*(1), 68-80. http://dx.doi.org/10.1016/S1474-4422(20)30412-9 PMID: 33340485

[38] Tian, A.; Ma, H.; Zhang, R.; Tan, W.; Wang, X.; Wu, B.; Wang, J.; Wan, C. Interleukin17A promotes postoperative cognitive dysfunction by Triggering β-Amyloid accumulation *via* the transforming growth factor-β (TGFβ)/Smad signaling pathway. *PLoS One,* **2015**, *10*(10), e0141596. http://dx.doi.org/10.1371/journal.pone.0141596 PMID: 26509545

[39] Faraco, G.; Brea, D.; Garcia-Bonilla, L.; Wang, G.; Racchumi, G.; Chang, H.; Buendia, I.; Santisteban, M.M.; Segarra, S.G.; Koizumi, K.; Sugiyama, Y.; Murphy, M.; Voss, H.; Anrather, J.; Iadecola, C. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response. *Nat. Neurosci.,* **2018**, *21*(2), 240-249. http://dx.doi.org/10.1038/s41593-017-0059-z PMID: 29335605

[40] Faraco, G.; Hochrainer, K.; Segarra, S.G.; Schaeffer, S.; Santisteban, M.M.; Menon, A.; Jiang, H.; Holtzman, D.M.; Anrather, J.; Iadecola, C. Dietary salt promotes cognitive impairment through tau phosphorylation. *Nature,* **2019**, *574*(7780), 686-690. http://dx.doi.org/10.1038/s41586-019-1688-z PMID: 31645758

[41] Kwart, D.; Gregg, A.; Scheckel, C.; Murphy, E.A.; Paquet, D.; Duffield, M.; Fak, J.; Olsen, O.; Darnell, R.B.; Tessier-Lavigne, M. A Large Panel of Isogenic APP and PSEN1 Mutant Human iPSC neurons reveals shared endosomal abnormalities mediated by APP β-CTFs, Not Aβ. *Neuron,* **2019**, *104*(2), 256-270.e5. http://dx.doi.org/10.1016/j.neuron.2019.07.010 PMID: 31416668

[42] Eggert, S.; Thomas, C.; Kins, S.; Hermey, G. Trafficking in Alzheimer's Disease: Modulation of APP transport and processing by the transmembrane proteins LRP1, SorLA, SorCS1c, sortilin, and calsyntenin. *Mol. Neurobiol.,* **2018**, *55*(7), 5809-5829. http://dx.doi.org/10.1007/s12035-017-0806-x PMID: 29079999

[43] Hampel, H.; Vassar, R.; De Strooper, B.; Hardy, J.; Willem, M.; Singh, N.; Zhou, J.; Yan, R.; Vanmechelen, E.; De Vos, A.; Nisticò, R.; Corbo, M.; Imbimbo, B.P.; Streffer, J.; Voytyuk, I.; Timmers, M.; Tahami Monfared, A.A.; Irizarry, M.; Albala, B.; Koyama, A.; Watanabe, N.; Kimura, T.; Yarenis, L.; Lista, S.; Kramer, L.; Vergallo, A. The β-Secretase BACE1 in Alzheimer's Disease. *Biol. Psychiatry,* **2021**, *89*(8), 745-756. http://dx.doi.org/10.1016/j.biopsych.2020.02.001 PMID: 32223911

[44] Capone, R.; Tiwari, A.; Hadziselimovic, A.; Peskova, Y.; Hutchison, J.M.; Sanders, C.R.; Kenworthy, A.K. The C99 domain of the amyloid precursor protein resides in the disordered membrane phase. *J. Biol. Chem.,* **2021**, *296*, 100652. http://dx.doi.org/10.1016/j.jbc.2021.100652 PMID: 33839158

[45] Sun, J.; Zhang, S.; Zhang, X.; Zhang, X.; Dong, H.; Qian, Y. IL-17A is implicated in lipopolysaccharide-induced neuroinflammation and cognitive impairment in aged rats *via* microglial activation. *J. Neuroinflammation,* **2015**, *12*, 165. http://dx.doi.org/10.1186/s12974-015-0394-5 PMID: 26373740

[46] Ravari, A.; Mirzaei, T.; Kennedy, D.; Kazemi, A.M. Chronoinflammaging in Alzheimer; A systematic review on the roles of toll like receptor 2. *Life Sci.,* **2017**, *171*, 16-20. http://dx.doi.org/10.1016/j.lfs.2017.01.003 PMID: 28087373

[47] Jin, J.J.; Kim, H.D.; Maxwell, J.A.; Li, L.; Fukuchi, K. Toll-like receptor 4-dependent upregulation of cytokines in a transgenic mouse model of Alzheimer's disease. *J. Neuroinflammation,* **2008**, *5*, 23. http://dx.doi.org/10.1186/1742-2094-5-23 PMID: 18510752

[48] Zhou, Y.; Chen, Y.; Xu, C.; Zhang, H.; Lin, C. TLR4 Targeting as a Promising Therapeutic Strategy for Alzheimer Disease Treatment. *Front. Neurosci.,* **2020**, *14*, 602508. http://dx.doi.org/10.3389/fnins.2020.602508 PMID: 33390886

[49] Chen, J.M.; Li, Q.W.; Jiang, G.X.; Liu, J.S.; Cheng, Q. IL-18 induced IL-23/IL-17 expression impairs Aβ clearance in cultured THP-1 and BV2 cells. *Cytokine,* **2019**, *119*, 113-118. http://dx.doi.org/10.1016/j.cyto.2019.03.003 PMID: 30903865

[50] Yang, J.; Kou, J.; Lalonde, R.; Fukuchi, K.I. Intracranial IL-17A overexpression decreases cerebral amyloid angiopathy by upregulation of ABCA1 in an animal model of Alzheimer's disease. *Brain Behav. Immun.,* **2017**, *65*, 262-273. http://dx.doi.org/10.1016/j.bbi.2017.05.012 PMID: 28526436

[51] Malpetti, M.; Kievit, R.A.; Passamonti, L.; Jones, P.S.; Tsvetanov, K.A.; Rittman, T.; Mak, E.; Nicastro, N.; Bevan-Jones, W.R.; Su, L.; Hong, Y.T.; Fryer, T.D.; Aigbirhio, F.I.; O'Brien, J.T.; Rowe, J.B. Microglial activation and tau burden predict cognitive decline in Alzheimer's disease. *Brain,* **2020**, *143*(5), 1588-1602. http://dx.doi.org/10.1093/brain/awaa088 PMID: 32380523

[52] Wu, Z.; He, D.; Zhao, S.; Wang, H. IL-17A/IL-17RA promotes invasion and activates MMP-2 and MMP-9 expression *via* p38

MAPK signaling pathway in non-small cell lung cancer. *Mol. Cell. Biochem.,* **2019**, *455*(1-2), 195-206. http://dx.doi.org/10.1007/s11010-018-3483-9 PMID: 30564960

[53] Schneeberger, E.E.; Lynch, R.D. The tight junction: A multifunctional complex. *Am. J. Physiol. Cell Physiol.,* **2004**, *286*(6), C1213-C1228. http://dx.doi.org/10.1152/ajpcell.00558.2003 PMID: 15151915

[54] Sweeney, M.D.; Zhao, Z.; Montagne, A.; Nelson, A.R.; Zlokovic, B.V. Blood-brain barrier: from physiology to disease and back. *Physiol. Rev.,* **2019**, *99*(1), 21-78. http://dx.doi.org/10.1152/physrev.00050.2017 PMID: 30280653

[55] van de Haar, H.J.; Burgmans, S.; Jansen, J.F.; van Osch, M.J.; van Buchem, M.A.; Muller, M.; Hofman, P.A.; Verhey, F.R.; Backes, W.H. Blood-brain barrier leakage in patients with early Alzheimer Disease. *Radiology,* **2017**, *282*(2), 615. http://dx.doi.org/10.1148/radiol.2017164043 PMID: 28099097

[56] van de Haar, H.J.; Jansen, J.F.A.; Jeukens, C.R.L.P.N.; Burgmans, S.; van Buchem, M.A.; Muller, M.; Hofman, P.A.M.; Verhey, F.R.J.; van Osch, M.J.P.; Backes, W.H. Subtle blood-brain barrier leakage rate and spatial extent: Considerations for dynamic contrast-enhanced MRI. *Med. Phys.,* **2017**, *44*(8), 4112-4125. http://dx.doi.org/10.1002/mp.12328 PMID: 28493613

[57] Sagare, A.P.; Bell, R.D.; Zhao, Z.; Ma, Q.; Winkler, E.A.; Ramanathan, A.; Zlokovic, B.V. Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nat. Commun.,* **2013**, *4*, 2932. http://dx.doi.org/10.1038/ncomms3932 PMID: 24336108

[58] Rahman, M.T.; Ghosh, C.; Hossain, M.; Linfield, D.; Rezaee, F.; Janigro, D.; Marchi, N.; van Boxel-Dezaire, A.H.H. IFN-γ, IL-17A, or zonulin rapidly increase the permeability of the blood-brain and small intestinal epithelial barriers: Relevance for neuro-inflammatory diseases. *Biochem. Biophys. Res. Commun.,* **2018**, *507*(1-4), 274-279. http://dx.doi.org/10.1016/j.bbrc.2018.11.021 PMID: 30449598

[59] Huppert, J.; Closhen, D.; Croxford, A.; White, R.; Kulig, P.; Pietrowski, E.; Bechmann, I.; Becher, B.; Luhmann, H.J.; Waisman, A.; Kuhlmann, C.R. Cellular mechanisms of IL-17-induced blood-brain barrier disruption. *FASEB J.,* **2010**, *24*(4), 1023-1034. http://dx.doi.org/10.1096/fj.09-141978 PMID: 19940258

[60] Kebir, H.; Kreymborg, K.; Ifergan, I.; Dodelet-Devillers, A.; Cayrol, R.; Bernard, M.; Giuliani, F.; Arbour, N.; Becher, B.; Prat, A. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat. Med.,* **2007**, *13*(10), 1173-1175. http://dx.doi.org/10.1038/nm1651 PMID: 17828272

[61] Ni, P.; Dong, H.; Wang, Y.; Zhou, Q.; Xu, M.; Qian, Y.; Sun, J. IL-17A contributes to perioperative neurocognitive disorders through blood-brain barrier disruption in aged mice. *J. Neuroinflam.,* **2018**, *15*(1), 332. http://dx.doi.org/10.1186/s12974-018-1374-3 PMID: 30501622

[62] Liu, Z.; Qiu, A.W.; Huang, Y.; Yang, Y.; Chen, J.N.; Gu, T.T.; Cao, B.B.; Qiu, Y.H.; Peng, Y.P. IL-17A exacerbates neuroinflammation and neurodegeneration by activating microglia in rodent models of Parkinson's disease. *Brain Behav. Immun.,* **2019**, *81*, 630-645. http://dx.doi.org/10.1016/j.bbi.2019.07.026 PMID: 31351185

[63] Schüler, R.; Efentakis, P.; Wild, J.; Lagrange, J.; Garlapati, V.; Molitor, M.; Kossmann, S.; Oelze, M.; Stamm, P.; Li, H.; Schäfer, K.; Münzel, T.; Daiber, A.; Waisman, A.; Wenzel, P.; Karbach, S.H.; Cell-Derived, T. T Cell-Derived IL-17A induces vascular dysfunction *via* perivascular fibrosis formation and dysregulation of ˙NO/cGMP Signaling. *Oxid. Med. Cell. Longev.,* **2019**, *2019*, 6721531. http://dx.doi.org/10.1155/2019/6721531 PMID: 31396305

[64] Siffrin, V.; Radbruch, H.; Glumm, R.; Niesner, R.; Paterka, M.; Herz, J.; Leuenberger, T.; Lehmann, S.M.; Luenstedt, S.; Rinnenthal, J.L.; Laube, G.; Luche, H.; Lehnardt, S.; Fehling, H.J.; Griesbeck, O.; Zipp, F. *In vivo* imaging of partially reversible th17 cell-induced neuronal dysfunction in the course of encephalomyelitis. *Immunity,* **2010**, *33*(3), 424-436. http://dx.doi.org/10.1016/j.immuni.2010.08.018 PMID: 20870176

[65] Zenaro, E.; Pietronigro, E.; Della, B.V.; Piacentino, G.; Marongiu, L.; Budui, S.; Turano, E.; Rossi, B.; Angiari, S.; Dusi, S.; Montresor, A.; Carlucci, T.; Nanì, S.; Tosadori, G.; Calciano, L.; Catalucci, D.; Berton, G.; Bonetti, B.; Constantin, G. Neutrophils promote Alzheimer's disease-like pathology and cognitive decline *via* LFA-1 integrin. *Nat. Med.,* **2015**, *21*(8), 880-886. http://dx.doi.org/10.1038/nm.3913 PMID: 26214837

[66] Taipa, R.; das Neves, S.P.; Sousa, A.L.; Fernandes, J.; Pinto, C.; Correia, A.P.; Santos, E.; Pinto, P.S.; Carneiro, P.; Costa, P.; Santos, D.; Alonso, I.; Palha, J.; Marques, F.; Cavaco, S.; Sousa, N. Proinflammatory and anti-inflammatory cytokines in the CSF of patients with Alzheimer's disease and their correlation with cognitive decline. *Neurobiol. Aging,* **2019**, *76*, 125-132. http://dx.doi.org/10.1016/j.neurobiolaging.2018.12.019 PMID: 30711675

[67] Yang, Z.Y.; Yuan, C.X. IL-17A promotes the neuroinflammation and cognitive function in sevoflurane anesthetized aged rats *via* activation of NF-κB signaling pathway. *BMC Anesthesiol.,* **2018**, *18*(1), 147. http://dx.doi.org/10.1186/s12871-018-0607-4 PMID: 30342469

[68] Shalom-Barak, T.; Quach, J.; Lotz, M. Interleukin-17-induced gene expression in articular chondrocytes is associated with activation of mitogen-activated protein kinases and NF-kappaB. *J. Biol. Chem.,* **1998**, *273*(42), 27467-27473. http://dx.doi.org/10.1074/jbc.273.42.27467 PMID: 9765276

[69] Witowski, J.; Książek, K.; Jörres, A. Interleukin-17: A mediator of inflammatory responses. *Cell. Mol. Life Sci.,* **2004**, *61*(5), 567-579. http://dx.doi.org/10.1007/s00018-003-3228-z PMID: 15004696

[70] Sun, D.; Novotny, M.; Bulek, K.; Liu, C.; Li, X.; Hamilton, T. Treatment with IL-17 prolongs the half-life of chemokine CXCL1 mRNA *via* the adaptor TRAF5 and the splicing-regulatory factor SF2 (ASF). *Nat. Immunol.,* **2011**, *12*(9), 853-860. http://dx.doi.org/10.1038/ni.2081 PMID: 21822258

[71] Hartupee, J.; Liu, C.; Novotny, M.; Li, X.; Hamilton, T. IL-17 enhances chemokine gene expression through mRNA stabilization. *J. Immunol.,* **2007**, *179*(6), 4135-4141. http://dx.doi.org/10.4049/jimmunol.179.6.4135 PMID: 17785852

[72] Zimmermann, J.; Krauthausen, M.; Hofer, M.J.; Heneka, M.T.; Campbell, I.L.; Müller, M. CNS-targeted production of IL-17A induces glial activation, microvascular pathology and enhances the neuroinflammatory response to systemic endotoxemia. *PLoS One,* **2013**, *8*(2), e57307. http://dx.doi.org/10.1371/journal.pone.0057307 PMID: 23468966

[73] Waisman, A.; Hauptmann, J.; Regen, T. The role of IL-17 in CNS diseases. *Acta Neuropathol.,* **2015**, *129*(5), 625-637. http://dx.doi.org/10.1007/s00401-015-1402-7 PMID: 25716179

[74] Varvel, N.H.; Neher, J.J.; Bosch, A.; Wang, W.; Ransohoff, R.M.; Miller, R.J.; Dingledine, R. Infiltrating monocytes promote brain inflammation and exacerbate neuronal damage after status epilepticus. *Proc. Natl. Acad. Sci. USA,* **2016**, *113*(38), E5665-E5674. http://dx.doi.org/10.1073/pnas.1604263113 PMID: 27601660

[75] Block, M.L.; Zecca, L.; Hong, J.S. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat. Rev. Neurosci.,* **2007**, *8*(1), 57-69. http://dx.doi.org/10.1038/nrn2038 PMID: 17180163

[76] Van Eldik, L.J.; Wainwright, M.S. The Janus face of glial-derived S100B: beneficial and detrimental functions in the brain. *Restor. Neurol. Neurosci.,* **2003**, *21*(3-4), 97-108. PMID: 14530573

[77] Vajkoczy, P.; Laschinger, M.; Engelhardt, B. Alpha4-integrin-VCAM-1 binding mediates G protein-independent capture of encephalitogenic T cell blasts to CNS white matter microvessels. *J. Clin. Invest.,* **2001**, *108*(4), 557-565. http://dx.doi.org/10.1172/JCI12440 PMID: 11518729

[78] Wang, D.D.; Zhao, Y.F.; Wang, G.Y.; Sun, B.; Kong, Q.F.; Zhao, K.; Zhang, Y.; Wang, J.H.; Liu, Y.M.; Mu, L.L.; Wang, D.S.; Li, H.L. IL-17 potentiates neuronal injury induced by oxygen-glucose deprivation and affects neuronal IL-17 receptor expression. *J. Neuroimmunol.,* **2009**, *212*(1-2), 17-25. http://dx.doi.org/10.1016/j.jneuroim.2009.04.007 PMID: 19457561

[79] Sommer, A.; Marxreiter, F.; Krach, F.; Fadler, T.; Grosch, J.; Maroni, M.; Graef, D.; Eberhardt, E.; Riemenschneider, M.J.; Yeo, G.W.; Kohl, Z.; Xiang, W.; Gage, F.H.; Winkler, J.; Prots, I.; Winner, B. Th17 lymphocytes induce neuronal cell death in a Human iPSC-based model of Parkinson's Disease. *Cell Stem Cell,* **2019**, *24*(6), 1006. http://dx.doi.org/10.1016/j.stem.2019.04.019 PMID: 31173705

[80] Wang, X.; Zhang, M.; Liu, H. LncRNA17A regulates autophagy and apoptosis of SH-SY5Y cell line as an *in vitro* model for Alzheimer's disease. *Biosci. Biotechnol. Biochem.,* **2019**, *83*(4), 609-621. http://dx.doi.org/10.1080/09168451.2018.1562874 PMID: 30652945

[81] Leavy, O. The T(H)17 kiss of death for neurons. *Nat. Rev. Immunol.,* **2010**, *10*(11), 750. http://dx.doi.org/10.1038/nri2876 PMID: 21080612

[82] Tanabe, S.; Yamashita, T. Repulsive guidance molecule-a is involved in Th17-cell-induced neurodegeneration in autoimmune encephalomyelitis. *Cell Rep.,* **2014**, *9*(4), 1459-1470. http://dx.doi.org/10.1016/j.celrep.2014.10.038 PMID: 25456136

[83] Lazarov, O.; Hollands, C. Hippocampal neurogenesis: Learning to remember. *Prog. Neurobiol.,* **2016**, *138-140*, 1-18. http://dx.doi.org/10.1016/j.pneurobio.2015.12.006 PMID: 26855369

[84] Moreno-Jiménez, E.P.; Flor-García, M.; Terreros-Roncal, J.; Rábano, A.; Cafini, F.; Pallas-Bazarra, N.; Ávila, J.; Llorens-Martín, M. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat. Med.,* **2019**, *25*(4), 554-560. http://dx.doi.org/10.1038/s41591-019-0375-9 PMID: 30911133

[85] Liu, Q.; Xin, W.; He, P.; Turner, D.; Yin, J.; Gan, Y.; Shi, F.D.; Wu, J. Interleukin-17 inhibits adult hippocampal neurogenesis. *Sci. Rep.,* **2014**, *4*, 7554. http://dx.doi.org/10.1038/srep07554 PMID: 25523081

[86] Tfilin, M.; Turgeman, G. Interleukine-17 Administration modulates adult hippocampal neurogenesis and improves spatial learning in mice. *J. Mol. Neurosci.,* **2019**, *69*(2), 254-263. http://dx.doi.org/10.1007/s12031-019-01354-4 PMID: 31254254

[87] Gao, L.; Li, P.P.; Shao, T.Y.; Mao, X.; Qi, H.; Wu, B.S.; Shan, M.; Ye, L.; Cheng, H.W. Neurotoxic role of interleukin-17 in neural stem cell differentiation after intracerebral hemorrhage. *Neural Regen. Res.,* **2020**, *15*(7), 1350-1359. http://dx.doi.org/10.4103/1673-5374.272614 PMID: 31960824

[88] Satoh, J.; Tabunoki, H.; Ishida, T.; Saito, Y.; Arima, K. Accumulation of a repulsive axonal guidance molecule RGMa in amyloid plaques: A possible hallmark of regenerative failure in Alzheimer's disease brains. *Neuropathol. Appl. Neurobiol.,* **2013**, *39*(2), 109-120. http://dx.doi.org/10.1111/j.1365-2990.2012.01281.x PMID: 22582881

[89] Tang, J.; Zeng, X.; Li, H.; Ju, L.; Feng, J.; Yang, J. Repulsive guidance molecule-a and central nervous system diseases. *BioMed Res. Int.,* **2021**, *2021*, 5532116. http://dx.doi.org/10.1155/2021/5532116 PMID: 33997000

[90] Okamura, Y.; Kohmura, E.; Yamashita, T. TACE cleaves neogenin to desensitize cortical neurons to the repulsive guidance molecule. *Neurosci. Res.,* **2011**, *71*(1), 63-70. http://dx.doi.org/10.1016/j.neures.2011.05.012 PMID: 21645559

[91] Small, D.H.; Mok, S.S.; Bornstein, J.C. Alzheimer's disease and Abeta toxicity: from top to bottom. *Nat. Rev. Neurosci.,* **2001**, *2*(8), 595-598. http://dx.doi.org/10.1038/35086072 PMID: 11484003

[92] Terry, R.D.; Masliah, E.; Salmon, D.P.; Butters, N.; DeTeresa, R.; Hill, R.; Hansen, L.A.; Katzman, R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann. Neurol.,* **1991**, *30*(4), 572-580. http://dx.doi.org/10.1002/ana.410300410 PMID: 1789684

[93] Selkoe, D.J. Alzheimer's disease is a synaptic failure. *Science,* **2002**, *298*(5594), 789-791. http://dx.doi.org/10.1126/science.1074069 PMID: 12399581

[94] D'Anna, L.; Abu-Rumeileh, S.; Fabris, M.; Pistis, C.; Baldi, A.; Sanvilli, N.; Curcio, F.; Gigli, G.L.; D'Anna, S.; Valente, M. Serum Interleukin-10 levels correlate with cerebrospinal fluid amyloid beta deposition in alzheimer disease patients. *Neurodegener. Dis.,* **2017**, *17*(4-5), 227-234. http://dx.doi.org/10.1159/000474940 PMID: 28719891

[95] Dubenko, O.E.; Chyniak, O.S.; Potapov, O.O. Levels of proinflammatory cytokines Il-17 and Il-23 in patients with Alzheimer's Disease, mild cognitive impairment and vascular dementia. *Wiad. Lek.,* **2021**, *74*(1), 68-71. http://dx.doi.org/10.36740/WLek202101113 PMID: 33851590

[96] Rakic, S.; Hung, Y.M.A.; Smith, M.; So, D.; Tayler, H.M.; Varney, W.; Wild, J.; Harris, S.; Holmes, C.; Love, S.; Stewart, W.; Nicoll, J.A.R.; Boche, D. Systemic infection modifies the neuroinflammatory response in late stage Alzheimer's disease. *Acta Neuropathol. Commun.,* **2018**, *6*(1), 88. http://dx.doi.org/10.1186/s40478-018-0592-3 PMID: 30193587