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Review article

Impact of aging immune system on neurodegeneration and potential immunotherapies

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ABSTRACT

The interaction between the nervous and immune systems during aging is an area of avid interest, but many aspects remain unclear. This is due, not only to the complexity of the aging process, but also to a mutual dependency and reciprocal causation of alterations and diseases between both the nervous and immune systems. Aging of the brain drives whole body systemic aging, including aging-related changes of the immune system. In turn, the immune system aging, particularly immunosenescence and T cell aging initiated by thymic involution that are sources of chronic inflammation in the elderly (termed inflammaging), potentially induces brain aging and memory loss in a reciprocal manner. Therefore, immunotherapeutics including modulation of inflammation, vaccination, cellular immune therapies and "protective autoimmunity" provide promising approaches to rejuvenate neuroinflammatory disorders and repair brain injury. In this review, we summarize recent discoveries linking the aging immune system with the development of neurodegeneration. Additionally, we discuss potential rejuvenation strategies, focusing aimed at targeting the aging immune system in an effort to prevent acute brain injury and chronic neurodegeneration during aging.

Contents

Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; ADCC, antibody dependent cell-mediated cytotoxicity; ALS, amyotrophic lateral sclerosis; APCs, antigen presenting cells; APOE, apolipoprotein E; APP, amyloid precursor protein; APP/PS1, amyloid precursor protein and presenilin; α-Syn, α-synuclein protein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; C/EBP, CCAAT/enhancer binding protein; CMV, cytomegalovirus; CNS, central nervous system; COX, cyclooxygenase CP choroid plexus; CRP, C-reactive protein; CSEF, circulating systemic environmental factor; CSF, cerebrospinal fluid; CTFs, C-terminal fragments; CTL, Cytotoxic T Lymphocytes; EAE, experimental autoimmune encephalomyelitis; GM-CSF, granulocyte-macrophage colony-stimulating factor; GCs, glucocorticoids; GnRH, gonadotropin-releasing hormone; GR, glucocorticoid receptor; HIV, human immunodeficiency virus; IFN, interferon; IL-β, interleukin-β; i.p., intraperitoneal; i.v., intravenous; LPS, lipopolysaccharides; LTP, long-term potentiation; $M_{ø}$, macrophage; MBL, mannan-binding lectin; MBP, myelin basic protein; MCAO, middle cerebral artery occlusion; MHC, major histocompatibility complex; miR, microRNAs; MOG, myelin oligodendrocyte glycoprotein; MS, Multiple sclerosis; mTOR, mechanistic target of rapamycin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFT, neurofibrillary tangles; NLRP3, nod-like receptor protein 3; NOS2, nitric oxide synthase; NSAIDs, non-steroidal anti-inflammatory drugs; NSCs, neuron stem cells; NT-3, neurotrophin-3; PD, Parkinson's disease; POCD, postoperative cognitive dysfunction; ROS, reactive oxygen species; RRMS, relapse-remission multiple sclerosis; SA-βGal, senescence-associated beta-galactosidase; SASP, senescence-associated secretory phenotype; TCR, T cell receptor; TCV, T-cell vaccine; TGF-β, transforming growth factor-beta; Th1/2/17, T helper cell 1/2/17; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; TREM2, triggering receptor expressed on myeloid cells 2; WT, wild-type.

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1. Introduction

The mutual interactions and dependency of nervous and immune systems have been recognized for long and recently cause more and more attentions (McAllister and van de Water, 2009; Trakhtenberg and Goldberg, 2011). This is simply because the nervous and immune systems interact and crosstalk each other over many physiological processes, like development, homeostasis, pathogenesis, and aging. The immune system has both detrimental and beneficial effects on the nervous system. The autoimmune demyelinating disease multiple sclerosis (MS) is a typical example of an abnormal immunity-induced pathological damage in nervous system (Naegele and Martin, 2014). The central nervous system (CNS) in turn induces immunological changes via the neuro-endocrine network (Procaccini et al., 2014; Rosas-Ballina and Tracey, 2009; Tanriverdi et al., 2003). Stroke-induced global immunosuppressant effect is a well-known example (Meisel and Meisel, 2011). However, the beneficial effects of the immune system on the nervous system have only recently and gradually been recognized (Schwartz et al., 2013). For example, the immune cells and inflammation have been demonstrated to be required for brain healing (Raposo et al., 2014; Ziv et al., 2006a). Even autoimmunity can play both detrimental and beneficial effects to the CNS. While autoimmunity induced neuroinflammation and neurodegeneration (Bhat and Steinman, 2009), brain antigen-induced "autoimmunity" (so-called "protective autoimmunity") may be involved in the maintenance of CNS functional integrity (Moalem et al., 1999).

The interaction and mutual dependency between the nervous and immune systems lead to reciprocal affects on both systems during aging process. It is a question that which system goes first during neurodegeneration. As we know, cellular immune system aging, particularly of the T cell system resulting from age-related thymic involution which typically starts as early as in adolescence (Gui et al., 2012), takes place far before brain aging. Therefore, the significant age-related alterations of the immune system should causally influence nervous system homeostasis and regeneration. It is recognized that natural aging bring about immune activation and cell infiltration into the brain (Lucin and Wyss-Coray, 2009), which is probably due to aging-induced inflammatory conditions. This aging-relevant condition possibly promoted by pro-inflammatory cytokines produced by glial cells and senescent cells in other tissues would significantly increase the permeabilization of the blood-brain barrier (BBB), and recruit more immune cells to the CNS (Deverman and Patterson, 2009). Immunosenescence is believed to be directly associated with brain aging and memory loss (Di Benedetto et al., 2017; Ron-Harel and Schwartz, 2009). On the other hand, age-related neurodegeneration and the subsequent

alteration of endocrine system would in turn impact the immune system homeostasis and functional balance, forming an aging regulatory loop.

We herein review recent discoveries in immune system aging-associated brain injury and neurodegeneration. We also discussed the regulatory loop between nervous and immune systems during aging with potential immunological rejuvenation strategies.

2. Immune characteristics of acute brain injury and age-related chronic neurodegeneration

Except for acute cerebral trauma caused by outside hits, many brain injuries and neurodegenerative disorders are directly correlated with aging. For example, brain ischemic stroke is usually mediated by insufficient blood flow to the brain likely owing to age-related blood vessel and flow abnormalities, while neurodegeneration is mostly caused by chronic inflammation during the aging process (termed inflammaging, discussed in Section 3) (Brunner et al., 2011; De Martinis et al., 2005; Franceschi et al., 2007; Freund et al., 2010). Furthermore, autoimmune demyelinating disease MS is not only associated with age (20–40 years old), but also tends to worsen with aging (>40 years old). In this section we will focus on the immunopathology of three typical types of age-related CNS diseases: acute brain injury caused by blood flow abnormalities, autoimmune CNS damage induced by autoreactive T cells, and chronic neurodegeneration associated with inflammaging.

2.1. Neuroinflammation and degeneration

Both acute brain injury and chronic neurodegeneration are usually companied with a process of whole body and/or local inflammation, although inflammation also provides protection and benefits by clearing and destroying cellular debris. However, too strong acute inflammation, such as cerebral stroke-induced inflammation, results in secondary injury in the CNS, while long-term low-level uncontrolled chronic inflammation likely causes neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Daulatzai, 2016; Harris and Harris, 2015). Acute and chronic neuroinflammation is closely related to both innate and adaptive cellular immune responses. Generally, the resting microglia are the resident immune cells in the CNS, which upon activation become M1- and M2- macrophage-like types to participate actively in establishing neural homeostasis. The M1 type is involved in inflammation in CNS injury by releasing harmful and deadly neurotoxins such as reactive oxygen species (ROS) and pro-inflammatory substances. Although the BBB normally confers immune privilege to the brain, during CNS injury and neuroinflammation blood-derived macrophages ($M_{\emptyset}$), which are also activated into M1 and M2 types, enter the CNS to clear the injury debris. Furthermore, T cells enter the CNS in the event of injury and neuroinflammation to play an important role in both inflammation and modulation depending on their subtypes (discussed below).

2.2. Immunopathological alterations in age-related neurodegenerative diseases

As mentioned above, the three typical types of age-related CNS diseases should exhibit different immunopathological characteristics, because they have different etiologies. Acute brain injury induced by blood vessel and flow abnormalities is always accompanied by acute inflammation, which is associated with both the innate and adaptive immune responses; autoimmune reactive CNS injury should elicit a strong autoreactive adaptive immunity; and chronic neurodegeneration, such as in AD and PD, is mainly induced by generally accumulated misfolded protein-induced neuro-inflammation closely associated with long-term, low-grade sustained inflammatory factors involving the innate and adaptive immunities (Coder et al., 2017; Rawji et al., 2016). In brief, immunopathological alterations in these neurodegenerative disorders are greatly relevant to the immune alterations before (as etiology) and after (as outcome) occurrence of these diseases.

2.2.1. Acute brain injury: ischemic stroke and brain trauma

Focal ischemic stroke is the leading cause of death and disability in the world, which is correlated with age-related blood vessel and flow abnormalities. Post-cerebral ischemic stroke-induced injury of the neural system is not only due to occlusion but also involves immunopathogenic inflammation induced by both innate and adaptive immune responses. Mounting evidence clearly indicates that acute cerebral ischemic stroke is followed by a complex interplay between the CNS and the immune system (Chamorro et al., 2012; Iadecola and Anrather, 2011; Magnus et al., 2012), leading to amplification of the local inflammatory cascade in the brain (Dirnagl, 2004; Wang et al., 2007) and whole body immune suppression as well (Dirnagl et al., 2007; Offner et al., 2009). The increased immunopathogenic reaction in the CNS and impaired anti-infection immune response in the periphery contribute substantially to both secondary cerebral damage and severe infectious complications after ischemic stroke (Meisel et al., 2005), typically bacterial pneumonia, which accounts for about 20% of in-hospital deaths after cerebral stroke (Meisel and Meisel, 2011). Therefore, occlusion and immunopathogenic inflammation are two key elements of the pathogenesis of cerebral ischemic stroke.

Microglia and astrocytes, considered as the resident immune cell of the brain, are the major immune cells involved in the innate immunity-induced inflammation after ischemic stroke. Upon the ischemic stroke injury onset, microglia respond rapidly and undergo morphologic transformation from resting state to an active state (Saijo and Glass, 2011). The M1 microglia has been detected in ischemic injury region for the first 24 h and is able to release proinflammatory cytokines including IL-6, TNF-α, and IL-1β (Nguyen et al., 2011). The activation of proinflammatory M1 leads to secondary injury for a few days afterward (Fig. 1). On the other hand, M2 type of microglia increased and was predominated in the core of ischemic injury at the end of first 24 h after ischemia onset (Taylor and Sansing, 2013). The M2 type microglia facilitates the neuroprotection and repair effect by producing anti-inflammatory cytokines such as IL-4 and nerve growth factor (NGF) (Colton, 2009; Lin et al., 2017; Lou et al., 2016) (Fig. 1). Astrocytes also release a variety of proinflammatory factors after ischemic attack and resulted in reactive gliosis and glial scar formation. This astrogliosis process last from day 1 to day 28 in stroke models (Nowicka et al., 2008). Traditionally, the glia scar formation is considered as deleterious process for brain recovery, which prevents axon in growth and regeneration. However, recent study by Anderson showed that astrocyte scar formation support rather than prevent brain axon regeneration (Anderson et al., 2016). It is recently reported that IL-33/ST2 signaling promotes beneficial microglial response and limits acute ischemic brain injury after stroke (Yang et al., 2017). Thus, the innate immunity has beneficial and destructive properties for acute injured brain.

7 In addition to innate immunity-induced inflammation by the resting microglia and blood-derived $M_{\emptyset}$ cells, two major adaptive immune mechanisms are closely involved in post-ischemic stroke-induced inflammation. The first is interleukin-17 (IL-17)-induced inflammation. IL-17 is mainly produced by γδT cells in this inflammatory process (Shichita et al., 2009), and neutralization of the IL-17 axis was able to greatly diminish brain damage (Gelderblom et al., 2012). The second is IFN-γ-producing T helper cell 1 (Th1)-induced inflammation-caused brain injury. Increasing

evidences show that this Th1 cell-dependent pro-inflammatory pathway occurs through IFN-γ-mediated polarized immune response (Becker et al., 2011; Denes et al., 2010; Gelderblom et al., 2012), whereas Th2 cells, which is an IL-4- and IL-10-mediated polarized adaptive immune response, is able to significantly protect from post-ischemic stroke inflammation-caused brain injury (Bodhankar et al., 2013; Xiong et al., 2011). Both IL-17 and Th1 immune response-mediated pro-inflammatory pathways synergistically enhance recruitment of inflammatory neutrophils into the CNS to lead to cerebral injury (Gelderblom et al., 2012).

2.2.2. Typical autoimmune neurodegenerative disorder: MS

MS is an autoimmune inflammatory disorder of the brain and spinal cord mainly characterized by demyelination of the axonal myelin sheath, vascular abnormalities, and cutaneous and visceral fibrosis. The clinical manifestations of MS mainly include defects in the motor and sensation systems, vision, and cognition. Although symptoms emerge in young adults between the ages of 20 and 40 years, patients with MS undergo an aging-related acceleration in progressive axonal loss, likely due to the synergistic effects of age and neurologic illness (Rist and Franklin, 2008; Stern et al., 2010). Of the four versions of the disease, relapsing-remitting MS (RRMS) (Confavreux and Vukusic, 2006), in which there is full recovery between initiation and relapses, is the most common. RRMS appears to be associated with age-related thymic atrophy, since reduction in naïve T cell output from the thymus, which is a typical phenotype of thymic aging, plays an important pathogenic role in RRMS (Hug et al., 2003).

The pathological alterations in MS are very complex, including the infiltration of T cells into the CNS, activation of autoimmune T cells, axonal degeneration, demyelination, and remyelination (Glass et al., 2010), but it significantly differs from AD and PD in the absence of abnormal protein aggregates that initiate the degeneration of neurons. Viral and bacterial infections initiate this disease by triggering the activation of astrocytes and microglia in the CNS, leading to the productions of a wide array of pro-inflammatory cytokines. Fundamentally, MS is generally considered as an autoreactive Th1-mediated nervous disease, including involvement of Th17 cells and T regulatory cells (Treg) playing a crucial role in the pathogenesis of MS (Glass et al., 2010).

Inflammation is correlated with the activity of demyelination and neurodegeneration in the brains of MS patients, and the extent of T and B cell infiltration is also associated with the extent of demyelinating lesions and axonal injury (Arneth, 2016; Frischer et al., 2009). The inflammation in MS brain involves activated macrophage/microglia, T cells, B cells, and others (Frischer et al., 2009; von Kutzleben et al., 2017). M1 phenotype of macrophages/microglia is considered as pro-inflammatory immune cells which produce cytokines such as IL-1, TNF-α and induce neuronal damage, whereas M2 phenotype act as anti-inflammatory immune cells and promote brain repair. The imbalance of pro-inflammatory M1 and immunomodulatory M2 profiles leads to the relapse of this disease in experimental autoimmune encephalomyelitis (EAE) model, indicating the involvement of macrophages/microglia in MS pathogenesis (Mikita et al., 2011). The circulating Ly6C^{hi}CCR2^{+} monocytes also play a pathological role in EAE (Ji et al., 2013). T cell-derived GM-CSF could induce the expansion of myeloid cells and cause CNS inflammation and neurological deficits (Spath et al., 2017). pDCs are also thought to play a pathological role in MS because more pDCs are found in the CSF of MS patients (Longhini et al., 2011). What's more, pDCs from MS patients express high level of CCR7 and CCR5, which promotes the migration of pDCs to the CNS-draining lymph nodes and the activation of autoimmune T cells (Thewissen et al., 2014). Different subsets of CD4^{+} T cells play different roles in the pathogenesis of MS by promoting or inhibiting inflammation and neuronal re/de-generation (Ellwardt and Zipp, 2014). Th17 cells, which secret IL-17A and IL-17F, are thought to be bad guys in autoimmune disorders such as MS (Steinman, 2007; Wu et al., 2017). However, Foxp3^{+} Treg cells are considered as good guys as they control the immune response and suppress the development of autoimmune disease. In EAE animal model, the accumulation of Foxp3^{+} Treg cells in the brain correlated with the recovery EAE, as transfer of CNS-derived Treg cells results in better outcome and depletion of Treg cells inhibit recovery (McGeachy et al., 2005). The involvement of Th9 cells in MS was also recently recognized (Elyaman and Khoury, 2017; Jager et al., 2009). However, the pathological phenotypes of Th1, Th17 and Th9 cells induced EAE displayed different changes (Jager et al., 2009). The activation of CD8^{+} CTLs and local production of pro-inflammatory cytokines such as IFN-γ and TNF-α are found associated with neurodegeneration and demyelination (Brenu et al., 2016; van Nierop et al., 2016). Therefore, the imbalanced local innate and adaptive immunity is involved in the process of MS.

2.2.3. Aging-associated neurodegenerative diseases: AD and PD

AD, the leading cause of dementia (Berchtold and Cotman, 1998; Sardi et al., 2011), is one of the most common age-related neurodegenerative diseases, which results in neuron death, and thereby, progressive impairment of cognition. The typical clinical

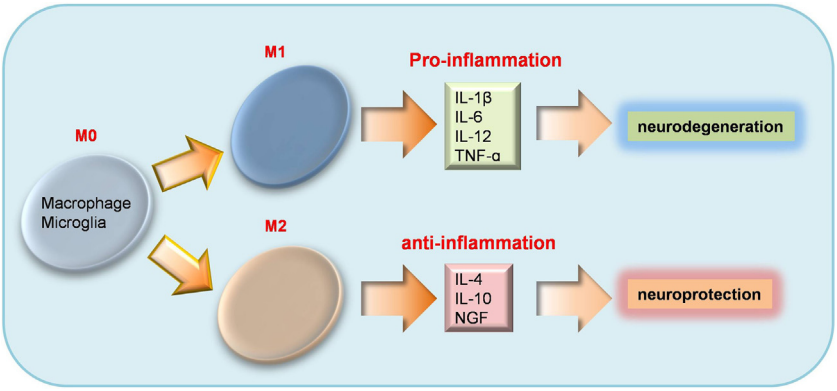

Fig. 1. The roles of macrophage/microglia in ischemic stroke.
During the first 24 h after ischemic stroke, the resting macrophage/microglia (M0) transform to a proinflammatory state (M1) which release pro-inflammatory cytokines including IL-1β, IL-6, IL-12 and TNF-α. These pro-inflammatory cytokines lead to neurodegenerative disease. By the first 24 h after ischemia onset, the resting macrophage/microglia (M0) transform to an anti-inflammatory state (M2) which release anti-inflammatory cytokines including IL-4, IL-10 and NGF. These anti-inflammatory cytokines have neuroprotective roles.

manifestations of AD are the progressive decline in memory, diminished cognitive and intellectual abilities, and various behavioral and neuropsychiatric impairments. The pathological alterations of AD at least include extracellular deposition of amyloid-beta (Aβ) protein and intracellular accumulation of neurofibrillary tangles (NFT) generated by abnormal hyperphosphorylated Tau protein (Selkoe, 2001; Takahashi et al., 2017). Aβ is produced by proteolysis of the amyloid precursor protein (APP), which is achieved by the cleavage of α-, β- and γ-secretases. Mounting evidence indicates that a complex neuroinflammatory response, including activation of resident immune cells such as microglia and astrocytes (Perry et al., 2010), by Aβ and Tau proteins (Serrano-Pozo et al., 2011) that in turn release inflammatory mediators, leads to AD pathogenesis (Akiyama et al., 2000). The activation of microglial cells in the AD brain has both positive and negative effects on AD pathogenesis process. On the negative side, activation of microglial cells in the AD brain promotes the production of pro-inflammatory cytokines including TNF-α, IL-1β and IL-6 (McCoy and Tansey, 2008; Morales et al., 2013; Simi et al., 2007; Wang et al., 2015), which act directly on cholinergic neurons and induce their apoptosis. On the positive side, the activated microglial cells produce proteolytic enzymes such as matrix metalloproteinases and insulin-degrading enzyme to degrade Aβ (Leissring et al., 2003; Li et al., 2011). Furthermore, activated microglial cells can also secrete growth factors such as glial cell-derived neurotrophic factor (GDNF) to enhance the survival of neurons (Liu and Hong, 2003; Naert and Rivest, 2011). Therefore, it is crucial to understand the overall impact of microglia on AD pathology.

PD is another neurodegenerative disease resulting of aging (Rodriguez et al., 2015). The clinical symptoms of PD mainly include tremor, bradykinesia, rigidity, postural instability and gait imbalance. These motor symptoms are generally considered to be the result of loss of dopamine neurons in the substantia nigra pars compacta. The critical pathological hallmark of PD is the intracellular deposition of Lewy bodies and Lewy neurites, which contain a fibrillar and misfolded protein called α-Synuclein (α-Syn) (Phani et al., 2012) responsible for inducing a complex immunopathogenic response during PD process. T cell infiltration into the PD brain clearly involves the disease process (Brocard et al., 1997), since immunodeficient mice lacking $CD4^+$ T cells displayed significant reduction in dopaminergic neuron death. The increased type-1 pro-inflammatory cytokine expression and the IgG deposition in dopaminergic neurons of PD patients hint at an underlying Th1 cell-dependent autoimmunity associated with the neuronal damage. This is likely due to dopamine receptor D3 expressed on $CD4^+$ T cells, which favors acquisition of the Th1 phenotype, and neurodegeneration of dopaminergic neurons during PD process (Gonzalez et al., 2013). Additionally, an autoimmune model for PD has been proposed where peripheral T cells specific for the neuromelanin (NM) pigment in dopaminergic neurons are activated by dendritic cells in the cervical lymph nodes and then facilitate the activation of NM-specific B cells leading to autoantibody production. These autoreactive NM-specific T cells also migrate into the brain and subsequently participate in dopamine neuronal damage and further activation of microglia (Koutsilieri et al., 2013; Shameli et al., 2016).

Intraneuronal aggregation of the α-Syn protein activates resting microglia and astrocytes, which in turn produce pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, IFN-γ and ROS (Hirsch and Hunot, 2009; Long-Smith et al., 2009; Saijo et al., 2009). These pro-inflammatory mediators are toxic to dopaminergic neurons and induce apoptosis in PD. The α-Syn protein in PD also causes the induction of major histocompatibility complex-II (MHC-II) expression by microglial cells (Thome et al., 2016), which are then capable of driving the proliferation and activation of $CD4^+$ T cells and the secretion of IFN-γ and TNF-α. Knock-out of MHC-II molecule has been shown to prevent α-Syn-induced microglia activation, antigen presentation, IgG deposition, and the degeneration of dopaminergic neurons (Gonzalez et al., 2013; Harms et al., 2013; Kustrimovic et al., 2016).

2.2.4. Neuroinflammation in the aging-related cognitive decline

Mounting evidence points to neuroinflammation as a key contributor of cognitive decline, which makes the memory impaired (Papenberg et al., 2016; Pistell et al., 2010). The age-related cognitive impairment can be explained by the changes of inflammatory and anti-inflammatory networks (Bulzacka et al., 2016). It is also reported that monocyte phenotype and polyfunctionality in the peripheral blood are closely associated with elevated soluble inflammatory markers, cytomegalovirus infection, and functional and cognitive decline in elderly population (de Pablo-Bernal et al., 2016). However, little is known about the underlying mechanisms that the involvement and effects of neuroinflammation on cognitive function so far. It has been suggested that spatial memory is impaired by IL-1β injection alone via Morris water maze assessing, indicating the potential direct role of inflammatory mediators in cognition and memory (Gibertini et al., 1995). Although the proinflammatory cytokines IL-1β and TNF-α aims to protect and defend against the infections, the huge amount of productions result in long-term potentiation (LTP) and then provokes the cognitive impairment following the infection (Balschun et al., 2003; Cumiskey et al., 2007; Hennessy et al., 2017). Administration of TNF-α receptor antagonist significantly attenuates isoflurane-induced cognitive impairment in aged rat models (Yang et al., 2016b). The immune system altered with age and the elder individuals are vulnerable to be infected, meaning the neuroinflammation accumulates over time and take the risk for cognitive decline with the age. One prospective study showed that high levels of TNF-α were closely associated with a four-fold increase in the rate of cognitive decline, while subjects who had low levels of TNF-α showed no cognitive decline over 6-month period (Holmes et al., 2009). Inflammation is both friends and foes, not only providing the protection for the body but also exerting the risk for cognitive impairment, which might be the potential therapy target for neurological diseases.

2.2.5. Genetic factors and environmental factors on the pathogenesis of age-related neurodegenerative diseases

Some genetic factors also affect pathogenesis of age-related neurodegenerative diseases. The role of Apolipoprotein E (APOE) and Triggering Receptor Expressed On Myeloid Cells 2 (TREM2) on the progression of AD is now widely studied. As a lipid binding protein, APOE functions in the transport of cholesterol and triglycerides in various tissues, including brain, by interacting with lipoprotein receptors on target cells (Riedel et al., 2016; Wang et al., 2006). APOE is critical for the mobilization and redistribution of cholesterol between cells (Leduc et al., 2010). These function of APOE is particularly important for the nervous system because the APOE transport of cholesterol is critical for the maintenance of myelin and neuronal membranes (Leduc et al., 2010). APOE have the function of inducing intracellular Aβ degradation through trafficking of amyloid to lysosomes. There are three APOE polymorphic alleles in humans: APOE-ε2, APOE-ε3 and APOE-ε4 (Mahley et al., 2009). Various evidences showed that APOE-ε4 is associated with AD. Up to 60% of AD patients carry at least one ε4 allele (Riedel et al., 2016). The APOE-ε4 allele accounts for as much as 50% of the genetic attribution of AD risk (Raber et al., 2004). The mean age of AD at clinical onset is 68 years old in ε4 homozygotes, and 76 years old in ε4 heterozygotes, and 84 years old in ε4 noncarriers (Liu et al., 2013). These results indicate that APOE-ε4

alleles significantly increase the risk of AD and lead to an earlier age of onset.

The TREM2 gene is located within the TREM gene cluster which contains 4 TREMs (TREM1, TREM2, TREM4 and TREM5) in humans and an additional TREM3 in mice (Ulrich and Holtzman, 2016). TREM2 is a member of the Ig superfamily receptors expressed in various cell types including macrophages, dendritic cells and microglia in the brain (Yeh et al., 2017). TREM2 participated in many cellular processes including survival, proliferation, phagocytosis and inflammatory cytokine production (Wu et al., 2015). Some studies showed that the individuals with R47H mutation of TREM2 gene have increased risk of AD up to 3–4 folds (Jonsson et al., 2013). Some other variants of TREM2, including R62H, D87N and T96K, have also been linked with AD (Jin et al., 2014; Song et al., 2017). The mechanism of how TREM2 variants affect the onset and progression of AD has not been precisely illustrated. It is shown that the expression of TREM2 is induced in microglia of the Aβ deposition area in the aged APPP23 transgenic mice and the expression of TREM2 is positively correlated with Aβ deposition in AD patients (Frank et al., 2008; Varvel et al., 2015). There are more works need to be done in the future to clarify the precisely mechanism of how TREMs variants affect the onset and progression of AD.

3. Role of inflammation in neurodegenerative diseases

Inflammation is a response of the innate immune system, that defend against the pathogens or dangers and aims to prime the protective mechanisms (Le Thuc et al., 2015). Neuroinflammation is one of the triggers which have been proposed for the aetiology of some neurological diseases. Postoperative cognitive dysfunction (POCD) is a decline in cognitive function following the surgery and general anesthesia that may last from a few days to weeks (Folks et al., 1988). Surgery procedures always bring inflammation storm, as well as the key proteins, such as the inflammatory marker C-reactive protein, leading to the cognitive impairment and decline. High levels of cytokines TNF-α, IL-6, and IL-1β in plasma are associated with the cognitive impairment or dysfunction and implicated in the pathogenesis of POCD (Cibelli et al., 2010; Kline et al., 2016; Parolari et al., 2007). Cytokine-dependent glia activation and glia proinflammatory productions are significantly involved in memory injury (Wan et al., 2007). Chronic neuroinflammation in brain is the crucial hallmark of AD (Azizi et al., 2015). MS is another disease caused by chronic neuroinflammation and is characterized by CNS demyelination and inflammation (Lyman et al., 2014). Thus, the neuroinflammation is a common trigger for the pathologenesis of the chronic neurodegenerative diseases. However, it is worth to be pointed out that acute inflammatory mediators can serve as the risk factors for the chronic neurological diseases such as AD (Eikelenboom et al., 2012). Clinical observation showed that acute systemic inflammation with the high levels of TNF-α significantly increased in the rate of cognitive decline over a 6-month period (Holmes et al., 2009). Periodontitis caused by tooth loss or infection in elder people were associated with the progression of AD (Kamer et al., 2012). A traumatic brain injury is linked to an increased risk for the later development of dementia (Daneshvar et al., 2015). Therefore, acute neuroinflammation increases the risk and accelerates the progression of the chronic neurological diseases, like AD and PD. However, it was recently reported that serum levels of soluble ST2, a decoy receptor for IL-33, significantly increased in patients with mild cognitive impairment, indicating that impaired IL-33/ST2 signaling pathway may contribute to the pathogenesis of AD in APP/PS1 mice (Fu et al., 2016). The injection of IL-33 ameliorates AD-like pathology and cognitive decline by polarizing microglia/macrophages to an anti-inflammatory phenotype and reducing the expression of proinflammatory genes, like IL-1β, IL-6, and NLRP3 (Fu et al., 2016). These results suggest that IL-33 may have protective role on cognitive decline and may be a potential therapeutic target for AD. In the following section, we will mainly discuss the roles of cellular senescence-associated secretory phenotype (SASP), inflammasomes, exosomes and inflammaging in age-related neurodegenerative diseases particularly in AD and PD.

3.1. Pro-inflammatory factor production by SASP in age-related neurodegeneration

Chronic neurodegeneration during aging is greatly attributed to persistently increased levels of pro-inflammatory factors, which are likely produced by cellular (mostly non-immune, such as endothelium) SASP (Campisi, 2011; Freund et al., 2010; Olivieri et al., 2013, 2012) and progressive activation of immune cells due to latent viral (such as cytomegalovirus, CMV) infection-induced "foreign-reaction" (Brunner et al., 2011; High et al., 2012; Nikolich-Zugich, 2008). We recently reported that autoreactive T cells derived from the atrophied thymus are yet another source of pro-inflammatory factors (Coder and Su, 2015; Coder et al., 2017). SASP produces a large number of pro-inflammatory factors, like IL-6, TNF-α, IL-1β and C-reactive protein (CRP), which strongly contribute to tissue degeneration, including neurodegeneration. Although the precise molecular mechanisms that control SASP in senescent cells are unclear (potentially via DNA damage response (DDR) and p38-NF-kB signaling pathways) (Freund et al., 2010, 2011), it may not be the same as in the inflammasome [a protein complex called nod-like receptor protein (NLRP), mainly in $M_{\emptyset}$ cells]-mediated signaling pathway in the brain (Goldmann et al., 2013; Kaushal et al., 2015; Singhal et al., 2014).

Cellular replicative senescence was initially described as limited proliferation (growth arrest) in the *in vitro* cultured fibroblasts. However, senescent cells were also found *in vivo* and is now known to have many phenotypes (Campisi, 2011; Rodier et al., 2009), particularly with respect to their metabolic activities and secretory phenotype, i.e. SASP, generating many pro-inflammatory cytokines, chemokines, growth factors and proteases (Coppe et al., 2008). These pro-inflammatory factors could induce and/or exacerbate aging-related pathogenesis in cardiovascular and neurodegenerative diseases (Chinta et al., 2014; Zhu et al., 2014b). Although the exact nature of senescent cell types in the aging brain is unclear so far, mounting evidence indicates that astrocytes and microglial cells potentially grow senescent with advancing age (Chinta et al., 2015; Salminen et al., 2011). The neurotoxic effect of astrocytes is mediated via SASP involving pro-inflammatory cytokines (e.g., IL-6), while their neuroprotective effect is attributed to neurotrophic growth factors (NGF) (Turnquist et al., 2016). Astrocytes of aged rat brains are positive for senescence-associated beta-galactosidase (SA-βGal), a senescence-associated biomarker (Dimri et al., 1995), and display the increased expressions of the senescence molecules like p21 and $p16^{INK4a}$ (Bitto et al., 2010). Microglia undergo telomere shortening with advancing age (Flanary and Streit, 2003), which can significantly lead to cellular senescence. However, the activation, but not senescent, phenotype of microglia was reported to be increased in aged brain (Lucin and Wyss-Coray, 2009). This activation is probably caused by senescent cell secreted pro-inflammatory cytokines. Whether the aged microglial cells are more sensitive to an inflammatory microenvironment is unknown so far (Streit et al., 2008), and there is little evidence for the role of microglia and astrocyte senescence in SASP-mediated inflammation (Blasko et al., 2004). Nevertheless, SASP pro-inflammatory factors promote a persistent low-level inflammatory microenvironment with advancing age that can profoundly affect

neighboring cells and systemic milieus, and significantly induce and/or enhance neurodegenerative diseases such as AD and PD (Franceschi and Campisi, 2014; Martinez et al., 2012). Although the precise molecular mechanisms of the SASP signaling pathways are not well known, activation of the DNA damage response (DDR), p38 mitogen-activated protein kinase (p38MAPK), and mechanistic target of rapamycin (mTOR) to trigger nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and CCAAT/enhancer binding protein (C/EBP) transcription factors are proposed to be involved in this process (Coppe et al., 2008; Freund et al., 2010, 2011). Importantly, activation of NF-kB signaling is a major trigger of SASP in senescent cells (Chien et al., 2011; Salminen et al., 2012). It was recently reported that Delta133p53 enhances the neuroprotective ability of aged and senescent astrocytes (Turnquist et al., 2016), supporting that the p53 isoforms may be the potential target for therapeutic intervention in neurodegenerative diseases.

3.2. Inflammasomes in age-related neurodegeneration

Activation of the inflammasomal signaling pathway triggers IL-1β and IL-18 productions by cleaving their precursors into active forms in activated microglial and $M_{Ø}$ cells (potentially, M1-like polarized) (Bezbradica et al., 2017; Martinon et al., 2002; Yang et al., 2016c). In brain trauma and ischemia-elicited brain acute inflammation, resident microglia, the cerebral $M_{Ø}$, and recruited blood-derived $M_{Ø}$ (Shechter et al., 2009) play an important role in the inflammatory process. In response to environmental stimulation, microglia and $M_{Ø}$ differentiate into two types—M1 and M2 macrophages with physiological and functional differences (Mantovani et al., 2004, 2002; Zhu et al., 2015). M1 cells clear debris and induce inflammation (Cohen and Mosser, 2013), whereby the inflammasomes (typically, NLRP3 and NLRP1) are activated to trigger increased production of pro-inflammatory factors such as IL-1β, IL-18, and iNOS (Goldmann et al., 2013; Zhu et al., 2014a). However, the M2 phenotype is closely involved in anti-inflammation via immune modulation (Mantovani et al., 2013; Miron et al., 2013; Sica and Mantovani, 2012). If NLRP3 becomes inactivated, the microglia and $M_{Ø}$ display M2 phenotype with increased IL-4 and Arg1, and decreased pro-inflammatory productions (Heneka et al., 2013). Both M1 and M2 polarizations of microglia and $M_{Ø}$ are essentially required for recovery from CNS injury (Yong and Rivest, 2009). There is a switch from an M1- to M2-dominant response, involving cleanup of brain cellular debris in the early stage and anti-inflammation at the later recovery stage of this process (Miron et al., 2013). In the chronic neuroinflammatory aging environment, the inflammasome-mediated inflammatory pathway also plays an instrumental role in causing and/or aggravating neuroinflammation (Singhal et al., 2014). NLRP3 polymorphisms were found to be significantly related with late-onset AD (Tan et al., 2013b).

NLRP3 in the microglia and $M_{Ø}$ in the brain could be potentially activated by pro-inflammatory cytokines which is secreted by senescent cells, possibly through the up-regulated NF-kB signaling pathway (Salminen et al., 2012). Therefore, NLRP3 activation-induced increase in IL-1β levels can be seen not only in acute infection, brain trauma, and ischemia, but also in the aged brain with chronic inflammation, such as in AD patients (Heneka et al., 2013; Saresella et al., 2016). Recently, a new stress-induced intra-neuronal inflammasome activation pathway (NLRP1/Casp1/Casp6) was reported in AD patients (VanItallie, 2017), in which NLRP1 activation triggers Casp1 activation to induce IL-1β maturation, while Casp1 activation also induces Casp6 activation to mediate axonal degeneration. It is evidenced that $NLRP1^{+}$ neurons in the AD brain were 25- to 30-fold higher than those in non-AD brains (Kaushal et al., 2015).

3.3. Exosome in age-related neurodegeneration

Exosomes are ~30–100 nm phospholipid bilayer membrane-enclosed microvesicles containing proteins and genetic information (Schneider and Simons, 2013). They can be secreted by various kinds of cells such as B lymphocytes, DCs and epithelial cells (Raposo et al., 1995, 1996; van Niel et al., 2001). Exosomes can mediate the communication between cells by transferring proteins, lipids and RNAs (mRNA and miRNA) (Chopp and Zhang, 2015). More and more studies showed that some neural cells, including astrocytes and neurons, also secret exosomes which contain not only the typical exosomal markers but also some neuron-specific components implying the important role of exosomes in central nervous system (Faure et al., 2006; Malm et al., 2016).

Rajendran and colleagues reported that exosomal proteins accumulate in the plaques of AD patients, indicating that exosomes may be involved in the pathogenesis of AD (Rajendran et al., 2006). It was recently recognized that exosomes can diffuse throughout the brain and may play a role in the dynamics of amyloid deposition in an AD mouse model (Zheng et al., 2017). Exosomes contains full length APP, C-terminal fragments (CTFs) of APP and some members of the secretase family of protease also localized in exosomes suggesting that exosomes may be another site for APP cleavage (Riancho et al., 2017; Sharples et al., 2008; Vingtdeux et al., 2007). Except of the full length APP and CTFs of APP, there is Aβ in exosomes of mouse brain as well (Mullins et al., 2017; Perez-Gonzalez et al., 2012). Furthermore, Dinkins et al. showed that exosome reduction in vivo is associated with lower amyloid plaque load in the 5XFAD mouse model of AD (Dinkins et al., 2014). These data support that exosomes loading with APP metabolites may contribute to amyloidogenesis. In addition to associating with Aβ formation, exosomes also contribute to accumulation of pathological tau proteins. Tau proteins can be secreted by M1C cells via exosomal release and exosome-associated tau is present in CSF samples from patients with mild AD (Saman et al., 2012). Both resource of tau can be phosphorylated at Thr-181 which is an established phosphotau biomarker for AD (Saman et al., 2012). A recent report demonstrated that microglia spread tau via exosome secretion and depletion of microglia and inhibition of exosome synthesis remarkably halt tau propagation (Asai et al., 2015). These results suggest that exosomes may play critical roles in the accumulation of pathological tau proteins in AD patients.

Exosomes can spread toxic α-Syn between neuronal and non-neuronal cells (such as astrocytes and microglia) and induce apoptosis, so they may pay a key role in the spread of α-Syn aggregates in the brain and the acceleration of pathological changes in PD (Chistiakov and Chistiakov, 2017; Russo et al., 2012; Shi et al., 2016; Stuendl et al., 2016). However, potential neuroprotective roles of exosomes in PD have also been reported (Wu et al., 2016). In addition, exosomes can deliver siRNAs and catalase to the brain, and have shown therapeutic effects in a PD mouse model (Hall et al., 2016). These features of exosomes in PD make them very attractive to develop novel diagnostic and therapeutic approaches.

More and more evidence showed that exosomes also involve in MS. Sbai et al. demonstrated that exosomes secreted by astrocytes contain metalloproteinases implying they may involving in BBB disruption during MS (Carandini et al., 2015; Sbai et al., 2010). Elevated plasma exosomes shed by endothelial cells have been documented in MS patients (Lee et al., 2016). Jy et al. showed that exosomes released by endothelial cells could enhance inflammation and increase transendothelial migration of monocytes in MS

by binding to and activating monocytes through CD54 (Jy et al., 2004). Furthermore, exosomes secreted by activated T cells contain the chemokine CCL5 and arachidonic acid which can promote the recruitment of monocytes and the expression of Mac-1 on monocytes and the expression of ICAM-1 on endothelial cells (Barry et al., 1998). The interaction of Mac-1 and ICAM-1 facilitate the transendothelial migration of monocytes (Saenz-Cuesta et al., 2014). In summary, these data collectively suggest that exosomes secreted during MS mainly promote the immigration of monocytes and lymphocytes through BBB and then accelerate the progression of MS.

There were relative rare reports about the role of exosomes in ischemic stroke and brain trauma. A recent study showed that the expression of microRNAs (miR) isolated from exosomes changes significantly after traumatic brain injury (Harrison et al., 2016). In this study the author found that the expression of miR-212 decreased, while miR-21, miR-146, miR-7a, and miR-7b were significantly increased with injury (Harrison et al., 2016). It is also reported that circulating miR-30a and miR-126 levels are markedly down-regulated in patients with ischemic stroke (Long et al., 2013). These results indicate that miRs may be potentially used as biomarkers for ischemic stroke and brain trauma. Exosomes are suitable for small functional molecule delivery and there are more and more research focusing on the delivery of miRs via exosomes for the treatment of ischemic stroke (Zomer et al., 2010). Xin et al. reported that exosomes from mesenchymal stromal cells mediate the miR-133b transfer to astrocytes and neurons, which regulate gene expression, subsequently benefit neurite remodeling and functional recovery after stroke (Xin et al., 2013b). Systemic administration of exosomes released from mesenchymal stromal cells promotes functional recovery and neurovascular plasticity after stroke in rats (Xin et al., 2013a).

3.4. Inflammaging

A low-grade, but above base-line, and sustained chronic inflammation associated with aging is termed “inflammaging” (Brunner et al., 2011; De Martinis et al., 2005; Franceschi et al., 2000, 2007; Freund et al., 2010). It is a high risk factor for age-related cardiovascular and neurodegenerative diseases, as well as late-life cancer (Frasca and Blomberg, 2016). This process can be driven by persistent exogenous and endogenous oxidative stress. Although the etiology is not fully understood, inflammaging has been attributed to a combination of cellular senescence-induced SASP that releases low levels of pro-inflammatory cytokines, such as IL-6, TNF-α, IL-1β, and CRP (Campisi, 2011; Freund et al., 2010; Olivieri et al., 2013, 2012), and the persistent activation of immune cells by chronic viral infections like CMV (Brunner et al., 2011; Franceschi et al., 2007; High et al., 2012; Licastro et al., 2005; Nikolich-Zugich, 2008) and/or self-reactivity of autoimmune cells (Coder et al., 2015; Xia et al., 2012).

Soluble TNF-α has been implicated in the pathogenesis of PD patients and was shown to induce ceramide accumulation in dopaminergic neurons leading to endoplasmic reticulum stress, loss of mitochondrial membrane potential, and caspase-3 activation (Martinez et al., 2012). These effects could be remarkably attenuated with inhibitors of TNF-α (Martinez et al., 2012). Additionally, studies have found that increased peripheral cytokines, like serum IL-6 and IL-1β, correlates with AD (Licastro et al., 2005), while other studies have found that there is no correlation between peripheral inflammation and AD (Julian et al., 2015). More studies needs to be performed to determine the extent to which neurodegenerative diseases are impacted by systemic inflammation and to what extent systemic inflammation is a result of neuroinflammation in the future.

In addition to the persistent activation of “foreign-reactive” immune cells by chronic infections, we found that autoreactive T cells significantly contribute to the emergence of an inflammatory state with advanced age. Thymic involution, one of the natural features for the aging process, is sufficient to stimulate chronic inflammation. Using a conditional knock-out of *FoxN1* to induce thymic involution, we showed that recently emigrated T cells from the atrophied thymus could significantly react to self-antigens and became functionally activated in the periphery, which ultimately led to inflammatory infiltrates in non-lymphoid organs and increased levels of the pro-inflammatory cytokines like TNF-α and IL-6 (Coder and Su, 2015; Coder et al., 2015).

Chronic neuroinflammation during aging is both a part of broader systemic inflammaging and a result of locally activated resident inflammatory cells (microglia) in the brain and the migration of innate and adaptive hematopoetic cells, such as blood-derived $M_{\emptyset}$ into the brain (Fulop et al., 2016). Enhanced local pro-inflammatory factors have been shown to exacerbate neurodegenerative conditions. In particular, the NLRP3 inflammasome, which controls the expression of active IL-1 family pro-inflammatory cytokines, play an important role in the development of AD, and polymorphisms in the NLRP3 gene have been significantly linked with late-onset AD (Tan et al., 2013a). Using the APP/PS1 mouse model for AD, Heneka et al. showed that the NLRP3 inflammasome in microglia is closely involved in AD pathogenesis (Heneka et al., 2013). In $Nlrp3^{-/-}$ or $Casp1^{-/-}$ mice, AD associated cognitive impairments in the respects of object recognition, memory and long-term potentiation were reversed. Interestingly, although NLRP3 activation and IL-1 secretion would normally signal an activated and functional microglia, phagocytosis of Aβ plaques was increased in $Nlrp3^{-/-}$ mice. They found that NLRP3 activation skews microglia toward an inflammatory M1 phenotype which is associated with inducible nitric oxide synthase (iNOS) expression and tyrosine nitration of Aβ which can lead to its aggregation and formation of new plaques (Kummer et al., 2011). However, removal of the NLRP3 inflammasome shifts microglia toward the anti-inflammatory M2 phenotype associated with wound healing and decreased Aβ deposition in the APP/PS1 mice (Heneka et al., 2013). These findings identified the NLRP3 inflammasome and inflammatory mediators (IL-1β) as key therapeutic targets for the treatment of AD. All these evidence support that aging immune system contributes to the aging-related neurodegenerative diseases through multiple pathways (Fig. 2).

4. Role of complement system in neurodegenerative diseases

Complement system, one of the major parts in innate immunity, plays pivotal roles in defending against pathogens and in maintaining host homeostasis. Complement system is composed of more than 40 proteins, including soluble proteins produced mainly by the liver and membrane proteins expressed on cell surface (Hill et al., 2005). The complement system can be activated by three different pathways, including the classical pathway, the alternative pathway and the lectin pathway (Merle et al., 2015). More and more evidence showed that the complement system has great influence on the progression of neurological diseases. Some complement elements significantly contribute to the neurodegenerative disease and injury, whereas some play a protective role during neurodegeneration (Table 1). In this section, we will summarize the current understanding on the roles of complement system in the pathogenesis of ischemic stroke, AD and PD.

4.1. Role of complement system on ischemic stroke

The involvement of complement system in ischemia/reperfusion injury was first discovered by Hill and Ward in 1970s. It is generally accepted that the complement system plays pivotal roles in the process of ischemic stroke. The activation of the complement system was found in plasma or serum samples of ischemic stroke patients. The plasma levels of C3a, C4d and SC5b-9 were acutely increased following human ischemic stroke, while the plasma level of C5a showed delayed elevation 7–14 days after cerebral ischemia (Mocco et al., 2006b; Szeplaki et al., 2009). Other studies showed that the level of terminal SC5b-9 complement complex is positively correlated with the clinical severity of stroke (Szeplaki et al., 2009). Importantly, the presence of complement components in the post-mortem brain tissues of stroke patients has also been verified. More complement components C1q, C3c and C4d were detected in ischemic lesions and the expression of complement regulators CD59 and CD55 were decreased in ischemic lesions (Pedersen et al., 2009), indicating the deposition of complement components combined with reduction of complement regulators is a potential cause for tissue damage of stroke patients. These results collectively demonstrated the complement system play an important role in the process of ischemic stroke.

Next, we will discuss the role of individual complement components in the progression of ischemic stroke. The roles of C1q, the initiator of classical pathway, on ischemic stroke is complicated. It has been reported that the accumulation of C1q occurs between 3 and 6 h post-ischemia and C1q protein was co-localized with neural cell bodies as well as necrotic cellular debris (Mack et al., 2006). In addition, a dramatic and widespread increase of C1q biosynthesis by microglia 24 h after ischemic insult was observed and the C1q functional activity in the cerebrospinal fluid was also significantly enhanced (Schafer et al., 2000). Importantly, the administration of C1q inhibitor showed a protective role by efficiently reducing ischemia-reperfusion injury (De Simoni et al., 2003). However, Mocco et al. reported that C1q-deficient mice have no protective role after transient focal cerebral ischemia (Mocco et al., 2006a). Conversely, neonatal C1q-deficient mice showed significantly less neurofunctional deficit and activation of circulating leukocytes compared with WT mice (Ten et al., 2005). The discrepancy role of C1q between adult and neonatal mice may be due to the different increase of C1q expression in the CNS of adult and neonatal mice (Stephan et al., 2013).

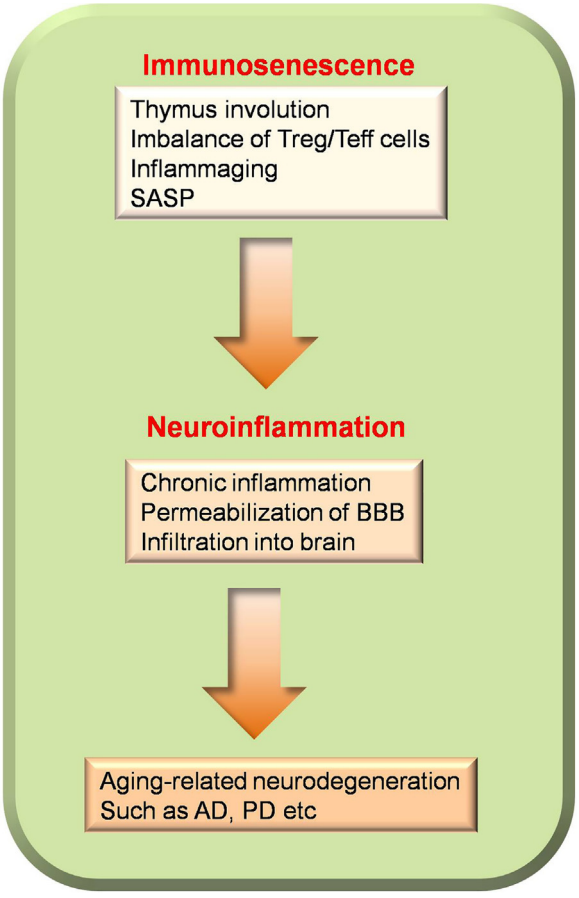

Fig. 2. Immunosenescence contributes to aging-related neurodegenerative diseases.
Thymus involution, imbalance of Treg/Teff cells, inflammaging and SASP all lead to neuroinflammation. Neuroinflammation results in permeabilization of BBB and infiltration of immune cells into brain which eventually cause aging-related neurodegeneration, such as AD, PD etc.

According to recently studies, mannan-binding lectin (MBL), the initiator of lectin pathway, plays detrimental roles during ischemic stroke. Cervera et al. demonstrated that genetic MBL-deficiency is associated with a better outcome after acute stroke in mice and humans (Cervera et al., 2010). Another group showed the similar results that MBL deficiency is associated with smaller cerebral infarcts in patients receiving conservative treatment (Osthoff et al., 2011). MBL-deficient mice are protective from both transient and permanent ischemic injury and inhibition of MBL by polyman2 and anti-MBL-antibody significantly improves neurological deficits (Orsini et al., 2012). These results collectively indicated that lectin pathway plays an important role in the pathophysiological changes of ischemia/reperfusion injury and that inhibition of MBL may be a potential approach for the treatment of ischemic stroke patients.

Compared with classical pathway and lectin pathway, there are few reports about the role of alternative pathway of complement activation on the progression of ischemic stroke. Mice deficient in factor B or mice treated with alternative pathway inhibitor CR2-fH have improved outcomes after 60-min middle cerebral artery occlusion and 24-h reperfusion (Elvington et al., 2012). Because factor B deficient or CR2-fH treated mice, but not C1q or MBL deficient mice, have detectable C3d deposition in the ipsilateral brain (Elvington et al., 2012), the alternative pathway alone may be not sufficient to efficiently initiate complement activation. Recently, it was reported that, in addition to reducing the activation of complement pathway, inhibition of alternative pathway has the benefits to promote the expression of neurogenesis markers, enhance neuronal migration and increase VEGF expression (Alawieh et al., 2015). Thus, selective inhibition of alternative complement pathway may provide self-limiting inhibition of complement activation and reduce acute injury after stroke (Alawieh et al., 2015).

4.2. Role of complement system on AD and PD

The role of complement system on AD was found since 1980s. Up to date, the correlation of complement components with AD has been widely investigated. The different complement components display different roles during various pathological stage of AD (Michailidou et al., 2015). The *in vitro* and *in vivo* studies showed that C1q has a protective role during the early stage of AD by enhancing the viability of neurons and preventing toxicity induced by oligomeric forms of Aβ (Benoit et al., 2013; Pisalyaput and Tenner, 2008). In the early stage of disease progression in a transgenic mouse model of AD, C1q induces the expressions of LRP1B and GPR6 which are beneficial for neuronal survival and neurite outgrowth (Benoit et al., 2013). Conversely, in the late stage

Table 1
The role of complement system in neurodegenerative diseases.

Disease types	Complement components	Involved pathways	Function	Detrimental/ Beneficial
ischemic stroke	C1q	Classical pathway	C1q accumulates in neural cell bodies and necrotic cellular debris and C1q inhibitor has a protective role after ischemic	Detrimental
	MBL	Lectin pathway	MBL deficiency or inhibition of MBL have a protective role after ischemia/reperfusion injury	Detrimental
	Factor B	Alternative pathway	Factor B-deficient mice have improved outcomes after middle cerebral artery occlusion and reperfusion; Inhibition of alternative pathway promotes neurogenesis	Detrimental
AD	C1q	Classical pathway	C1q enhances the viability of neurons and prevents toxicity induced by oligomeric forms of Aβ	Beneficial in early stage
			C1q exerts a detrimental effect on neuronal integrity in late stage of AD	Detrimental in late stage
	C3	Alternative pathway	Prevent the deposition of Aβ	Beneficial
	C5a	Terminal pathway of complement system	Inhibition of C5a-C5a receptor signaling reduces the pathological alterations and improves cognition	Detrimental
PD	Many components (C1q, C3, C3d, C4d, C7 and C9) of complement system involve in PD		The complement system mediated inflammation may have a role for neurodegeneration in PD	Detrimental

of AD progression, C1q-deficient mice showed significantly lower level of activated glia surrounding the plaques and reduction of pathology compared with WT mice, indicating C1q exerts a detrimental effect on neuronal integrity in late stage (Fonseca et al., 2004).

Increased C3 level in the cerebrospinal fluid of AD patients and C3 expression in brain in aged AD mice were reported (Daborg et al., 2012). In APP transgenic mice, the expression of C3 substantially elevated during amyloid formation (Reichwald et al., 2009). Inhibition of C3 activation leads to 2- to 3-fold higher deposition of Aβ by using hAPP/sCrry mouse models (Reichwald et al., 2009). Aged C3-deficient APP transgenic AD mice showed significant changes of up to two folds increased total Aβ and fibrillar amyloid plaque burden in midfrontal cortex and hippocampus compared with C3-sufficient APP transgenic AD mice (Maier et al., 2008). These results indicate that C3 plays a beneficial role in plaque clearance and neuronal health.

In contrast to C3, the terminal components of complement system exert harmful effects during AD progression. Loeffler et al. reported that the presence of C9 increased 2.5- to 3-fold in AD patients than control group (Loeffler et al., 2006). The expression of C5a receptors CD88 and C5L2 increased during AD progression and inhibition of C5a-C5a receptor signaling decreased the pathological alterations and improved cognition in transgenic mouse models of AD (Fonseca et al., 2013). These results showed that pharmacological inhibition of C5a-C5a receptors may be a potential way for the treatment of AD.

In contrast to many studies on the roles of complement system in AD, there are fewer reports regarding the involvement of complement system in PD. The complement components C3d, C4d, C7 and C9 were found in intra- and extraneuronal Lewy bodies and dendritic spheroid bodies of PD patients (Yamada et al., 1992). Additionally, elevated levels of membrane attack complex (MAC) and C3 have been observed in the cerebrospinal fluid and SN of PD patients (More et al., 2013). The increased levels of C1q was observed in PD patients and mouse models of PD indicating that C1q may be involved in the progression of PD through microglial-mediated synaptic injury (Depboylu et al., 2011). However, a recently report showed that C1q variation is not a major contributor to cognitive impairment in PD making the role of C1q during PD is complicated (Carbutt et al., 2015). Pentraxin could activate complement system by binding to C1q. Glial cells in the CNS may be the source of pentraxin. Increased plasma pentraxin 3 level was observed in PD patients (Yin et al., 2009) and the expression neuronal pentraxin receptor in the cerebrospinal fluid of PD patients also increased (Yin et al., 2009). Overall, the complement system mediated inflammation may have a role for neurodegeneration in PD. It is clear that more studies need to be done to uncover the complicated roles of complement system in the progression of PD.

5. Role of T cells in neural de/re-generation during aging

T cell pool in the periphery is highly heterogeneous in respects of the T cell subpopulations, antigens-recognizing specificity, and the profiles of cytokines and chemokines they potentially produce. Actually, the peripheral T cell compartment displays a high degree of plasticity and functional shifting over the life span of an individual, including an age-related shift towards memory and senescent $CD28^{null}$ T cells (Goronzy et al., 2013), accumulation of Tregs, decreased T cell receptor (TCR) repertoire diversity, and enhanced frequency of autoreactive T cells in the elderly (Coder et al., 2017; Goronzy and Weyand, 2003). In this chapter, we will discuss the roles of T cells in neuron degeneration and regeneration during aging (Fig. 3 and Table 2).

5.1. T cells developed in the aged thymus

The thymic aging and involution, which begin as early as in adolescence, are one of the key reasons for many of the age-related peripheral T cell changes (Gui et al., 2012). The thymus atrophies at a rate of about 3% per year, and only less than 15% of their thymic tissue remains in individuals over 50 years old (Goronzy and Weyand, 2003). Thymic involution remarkably results in the deterioration of the thymic epithelium and a severe decline of naïve T cell output, which subsequently leads to less TCR diversity and a obvious shift towards memory and senescent T cells (Goronzy et al., 2013). These alterations definitely result in the ineffectiveness of host cellular immunity in response to emerging infections and vaccinations. Due to the autoreactive T clones could not be efficiently depleted in the involuted thymus and are instead released into the periphery, thymic involution is also closely related with increased susceptibility to autoimmune disorders during aging. Patients with RRMS display premature thymic involution with a significant decline in naïve T cells and remarkably increased senescent T cells in the periphery (Duszczyszyn et al.,

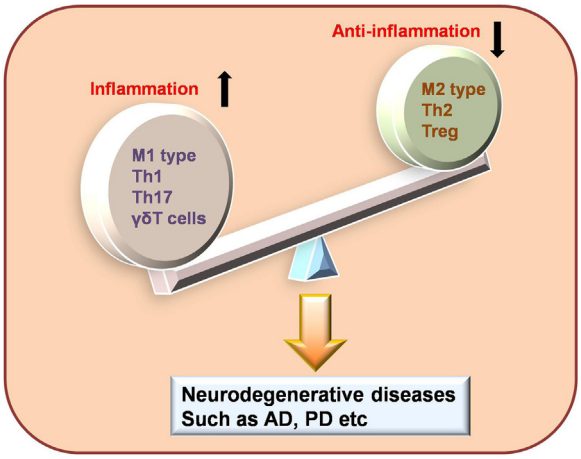

Fig. 3. The detrimental and beneficial roles of different immune cells in neurodegenerative diseases.
The M1 type macrophages, Th1, Th17 and γδ T cells release pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-17, GM-CSF etc and play detrimental roles in neurodegenerative diseases. The M2 type macrophages, Th2 and Treg cells release anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β etc and play beneficial roles in neurodegenerative diseases.

2010). Our recent studies showed that thymic involution is closely related with the elevated chronic inflammation (Coder et al., 2015), which is not an overt autoimmune disease, as it lacks obvious clinical manifestations, but a condition that significantly exacerbates the severity, incidence, and mortality of many age-related inflammatory diseases. Using a mouse model of accelerated thymic involution, we found that the involution of the thymus leads to the elevated output of autoreactive T cell clones from the thymus (Coder et al., 2017). These released autoreactive T cells are activated upon encountering self-antigens in the periphery and infiltrate into non-lymphoid tissues, and lead to the increased levels of inflammatory cytokines such as IL-6 and TNF-α.

5.2. Role of T cell subsets in age-related neurodegenerative diseases

In this section, we will mainly summarize the involvement of the different subsets of T cells in the pathogenesis of age-related neurodegeneration. We will highlight the pathological effects of T helper 1 (Th1), Th17, and cytotoxic T lymphocytes (CTL) in AD, PD, MS, the myelin oligodendrocyte glycoprotein (MOG) peptide-induced experimental autoimmune encephalomyelitis (EAE) mouse model for MS, and amyotrophic lateral sclerosis (ALS).

5.2.1. Th1 cells

Th1 cells are a subset of $CD4^+$ Th cells expressing the master transcription factor *T*-bet and secreting Type 1 cytokines (most notably IFN-γ and TNF-α) (Romagnani, 2014). They can activate innate immune cells and cytotoxic $CD8^+$ T cells, and induce IgG class switching in B cells (Romagnani, 2014). Th1 infiltration into the CNS has been recognized in many neurodegenerative conditions, including AD, PD, the human immunodeficiency virus (HIV)-caused neurodegeneration, and MS. The pathogenesis of these neurodegenerative diseases are predominantly associated with the elevated inflammation driven by the release of pro-inflammatory cytokines. Much of the inflammatory damage associated with Th1 cells can be attributed to the IFN-γ and TNF-α induced functional polarization of $M_ø$ and microglia toward the inflammatory M1-like phenotype. The classical activation of the pro-inflammatory and highly phagocytic M1 microglia would significantly aid in the progression of neurodegenerative diseases in AD and PD by promoting neurotoxicity and extracellular matrix damage (Sanchez-Guajardo et al., 2013).

T-bet$^+$ Th1 cells have been found in human AD patients and in experimental animal models of AD (Baglio et al., 2013). In a rat model of AD, injection of $A\beta_{1-42}$ into the hippocampus resulted in T cell infiltration into the brain parenchyma and the up-regulated expressions of *T-bet* and IFN-γ (Zhang et al., 2013). This response would increase in Aβ plaque formation and impaired cognitive ability. Furthermore, it is reported that CNS-infiltrating T cells secrete large amounts of IFN-γ and IL-17 in a transgenic mouse AD model in which amyloid precursor protein and presenilin 1 (APP/PS1) were over-expressed. The released IFN-γ then leads to microglial activation and enhances Aβ plaque burden, resulting in impaired cognitive function (Browne et al., 2013). Administration of anti-IFN-γ antibody in the APP/PS1 mouse model and immunosuppressive TGF-β in the inducible $A\beta_{1-42}$ rat model was able to ameliorate the Th1-mediated effects on Aβ plaque burden and cognitive impairment (Browne et al., 2013; Chen et al., 2015). Thus, Th1 cells play an important role in AD pathology.

However, it should be noted that Th1 cells do not always play harmful roles in neurodegenerative diseases. Twenty-eight days post intracerebroventricular (ICV)-injection into an APP/PS1 mice

Table 2
Role of T cells in neural de/re-generation.

Cell type	Main cytokines	Function	Detrimental/ Beneficial
Th1 cells	IFN-γ, TNF-α	Polarize $M_ø$ and microglia to M1 which exacerbate AD and PD by enhancing neurotoxicity and extracellular matrix damage	Detrimental
Th17 cells	IL-17, IL-22, GM-CSF	IL17 and IL22 activate IL17 and IL22 receptors on BBB endothelium leading to its disruption and permeabilization, GM-CSF and IL17 drive the production of granulocytes and monocytes implicating in MS and EAE	Detrimental
$CD8^+$ T cells	IFN-γ	Activation and IFN-γ production of $CD8^+$ T cells implicate in MS, AD, PD and ALS	Detrimental
γδT cells Vγ4γδT cells	IL-17, GM-CSF, IL-21, IL-23	IL17 and GM-CSF recruit neutrophils in a post-stroke setting, IL-21 and IL-23 restrain the function of Tregs and exacerbate pathology	Detrimental
Vγ1γδT cells	IL-4, IL-5, CCR5 ligands	IL-4 and IL-5 have the function of anti-inflammatory, CCR5 ligands promote Treg differentiation	Beneficial
Tregs	TGF-β, IL-1, IL-4	Suppress activated microglia and pathogenic T cells	Beneficial
Th2 cells	IL-4, IL-5, IL-13	Suppress the Th1-driven immune response and microglial activation in AD-, PD-, and HIV-associated dementia	Beneficial
brain antigens-specific $CD4^+$ T cells	IFN-γ	Facilitate injury recovery by control blood-derived $M_ø$ traffic through the CP gate and into the CNS in an IFN-γ signaling- dependent manner	Beneficial

of AD, Aβ-specific Th1 cells reduce Aβ plaque load, and do not impact apoptosis, but rather slightly enhance neurogenesis (Fisher et al., 2014). These results are in contrast to the Th1-mediated pathogenesis observed with Aβ-specific Th1 cells injected intravenously (i.v.) and observed ~21 days post injection (Browne et al., 2013). Thus, it seems that the route of migration and temporal factors may play different roles in neurodegeneration, that is autoimmune T cells may be beneficial or harmful. Nevertheless, it is general conclusion that Th1 cells participate in the pathogenesis of neurodegenerative disorders.

5.2.2. Th17 cells

Th17 cells are a subset of $CD4^+$ Th cells characterized by the expression of the master transcription factor RORγt and a distinctive cytokine gene expressing profile including IL-17 and IL-22 (Annunziato et al., 2013). Th17 cells have double-edged sword function. They are predominantly involved in antimicrobial immunity by activating and recruiting inflammatory neutrophils with IL-17 and stimulating epithelial cells to produce antimicrobial peptides with IL-22, as well as in the pathogenicity of many neurodegenerative diseases including AD and PD (Saresella et al., 2011). However, their roles in the development of neurodegenerative disease and neuroinflammation are best understood in MS and EAE. Autoreactive myelin-specific Th17 cells are activated in the periphery and then translocate into the CNS. Th17 secreted cytokines IL-17 and IL-22 bind and activate IL-17 and IL-22 receptors present on the BBB endothelium, leading to its disruption and permeabilization of BBB (Kebir et al., 2007), and the subsequent inflammation driven destruction of myelin and eventually axons. The precise molecular mechanisms facilitating Th17-mediated neuronal damage in MS are not fully understood today. Recent studies showed that recruitment of inflammatory neutrophils and monocytes into the CNS and even direct contact of Th17 cells with neurons through the repulsive guidance molecule-a (RGMa) would lead to neuronal death. Many experiments demonstrate that autoreactive Th17 cells lead to the occurrence of MS (Rumble et al., 2015; Tanabe and Yamashita, 2014), including adoptive transfer of MOG-stimulated Th17 cells into SLJ mice resulting in an EAE mouse model. Interestingly, ablating production of the classical Th17 cytokines IL-17 and IL-22, either through genetic knockout or neutralizing antibody, only partially reduces the severity of disease, indicating that atypical Th17 cytokines might be additional drivers of MS and EAE. This speculation led to the identification of Th17 production of granulocyte-macrophage colony-stimulating factor (GM-CSF) to be essential in the Th17 cells mediated encephalogenicity and the induction of EAE (Codarri et al., 2011). GM-CSF drives the development of stem cells into granulocytes (including neutrophils) and monocytes, both of which have been implicated in MS and EAE pathology. GM-CSF production by Th17 cells is induced via IL-23 produced by APCs, including perivascular cuff dendritic cells and microglia (Li et al., 2007), which in turn forms a pathogenic regulatory feedback loop where GM-CSF induces APCs to release more IL-23 (El-Behi et al., 2011).

5.2.3. $CD8^+$ CTLs

$CD8^+$ CTLs recognize antigens presented on MHC Class-I (MHC-I) (Shresta et al., 1998). Most notably, $CD8^+$ T cells can directly kill target cells through apoptotic Fas receptor-Fas ligand (FasL) interaction or by releasing enzymes like granulysin, perforin, and granzyme, giving rise to the name CTL (Harty et al., 2000). CTLs primarily kill target cells infected with virus, intracellular bacteria or parasites. However, they have also been implicated in the pathogenesis of neurodegenerative diseases. In fact, $CD8^+$ T cells outnumber and clonally expand more frequently than their $CD4^+$ counterparts in MS lesions (Goverman et al., 2005). Studies have shown that the antigen-specific $CD8^+$ T cells occur in CNS at a higher frequency than $CD4^+$ T cells (Crawford et al., 2004), and the adoptive transfer of $CD8^+$ T cells specific for myelin basic protein $(MBP)_{79-87}$ into wild-type mice induced a demyelinating disease with features similar to MS (Goverman, 2009; Huseby et al., 2001). Furthermore, $CD8^+$ T cell activation and IFN-γ production have been implicated in AD microstructural tissue damage and neuropsychological defects (Baglio et al., 2013; Lueg et al., 2015). Additionally, autopsies of PD patients have shown that $CD8^+$ T cells located in areas of the substantia nigra in close proximity with activated microglia and degenerating neurons (Brochard et al., 2009). Once again, $CD8^+$ T cells appear more frequently in the substantia nigra of PD patients than their $CD4^+$ counterparts (Brochard et al., 2009).

In addition, $CD8^+$ CTLs are also involved in the pathobiology of other neurodegenerative diseases. For example, in ALS neuronal damage the majority of the infiltrated lymphocytes found in the spinal cord and the lesion are $CD8^+$ CTLs (Kawamata et al., 1992). Interestingly, the locally increased $CD8^+$ CTLs are typically only detected in the late stages of ALS, whereas $CD4^+$ T cells are detected earlier, suggesting that $CD4^+$ T cells may mediate the activation of $CD8^+$ CTLs, possibly related to secondary injury and subsequent disease progression (Anderson et al., 2014).

5.2.4. γδT cells

Unlike $CD4^+$ and $CD8^+$ T cells that contain αβTCR, γδT cells contain γδTCR and do not always require MHC binding stimulation. γδT cells have been shown to infiltrate the brain and lead to post-stroke neurodegeneration (Shichita et al., 2009). The post-stroke immune response occurs much sooner than the 7–10 days normally required for an adaptive immune response. However, γδT cells can respond in the absence of TCR binding and costimulatory signals, resulting in much more rapid activation than for their αβTCR counterparts, and are the primary producers of IL-17 and recruiters of neutrophils in a post-stroke setting (Gelderblom et al., 2014; Swardfager et al., 2013). Similar to $CD8^+$ T cells, fully mature γδT cells can produce the cytolytic enzyme granzyme B, as well as FasL, allowing for direct cytolytic activity (Swardfager et al., 2013). Furthermore, IL-17-producing γδT cells release both IL-21 and IL-23, which have been shown to restrain regulatory T cell suppression of $CD4^+$ T effector cells, thereby exacerbating pathology by maintaining a sustained immune response during stroke (Peruzzotti-Jametti et al., 2014).

The role of γδT cells in the pathogenesis of MS is controversial. Depletion of γδT cells resulted in the acceleration of disease onset as well as relapse in B10.PL mice, suggesting a protective role for γδT cells during MS. Similarly, γδ TCR knockout in B10.PL mice resulted in the inability to resolve EAE disease symptoms, leading to a long-term chronic disease course (Ponomarev and Dittel, 2005; Ponomarev et al., 2004). One potential mechanism of γδT cell suppression during MS is Fas-FasL mediated killing of antigen-specific T cells (Ponomarev and Dittel, 2005). On the other hand, monoclonal antibody depletion or γδ TCR knockout in SJL or C57BL/6 mice reduced the severity and onset of EAE, suggesting that γδT cells are pathogenic and their pathogenicity may be affected by mouse strains or genetic variability (Rajan et al., 1996; Spahn et al., 1999). One likely explanation for the contested role of γδT cells during CNS inflammation is their differentiation into subsets, including regulatory γδT cells. Blink et al. identified two distinct subsets of γδT cells as defined by their variable TCR regions, Vγ1 and Vγ4. Vγ4γδT cells are pathogenic with a similar cytokine profile to Th17 cells including IL17, L-22, and GM-CSF. Vγ1 γδT cells are increased to 15 − 20% of the IL-17-producing cells in the CNS in EAE (Blink et al., 2014). Furthermore, IL-17-producing γδT cells that express CD16 have been found in the CSF of MS patients in relapse (Schirmer et al., 2013). These γδT cells can be

directly cytotoxic to oligodendrocytes (Saikali et al., 2007), which is facilitated by CD16 (Fc gamma receptor) binding to antibody-coated oligodendrocytes leading to antibody-dependent cell-mediated cytotoxicity (Chen et al., 2008). While γδT cells do not require TCR stimulation, the oligoclonal expansion of a restricted TCR repertoire in MS lesions suggests that these γδT cells may be autoreactive towards specific self-antigens (Sobel and Kuchroo, 1992; Wucherpfennig et al., 1992). Conversely, Vγ1 γδT cells play a protective role during EAE, by producing CCR5 ligand and promoting Treg cell differentiation (Blink et al., 2014). Additionally, Vγ1 γδT cells produce more anti-inflammatory Type-2 cytokines including IL-4 and IL-5 (Dong et al., 2014).

5.3. Potential beneficial roles of T cells in age-related neurodegeneration

It should be recognized that not all T cell functions and T cell setsets are detrimental during neurodegeneration process (Coder et al., 2017), some T cell subsets are even beneficial for neuroregeneration and repair (Fig. 3). We herein summarize the beneficial effects of T cell subsets such as Tregs, and Th2 cells during neuroinflammatory conditions associated with various neurodegenerative conditions including ALS, MS, PD, and AD.

5.3.1. Tregs

The development of $CD4^+CD25^+Foxp3^+$ Tregs differs from that of other $CD4^+$ T subsets in many respects. They can differentiate into Tregs either in the thymus (termed as to tTregs) or during the activation in the periphery via TGF-β induction (termed as to pTregs) (Abbas et al., 2013; Zhang and Zhao, 2007). Tregs primarily act to inhibit T effector cells to reduce the immune response in both auto- and foreign-source inflammation. They control the immune response through myriad mechanisms, acting on both T effectors and APCs (Josefowicz et al., 2012; Yi et al., 2006). Furthermore, Tregs can also induce the protective M2 macrophage/microglial phenotype (Hu et al., 2012; Liu et al., 2011). In turn, IL-10-producing M2 microglia have the ability to induce antigen-specific Tregs in EAE model (Zhang et al., 2014). It is also recognized that the impaired Tregs were present in aging mice and elderly (Hou et al., 2017; Zhao et al., 2007). The changed Tregs may be relevant to many age-related diseases such neurodegenerative diseases.

Tregs play a great role in slowing down disease progression and decreasing the severity of the pathogenesis in ALS mice by reducing pro-inflammatory cytokine levels and attenuating microglial activation (Beers et al., 2011). This is achieved by suppression of activated microglia and pathogenic T cells via TGF-β, IL-10-, and IL-4-expressing Tregs (Beers et al., 2011; Xie et al., 2015). However, Tregs, levels of FoxP3 protein expression, and TGF-β mRNA are significantly reduced in patients with rapidly progressing ALS, and these low levels are accurate indicators of disease progression (Henkel et al., 2013).

A functional Treg deficiency appears to be significantly associated with MS as the peripheral blood of relapsed MS patients shows a reduced percentage of Tregs and a multifold decrease in Treg/Th17 ratio compared to healthy controls (Jamshidian et al., 2013). Although newly generated naïve $CD4^+CD25^+FoxP3^+CD45RA^+$ Tregs have strong suppressive capabilities in MS, they are significantly reduced in MS patients (Schwarz et al., 2013), while memory $CD4^+CD25^+FoxP3^+CD45RA^-$ Tregs are linked to Treg dysfunction (Haas et al., 2007). The inability of the memory Treg pool, with diminished TCR repertoire diversity, to inhibit MS inflammation indicates the requirement for antigen-specific control of autoimmune T cell responses (Haas et al., 2007). Another Treg subset, PD-1^- Tregs, have the highest suppressive capacity than other populations in Tregs. Patients with severe AD have fewer PD-1^- Tregs than those with mild cognitive impairment, suggesting a critical role for Tregs-mediated immunosuppression in controlling AD severity (Saresella et al., 2010).

Tregs have been shown to confer neuronal protection and their frequency is elevated in the elderly. However, they are unable to control neurodegenerative disease in the elderly, indicating that Treg functionality and/or migration into the CNS might be impaired in neurodegenerative disease in the elderly. In fact, Tregs taken from the peripheral blood of MS patients showed the poor ability to inhibit T effector cell proliferation (Viglietta et al., 2004). While Tregs can be detected in both the cerebrospinal fluid (CSF) and peripheral blood of MS patients, their absolute cell numbers in MS brain lesions were extremely low or even undetectable, suggesting that Treg migration into the brain is impaired or Tregs rapidly undergo apoptosis in MS lesions (Fritzsching et al., 2011). Healthy Tregs have the ability to migrate across the human brain endothelium *in vitro*. However, the migratory capability of Tregs in RRMS patients was significantly impaired (Schneider-Hohendorf et al., 2010).

Further complicating the issue is the balance of immunosuppressive Tregs and the pathogenic Th17 subset implicated in many neurodegenerative diseases. Treg differentiation and maintenance is facilitated by TGF-β, particularly, autocrine production of TGF-β. However, Th17 differentiation is mainly facilitated by a combination of TGF-β and IL-6, where IL-6 is abundant in neuroinflammatory conditions. Even more complicate, Tregs can be converted into inflammatory Th17 cells in some cases thus accounting for the lack of Treg efficacy during neuroinflammatory diseases mediated by Th17 cells (Zheng, 2013). The dynamic alterations in these factors shape the balance of Treg and Th17 subpopulations during neurodegeneration.

5.3.2. Th2 cells

$CD4^+$ Th2 cells that produces Type-2 cytokines driven by the master transcription factor GATA3 also have the neuroprotective properties. The predominate role of Th2 cells is to help control extracellular parasitic infections by promoting humoral immunity through the production of signature antibody class switching cytokines IL-4, IL-5, and IL-13. These cytokines serve an additional anti-inflammatory function, and are able to suppress the Th1 IFN-γ-driven immune response. In the Th1/Th2 balance paradigm, Th1 cytokine IFN-γ significantly inhibits Th2 cell proliferation, while Th2-derived IL-10 blocks Th1 cell proliferation. In harmonious balance in young adults, reports show that the Th1/Th2 ratio may become biased toward a Type-2 microenvironment with advancing age (Alberti et al., 2006). This Type-2 microenvironment likely emerges in order to control the aged microenvironment that is prone to pro-inflammatory autoimmune disorders. Additionally, Th2 cells have strong neuroprotective effects in neurodegenerative diseases. For example, induction of EAE in GATA3-transgenic mice that overexpress GATA3, a key transcription factor required for Th2 differentiation, demonstrated that a Th2-skewed immune response (increased IL-4, and IL-10, decreased IFN-γ, and IL-17) significantly delays the onset of disease with a less severe maximum clinical score compared to WT control mice (Fernando et al., 2014). Th2 cells are capable of inhibiting microglial inflammatory responses in the presence of many neuro-pathological stimuli from AD-, PD-, and HIV-associated dementia (Roy and Pahan, 2013). In MS, Th2 cells are able to suppress microglial activation in a cell-to-cell contact manner, ultimately inhibiting the production of IL-1β and nitric oxide. Additionally, MBP-primed Th2 cells are capable of inducing neurotrophins, such as brain-derived neurotrophic factor and neurotrophin-3, in microglia and astroglia through cell-to-cell contact pathway via α5 and β3 integrins (Roy et al., 2007). Additionally, the mRNA levels of IL-4 and GATA3 were reduced in rapidly progressing ALS patients and inversely correlated with ALS progression rates. GATA3 was found

to be an accurate indicator of ALS disease progression (Henkel et al., 2013).

The beneficial properties of Th2 cells in neurodegeneration, by inducing a Type-2 skewed immune response, appear to hold great promise in controlling inflammation in many neurodegenerative diseases, which have a predominantly Type-1 microenvironment (Th1 and Th17 cytokines, i.e. IFN-γ and IL-17). For example, after inducing cerebral stroke in mice with middle cerebral artery occlusion (MCAO), IL-33 was used to induce a shift of the Th1/Th2 balance toward Th2 and suppress Th17 immune responses (Luo et al., 2015). recently, some immunomodulatory drugs, such as glatiramer acetate, have been used to treat MS and RRMS by re-balancing Type-1 versus Type-2 microenvironments via binding to MHC-II molecules. This leads to a shift from a Th1/Th17, i.e. IFN-γ/IL-17 pro-inflammatory microenvironment, to a Type-2, i.e. IL-4, IL-10, TGF-β anti-inflammatory microenvironment, dominated by Th2 cells and Tregs (Aharoni, 2014). Immunotherapeutic DNA vaccines (discussed below) for treating AD could increase the ratio of IL4/IFN-γ, decreased inflammation and microglial activation, and thus enhanced cognitive ability in APP/PS1 mice (Xing et al., 2012). It should be pointed out that skewing the Th1/Th2 balance away from the inflammatory Th1 and towards the protective Th2 is not always helpful and sometime even harmful. Too extremely skewed of a Th1/Th2 balance towards the so-called protective Th2 immunity has been shown to impart cognitive dysfunction in aged mice. An elevated IL-4/IFN-γ ratio triggers the choroid plexus (CP) to produce CCL11 (linked with cognitive dysfunction) (Baruch and Schwartz, 2013). Care has to be taken to maintain a healthy Th1/Th2 balance, and not shift the ratio too far in any one direction.

5.3.3. Brain antigen-specific CD4$^+$ T cells are required for maintenance of brain plasticity

It is true that some types of CD4$^+$ T cells are detrimental in brain injury and CNS inflammation as discussed above. However, brain antigen-specific CD4$^+$ T cells, particularly Th1 cells, at the choroid plexus (CP) are proposed to be beneficial to the brain in health and diseases (Schwartz et al., 2013). Experiments show that lacking these T cells, such as in *Rag*$^{-/-}$ or SCID mice, significantly impairs CNS injury repair (Baruch and Schwartz, 2013) and reduces spatial learning and memory, and is similar to age-associated memory loss (Kipnis et al., 2004b; Ziv et al., 2006b). Although Th1, Th2, and Treg CD4$^+$ T cells are all resident at the CP, the brain antigen-specific CD4$^+$ T cells at the CP are likely the Th1 subset (IFN-γ-producing T cells). IFN-γ receptor knockout mice, following spinal cord injury, exhibited reduced T cells at the CP, fewer T cells entering the cerebrospinal fluid, and impaired CNS recovery (Kunis et al., 2013). Furthermore, the lack of IFN-γ-producing Th1 cells limits the activation of the CP, thereby reducing the recruitment of M$_ø$ into the injured spinal cord parenchyma (Raposo et al., 2014). Tregs are considered to be beneficial T cells that suppress harmful immune responses (addressed above). However, Tregs at the CP may be detrimental CNS injury recovery, as decreasing Treg function could promote CNS antigens-specific CD4$^+$ Th1 cells, which could potentially cure/alleviate neurodegenerative disorders (Kipnis et al., 2004a; Schwartz and Kipnis, 2005). Weakening Treg function to break self-tolerance to CNS antigens is a proposed strategy to fight off chronic neuroinflammatory disorders (Schwartz and Baruch, 2014a). However, Tregs remain indispensable during CNS injury healing processes. Importance must be placed on the specificity of Treg regulatory activity with regards to therapeutic interventions (Raposo et al., 2014).

These brain antigens-specific CD4$^+$ Th1 cells are proposed to control blood-derived M$_ø$ traffic through the CP gate and into the CNS, in an IFN-γ signaling-dependent manner, for injury repair (Kunis et al., 2013; Raposo et al., 2014) by a so-called "gatekeeper" mechanism (Schwartz et al., 2013). Sufficient recruitment of circulating immune cells into the CNS is a key requirement for recovery from CNS injury and neuroinflammation (Schwartz and Baruch, 2014b). Although this model of brain antigens-specific CD4$^+$ Th1 cells serving as gatekeepers at the CP is very intriguing, many associated issues are still unclear. For example, what are the CNS-specific antigens? These antigens are not likely to be the whole brain tissue or whole spinal cord homogenate antigens, which are used to induce CNS immune pathology, such as EAE. Why have these self-reactive T cell clones not been depleted in the thymus during negative selection? If they are elicited in the periphery, what triggers this process? How are these T cells activated during CNS injury? Whether and how are these autoreactive T cells entering the CNS without attacking the CNS parenchyma?

6. Neuro-endocrine networks control immune system

Another important area of interest during neuroinflammation is neuronal control of the immune response. Research on how neuronal activities induce immune system changes has not shown much progress, but neuroendocrine-immune integration has been widely accepted due to mounting evidence from clinical, epidemiological, and experimental data. Neuroinflammation leads to brain-derived immunoregulatory output of stimulatory signals, including circulating pathogen-associated molecular patterns, which can locally activate components of the hypothalamic-pituitary-adrenal axis leading to the release of corticotropin-releasing factor. This factor triggers the release of adrenal corticotropic hormone (ACTH), ultimately leading to the secretion of glucocorticoids (GCs) into the bloodstream (Bellavance and Rivest, 2012). Interestingly, this neuro-endocrine-immune system communication works in both directions. GCs are regarded as strong immunoregulators due to their ability to regulate pro-inflammatory signaling and gene transcription. glucocorticoid receptor (GR) transactivation disrupts Toll-like receptor (TLR) transduction pathways by inducing inhibitors, such as I-kappa-B alpha protein (IkBα, mitogen-activated protein kinase (MPK-1), IL-10, lipocortin, glucocorticoid-induced leucine zipper (GILZ), and suppressor of cytokine signaling proteins (Bellavance and Rivest, 2012; Bhattacharyya et al., 2011). Furthermore, tethering of the GR monomer has been shown to enhance transcription of signal transducer and activator of transcription-3 and −5 (STAT-3 and STAT-5), and a cyclic AMP response element binding protein (Creb), while inhibiting NF-kB, activator protein (AP-1), activating transcription factors, and interferon regulatory factor 3 (Beck et al., 2009; Bellavance and Rivest, 2012; De Bosscher et al., 2010; Oakley and Cidlowski, 2011).

6.1. Glucocorticoids serve as a double-edged sword in neuroinflammation

The mechanistic control of immune responses by GCs in the CNS has been studied by utilizing lipopolysaccharide (LPS)-elucidated neuroinflammation via injections of LPS into the brain parenchyma. Nadeau et al. reported that the robust inflammatory response induced by intracerebral injections of LPS could be ablated by a prior systemic injection of LPS. The anti-inflammatory effect of peripherally administered LPS, counteracting the robust inflammatory response induced by the central administration of LPS, was mediated by plasma corticosterone, and the GR antagonist RU486 (mifepristone) prevents the anti-inflammatory effects of systemic immune challenge (Nadeau and Rivest, 2002). Additionally, rats pretreated with RU486 prior to intracerebral LPS injection had a significantly exacerbated and prolonged innate immune response with excessive IL-1β, TNF-α, and neuronal death. Furthermore, GCs have been shown to promote the differentiation

of $CD4^+FoxP3^+$ Tregs, thereby adding to their anti-inflammatory credentials (Baschant and Tuckermann, 2010).

Particularly in neuroinflammatory disease conditions, GCs have been shown to be neuroprotective. During ischemic stroke, a high-dose of GCs given shortly after transient cerebral ischemia could reduce the infarct size in mice, and these effects were reversed by administration of the GR antagonist RU486 (Limbourg et al., 2002).

Although GCs are classically known for being anti-inflammatory, many studies now show that GCs can potentiate pro-inflammatory events. Pre-treating murine $M_Ø$ or primary hippocampal microglia with GCs prior to immune stimulation increases the production of pro-inflammatory mediators (Frank et al., 2010; Smyth et al., 2004). Furthermore, in high stress conditions, GCs have been shown to shift the neuroimmune environment towards inflammation, including NF-kB activation, and increased inducible nitric oxide synthase (iNOS), TNF-α, cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) in the cortex of the rat brain and IL-1β, CD14, MHC-II, and IL-10 transcripts in the rat hypothalamus (Bellavance and Rivest, 2012; Blandino et al., 2009; Frank et al., 2007).

In AD, many patients exhibit hypercortisolemia and their plasma cortisol levels correlate with the severity of the disease. APP mice treated with exogenous GCs have increased amyloid burden and Tau phosphorylation. GCs involved in the pathogenesis of AD appear to mediate a misprocessing of the APP protein thereby increasing the generation of Aβ(Catania et al., 2009). Targeting GCs in AD therapy seems promising. The GR antagonist RU486 has been shown to have positive results in patients with AD, and decreases Aβ and Tau pathology in APP mice (Baglietto-Vargas et al., 2013). In PD, patients have been shown to exhibit hypercortisolemia as well, however, the role of GCs during PD is not well understood. Dopaminergic neurodegeneration triggered by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been shown to be significantly reduced by GC agonist treatment, but conversely, treatment with dexamethasone was able to protect against dopaminergic neuronal damage (Kurkowska-Jastrzebska et al., 2004). In PD, GR levels are decreased in the substantia nigra of both PD patients and MPTP-intoxicated mice (Ros-Bernal et al., 2011). Mice with selective inactivation of the GR gene had increased dopaminergic neuronal loss, which was facilitated by the persistent activation of microglia that lacked GRs (Ros-Bernal et al., 2011). Although PD patients have hypercortisolemia, they lack the neuroprotective effects of GR activation. This might arise from the persistent activation of the hypothalamic–pituitary–adrenal axis with chronically high cortisol levels compromising GR function (Dejager et al., 2014) and leading to decreased GR levels as is seen in the brain of PD patients (Ros-Bernal et al., 2011).

6.2. Evidence of direct neuronal regulation of immune cells and the immune response

Neurons have the ability to directly influence the local T cell response without endocrine involvement. Liu et al. showed that neurons are highly active in governing T cell responses in the CNS. Neurons can induce the proliferation of activated $CD4^+$ T cells through B7-CD28 and TGF-β1 signaling pathways. The interaction between neurons and T cells results in the conversion of encephalitogenic T cells into $CD25^+FoxP3^+$ Tregs that are capable of suppressing encephalitogenic T cells and inhibit EAE. Moreover, this immunosuppression is dependent on the cytotoxic T lymphocyte antigen-4 (CTLA-4) (Liu et al., 2006).

Emerging evidence has shown that the CNS controls the immune response to reach beyond the local (the brain) neuroinflammatory environment. Kim et al. showed that the brain-fat axis can facilitate the transition from an innate to an adaptive immune response. Using C57BL/6 mice infected with *L. monocytogenes,* they showed that a peripheral adaptive immune response against bacterial infection was dependent on brain TNF-α and hypothalamic TNF-α receptors. Furthermore, they found that the brain helps to initiate the adaptive immune response through lipolysis, resulting in elevated free fatty acids in the serum of infected mice, while inhibition of fatty acids attenuates brain TNF-α and the infection-induced adaptive immune response. Interestingly, they found that obesity and chronic neuroinflammation impair the ability to generate robust T and B cell populations (Kim et al., 2015).

Additional evidence supporting CNS control over the peripheral immune response has emerged from studies of acute neuroinflammation. Following ischemic stroke, a systemic immunosuppression, resulting from a Type-1 to Type-2 cytokine environment shift occurs as a compensatory mechanism to protect the post-ischemic brain from severe inflammation (Chamorro et al., 2012). Unfortunately, this systemic immunosuppression reduces the antimicrobial response of the immune system in both humans (Chamorro et al., 2006, 2012) and mice (Wong et al., 2011), which results in infection becoming one of the major causes of death following a stroke. Wong et al. showed that functional innervation of hepatic Invariant Natural Killer T (iNKT) cells is one mechanism of immunosuppression following stroke. The iNKT cells have a restricted TCR that recognizes lipid antigens, including bacterial glycolipids, presented by CD1d. Following the induction of MCAO in mice, Wong et al. found that the post-ischemic brain was able to control the behavior/activation of liver iNKT cells leading to increased expression of CD69, increased anti-inflammatory IL-10 production, and arrested intravascular crawling. Interestingly, although iNKT cells recognize antigens through CD1d, antibody blockade of CD1d had no effect on iNKT post-stroke behavior. Instead, post-ischemic iNKT behavioral changes were reversed by propranolol, a nonspecific B-adrenergic receptor blocker, and chemical depletion of peripheral neuronal terminals containing noradrenaline with 6-hydroxydopamine, suggesting that neural signals control iNKT behavior. Furthermore, administration of propranolol shifted the IL-10-dominated immunosuppressive post-stroke microenvironment toward an IFN-γ and Th1 dominant microenvironment (Wong et al., 2011).

7. Immunological therapeutic strategies for age-related neurodegeneration

Interest in immunotherapeutic strategies for acute and chronic neuroinflammation and neurodgeneration is greatly increasing today (Coder et al., 2017; von Euler Chelpin and Vorup-Jensen, 2017). Using anti-inflammatory drugs to modulate innate and/or adaptive immunities is one option. Long-term usage of anti-inflammatory drugs reduces the risk to suffer from AD and PD by roughly half (Chen et al., 2005; Vlad et al., 2008), whereas alteration of peripheral inflammation during neurodegenerative disease can significantly alter the disease course (Perry et al., 2007). However, as we discussed in previous sections, the immune components involved with the induction and suppression of chronic inflammation include many immune cell types, such as Th1 and Th2cells, Tregs, and $M_Ø$/microglia. Attenuating neuroinflammation is tightly dependent on rebalancing these activated immune cell populations. Some immunomodulatory drugs and therapeutic cytokines that maintain the balance between Type-1 and Type-2 environments are discussed in Section 3.4.2. Moreover, T cells can either induce the immune response to result in acute inflammation or further open the compromised BBB during neuroinflammation to recruit blood-derived $M_Ø$ into the CNS for debris removal. The latter is thought to involve a brain protein-

specific antigen effector T cell, which may be therapeutically enhanced via vaccination. Additionally, young serum-derived circulating systemic environmental factors (CSEFs) are proposed to enhance or rejuvenate the aged cellular immune system. Therefore, we discuss these potential immunological strategies for rejuvenation and treatment of age-related neurodegeneration in this section (Table 3).

7.1. Innate immunity-based immunotherapies for the alleviation of neuroinflammation

Considerable worldwide interest exists in developing efficient NF-kB inhibitors for neurodegenerative diseases (Srinivasan and Lahiri, 2015). Neurodegenerative diseases, such as AD, typically have cerebral inflammation with activation of NLRP3 inflammasome (Heneka et al., 2013). Recent reports show that certain small molecules, such as β-hydroxybutyrate (Youm et al., 2015) and MCC950 (Coll et al., 2015), can tame the NLRP3 inflammasome to block NLRP3 activation-induced pro-inflammatory cytokine IL-1β secretion by $M_{Ø}$ (Levy et al., 2015). Activation of inflammasomes in the microglia, in addition to $M_{Ø}$ in the brain, is also fundamental for IL-1β release and subsequent inflammation (Halle et al., 2008). These inflammasome-activated $M_{Ø}$ and microglial cells belong to the M1 subtype in the early stages of CNS injury, including cerebral ischemia (Trendelenburg, 2014), and display strong inflammasome-associated IL-1β-driven CNS inflammation (Ransohoff and Brown, 2012). Therefore, inhibition of the inflammasome pathway is a promising therapy that utilizes the innate immune response to treat neurodegeneration. In fact, Coll et al. showed that MCC950 inhibition of NLRP3 activation can attenuate the severity of EAE disease in a mouse model of multiple sclerosis. Levels of pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 were reduced when EAE mice were treated with MCC950, and the associated Th17 and IL-17-producing γδT cell response was also reduced, all of which led to a significant decrease in clinical pathology scores associated with EAE disease (Coll et al., 2015). It also could prove to be an important benefit of HMG-CoA reductase, as inhibiting microglial activity is a key factor in stemming the tide of chronic neuroinflammation (Lyman et al., 2014). By using EAE and Theiler's virus induced demyelinating disease (TMEV-IDD) models, a new finding on the role of the pair CD200-CD200R in MS is provided (Hernangomez et al., 2014). Since the interest of the cannabinoid system as inhibitor of inflammation, the role of endocannabinoids (eCBs) in promoting CD200-CD200 CD200R interaction and the benefits caused in TMEV-IDD is introduced, which may be the new therapy target in AD (Hernangomez et al., 2014).

With the established role of cyclooxygenase (COX) pathway in neuroinflammation, the non-steroidal anti-inflammatory drugs (NSAIDs) have been identified as the potential drugs for the neurological diseases treatment. Indeed, a COX-1 inhibitor aspirin reduces neuroinflammatory and oxidative insults by reducing prostaglandins and increasing anti-inflammatory lipoxin, signifying the key and effective role of COX-1 in anti-inflammation (Arfi et al., 2011; Wu et al., 2012; Yao et al., 2014). COX2 inhibitor was believed to reduce the risk of AD via blocking COX-2 activation caused by Aβ peptides (Woodling and Andreasson, 2016). However, NSAIDs have no remarkable protective effect to improve the established AD and PD (Jaturapatporn et al., 2012; Rees et al., 2011). Breitner et al. reported that NSAIDs may reduce the developing chance of AD and PD in an asymptomatic individual but they exacerbate later stage AD (Breitner et al., 2011). Thus, the efficiency of NSAIDs for AD treatment still remains controversy.

Table 3
Potential immunological therapeutic strategies for age-related neurodegeneration.

Therapeutic intervention	Agent name	Therapeutic pathway	Target cell or tissue	Diseases
Innate immunity-based immunotherapy	MCC950	Inhibition of NLRP3 inflammasome	Microglia	cerebral ischemia; MS
	HMG-CoA reductase	Inhibiting microglial activity	Microglia	chronic neuroinflammation
	Endocannabinoids	Promotion of CD200-CD200R interaction	neuron-microglia	MS; AD; VIDD
Microenvironment-based therapy	IL-4	Improvement of M2-dominantresponse	M2	CNS injury
	CD28SA	Amplification of the host's Tregs	Tregs	Acute CNS injury
	Trichostatin A	Activation of Foxp3 and promotion of Treg generation and function	Tregs	Cerebral ischemic stroke
	Young serum or plasma	Improving the aged brain hippocampus	Stromal cell	AD or other age-related cognitive impairments
Vaccination therapy	T-cell vaccine	Attenuating autoreactive T cells, decreasing Th1, and increasing $CD4^+$ Tregs	T cells	MS
	Non-viral DNA vaccines	Elicit host Th2-type immune response	Th2	Neuroregeneration after CNS injury
	AADvac1	Reducing the levels of tau oligomers	Neurons	AD
	ACI-35	Mimicing Tau epitope at residues pS396/pS404	Neurons	AD
	AV-1959R/AV-1980R formulated with Advax(CpG) adjuvant	Targeting Aβ and Tau epitopes	Neurons	AD
	ACI-24	Targeting tetra-palmitoylated amyloid 1-15 peptide	Neurons	AD
	Lu AF20513	Targeting Aβ and robusting "non-self" T-cell responses	Neurons	AD
	α-Syn	Decreasing accumulation of aggregated α-Syn	Neuronal cell bodies and synapses	PD; DLB
	9E4	Reducing the accumulation of calpain-cleaved α-Syn	Axons and synapses	PD; DLB
	AFF 1	Decreasing accumulation of α-Syn oligomers	Axons and synapses	PD; DLB

MS: multiple sclerosis; AD: Alzheimer's disease; VIDD: virus induced demyelinating disease; FTD: frontotemporal dementia; PD: Parkinson's disease; DLB: Dementia with Lewy bodies; M2: alternatively activated macrophages; Treg: T regulatory cell;Th2: T helper 2; CD28SA: CD28 super-agonistic monoclonal antibody; Aβ: amyloid beta; Tau: microtubule associated protein tau; 9E4: a novel monoclonal α-Syn antibody against the C-terminus of α-Syn.

7.2. Improvement of cellular microenvironment-based therapy

Improvement of the neuron stem cell (NSC) and immune cell microenvironment is a therapeutic strategy to recover and rejuvenate acute CNS injury and chronic neuroinflammation in the elderly. In this section, we will discuss strategies to improve M1 versus M2 microenvironment for $M_{\emptyset}$ and microglia, and promote a Treg microenvironment for enhanced suppressive functionality. The use of young serum-derived soluble factors as therapeutic strategies will be also discussed.

7.2.1. Balancing the aged CNS inflammatory process

It is well known that both M1 and M2 types of $M_{\emptyset}$ and microglial are required for acute CNS injury and chronic inflammatory neurodegeneration (Yong and Rivest, 2009). During the early stages of the recovery process blood-derived $M_{\emptyset}$ enter the CNS and act as M1-type cells. M1 cells are essential for cleaning up CNS cellular debris, though they have pro-inflammatory activity and are detrimental to the CNS. At later stages of the recovery, anti-inflammatory M2 cells are predominant and are beneficial in reducing secondary damage to the CNS (Shechter et al., 2013), thereby the switch from an M1- to M2-dominant response halts the inflammatory process (Miron et al., 2013). IL-4-deficient mice showed increased brain injury and worsened neurological outcomes (Xiong et al., 2011). Aged $M_{\emptyset}$ are less efficient at cleaning up cellular debris during CNS injury recovery (Ruckh et al., 2012) and much slower at switching from an M1- to M2-dominant response (Miron et al., 2013). Studies are attempting to reduce the time taken for the transition from M1- to M2-dominant response, in order to shorten the pro-inflammatory process and prolong anti-inflammatory effects. Intracerebroventricular infusion of rapamycin, an inhibitor of mTOR signaling, enhanced brain $M_{\emptyset}$ polarization to M2-dominant response, to attenuate CNS secondary damage after ischemic stroke (Xie et al., 2014). The administration of IL-4 enhances the M2-dominant response in the CNS after intracerebral hemorrhage (Yang et al., 2016a). Evidence shows that aged mice are less sensitive to the M2-promoting effects of IL-4 in LPS-induced neuroinflammation (Fenn et al., 2012). IL-4 may be potentially helpful in aged individuals during CNS injury.

7.2.2. Tregs as therapeutics for CNS inflammation

$FoxP3^+$ Treg cells are suppressors of inflammation (Kleinewietfeld and Hafler, 2014; Sakaguchi, 2004). The efficacy of Treg-based therapy in recovery from acute CNS injury, such as cerebral ischemic stroke, was established. Many experiments have indicated that enhancing Tregs could significantly reduce brain damage in post-ischemic stroke. This can be achieved with the following approaches: (1) adoptive transfer of Tregs into ischemic stroke individuals; (2) amplification of the host's own Tregs by intraperitoneal (i.p.) injection of a CD28 super-agonistic monoclonal antibody (CD28SA) (Na et al., 2015). CD28SA can efficiently expand and activate polyclonal Tregs *in vitro* and *in vivo* without TCR engagement (Gogishvili et al., 2009; Lin and Hunig, 2003); (3) enhancing the host's own Tregs through injection of trichostatin A, a histone deacetylase inhibitor, which can epigenetically activate FoxP3 gene and promote the generation and function of Tregs (Lichtman et al., 2013); Furthermore, Tregs have been shown to affect the attenuation of chronic inflammation-induced neurodegeneration (Reynolds et al., 2010; Rosenkranz et al., 2007). Clearly, the usage of Tregs to treat CNS injury and neurodegenerative disorders is of great interest (Fessler et al., 2013; Fransson et al., 2012). However, if Tregs from an individual other than the host are used, then the MHC matching may be required. Whether using expansion of Tregs in the elderly could efficiently treat age-related neurodegenerative diseases needs to be determined. Alternatively, Treg-derived exosomes are distinct from other Th cells and can suppress pathogenic Th1 cell proliferation and IFN-γ production (Okoye et al., 2014). Notably, Tregs-released exosomes are potentially therapeutic in CNS injury and inflammatory neurodegenerative diseases (Agarwal et al., 2014).

7.3. Soluble factor: young serum-derived CSEF improves the aged stem cell environment, and potentially improves the cellular immune system environment

Mounting evidence shows that aging of the CNS can be rejuvenated or restored after injury by providing old animals with young blood via "heterochronic parabiosis", in which the circulatory systems of young and aged mice are joined by surgery (Brack et al., 2007; Conboy et al., 2005; Pishel et al., 2012; Ruckh et al., 2012; Villeda et al., 2011; Villeda and Wyss-Coray, 2013), or through the infusion of young serum/plasma into old animals (Villeda et al., 2014). Although the identity of the factors in young blood is uncertain, a "rejuvenation factor" or "anti-geronic factor" in the naturally occurring young circulatory system (termed "circulating systemic environmental factor", CSEF) has been proposed. For example, the TGF-β superfamily member GDF-11 is one such factor (Katsimpardi et al., 2014). Injection (i.p.) of GDF-11 into aged mice for 4 weeks worked nearly as well as heterochronic parabiosis in improving proliferation of cerebral vasculature and promoting neurogenesis in the subventricular zone of the aged mouse brain (Katsimpardi et al., 2014). Moreover, injection (i.v.) of young serum into aged mice improved the aged brain hippocampus at the molecular, structural, functional and cognitive level with the same efficacy as heterochronic parabiosis (Villeda et al., 2014). The study further revealed that this hippocampus-dependent cognitive enhancement was partly mediated by cyclic AMP response element binding protein (Creb), which was activated by exposure to young blood factor (Villeda et al., 2014). These findings in the rejuvenation of aged brain function by CSEF are of great clinical potential for Alzheimer's patients and others suffering from age-related cognitive impairments (Kaiser, 2014; Paul and Reddy, 2014).

GDF-11 may not be the sole protein constituting the CSEF, because it is not as effective as whole blood plasma in mouse neurogenic rejuvenation. Daily injection of recombinant GFF-11 (rGDF-11) (0.1 mg/kg mouse body weight) for 4 weeks (28 injections) is required for a 50% increase in the volume of brain blood vessels (Katsimpardi et al., 2014), whereas, administration of a total of 8 injections of whole blood plasma (100 μl per injection) over 24 days can significantly improve the cognitive function of aged mice (Villeda et al., 2014). The results imply that plasma is more efficient than GDF-11 alone. Moreover, a recent re-investigated finding shows that GDF-11 is increased, rather than reduced, in the sera of aged rats and humans (Egerman et al., 2015). Therefore, the optimal mechanism of injection of GDF-11 into aged animal for rejuvenation needs to be determined. Two recent articles have reported contradictory roles for GDF-11 in skeletal muscle. The first is in reversing age-related dysfunction in mouse skeletal muscle (Sinha et al., 2014), while the other is in inhibiting skeletal muscle regeneration, particularly in young adult rats (Brun and Rudnicki, 2015; Egerman et al., 2015). The inhibitory mechanism is due to SMAD2/3 signaling to activate non-canonical MAPK pathways, thereby negatively regulating skeletal muscle proliferation, differentiation, and protein synthesis (Brun and Rudnicki, 2015; Egerman et al., 2015). Therefore, the role of GDF-11 as a rejuvenation factor should be re-examined.

In addition to the CNS, the CSEF rejuvenates aged systems including muscle (Sinha et al., 2014) and myocardium (Loffredo et al., 2013) through the activation of the aged stem cell (such as satellite cells in muscle) environment (Brack et al., 2007; Conboy et al., 2005; Sinha et al., 2014). Stem cells are regulated by their

surrounding microenvironment (stem cell niche) (Lo Celso and Scadden, 2011; Moore and Lemischka, 2006), which is comprised of stromal cells. Stem cells are similar to "seeds", while the stromal cells around them are similar to "soil". By making the aged milieu "younger", the young CSEF is actually improving the quality of the "soil".

Applying the young CSEF to rejuvenate aged systems is a promising strategy for interventional medicine with the potential to cure or prevent many age-related diseases, including Alzheimer's and heart diseases. These age-related diseases are generally associated with inflammaging (Freund et al., 2010), characterized by persistent low-grade, but exceeding baseline levels of, pro-inflammatory factors in the elderly. Aside from the direct role of CSEF in rejuvenating aged muscular, myocardial, and central nervous systems (Katsimpardi et al., 2014; Villeda et al., 2014), it is less clear whether CSEF can be applied to cellular immune systems to rejuvenate aged T cell pool profiles and ameliorate immune cell-mediated chronic inflammatory conditions (Brunner et al., 2011; De Martinis et al., 2005; Franceschi et al., 2000, 2007; Freund et al., 2010; Xia et al., 2012). Although initially it was unclear why in heterochronic parabiosis young CSEF could not restore the immune system of the older partner and may in fact even accelerate aging (Kim et al., 2015), our group found that GDF-11 and young serum-derived exosomes have the same positive effects in attenuating chronic inflammation by reducing IL-6, IL-1β, and TNF-α in aged mice (manuscript under preparation). It is worth determining the mechanism by which young serum-derived exosomes induce attenuation of inflammation in aged animals, and whether it is due to improvement of cellular immune function, such as thymic naïve T cell output, Th1/Th2 response, and peripheral autoreactive T cell suppression. This will help reduce the age-related risk factors for morbidity and mortality in cardiovascular and neurodegenerative diseases, as well as late-life cancer (Howcroft et al., 2013; Pizza et al., 2011).

7.4. Vaccination therapy

Conventional vaccination used to prevent infectious diseases. However, vaccination is also used for treatment of neurodegeneration, tumor and others.

7.4.1. Vaccination in autoimmune neurodegeneration

A typical example of autoimmune neurodegeneration is seen in MS, which results from the CNS being attacked by abnormal autoimmunity, particularly by myelin-reactive T cells, resulting in an inflammatory demyelinating disorder. A rodent model for human MS is EAE. Therapeutic vaccination, including the use of T-cell vaccine (TCV), TCR peptide vaccine, myelin basic protein-based DNA vaccine, and altered peptide ligand vaccine, shows great promise in ameliorating the disease, not only in rodents but also in humans (Achiron et al., 2004; Karussis et al., 2012). The most promising approach uses attenuated autologous myelin-reactive TCV, with attenuated autoreactive T cells from MS patients to induce T cell-dependent inhibition/neutralization of disease-causing T cells, and regulation of the autoimmune response (Huang et al., 2014; Vandenbark and Abulafia-Lapid, 2008). The T cells for TCV therapy are usually derived from the patient, attenuated with irradiation, and then re-injected into the patient to elicit an immune reaction or immune regulation, in order to reduce or eliminate myelin-reactive effector T cells, decrease Th1 cytokine (such as INF-γ)-producing cells in the CNS (Volovitz et al., 2010), and increase and activate $CD4^+$ Tregs, which can inhibit autologous myelin-reactive T cells (Hong et al., 2006; Vandenbark, 2005), thereby ameliorating inflammation and disease.

7.4.2. Therapeutic vaccination in AD and PD

Typical age-related chronic neurodegenerative diseases like AD and PD are mainly attributed to inflammaging and accumulation of misfolded proteins. Great progress was recently made in the areas of therapeutic vaccination for AD. Although previous views believed that AD arises from inflammation-induced abnormal extracellular deposition of misfolded Aβ protein which manifests as plaques, the recent evidence showed that the small soluble Aβ oligomers are the pathogenic forms (Selkoe and Hardy, 2016; Sengupta et al., 2016). The recent shift in the Aβ hypothesis from targeting all Aβ to small soluble oligomeric intermediates is instructing the therapeutics towards directly targeting the toxic small soluble Aβ oligomers. Importantly, the toxicity of Aβ oligomers are related to size and conformation as well as their influence on inflammation, which should be considered carefully in the developing of Aβ oligomer immunotherapy (Sengupta et al., 2016).

It has been indicated that targeting Aβ N-terminus would accelerate the conversion of Aβ into oligomers and enhance the neurotoxicity (Liu et al., 2015). Thus, antibodies against Aβ N-terminus should be taken into account for their toxicity in the therapy of AD. Recent work by using independent cohorts of AD transgenic mice demonstrated that passive antibodies of Aβ (3D6 and β1 antibody) were ineffective in treating neuronal dysfunction, even worsened it (Busche et al., 2015). Inflammatory effects of the passive therapy may be one reason for the failure of the anti-Aβ immunotherapies in repairing cognitive deficits. In contrast, rodent model research suggested specific targeting oligomers could be acted as the protective mechanism for cognition (Sengupta et al., 2016). During the effort to develop the effective methods for the treatment of AD, the antigens need to take into careful consideration. Many failure of the passive immunotherapy may due to these antibodies do not discriminate the different Aβ size and conformations. With the progression of AD, three Aβ forms exist: Aβ monomers, soluble Aβ oligomers, and insoluble fibrillar Aβ (Goure et al., 2014; Tekirian et al., 1999). All these three Aβ are heterogenerous and conclude many isoforms, which increase the difficulty of developing the specific antibodies against Aβ oligomers (Goure et al., 2014). Some antibodies, such as Bapineuzumab and Ponezumab, recognize the three forms of Aβ (La Porte et al., 2012; Zago et al., 2012). The recognition of Aβ plaque leads to its degradation, which will aggregate the disease in some conditions (Busche et al., 2015). What is encouraging is the emergence the Solanezumab which is a conformation-specific antibody that solely recognizes soluble Aβ and monomeric Aβ but not Aβ plaque (Racke et al., 2005; Sengupta et al., 2016; Seubert et al., 1992). Although some progress have been obtained about the effect of Solanezumab (Farlow et al., 2012), there is long way to go to cure AD using Solanezumab.

However, recent studies indicated aducanumab (BIIB037), a human mAb that selectively reacts with aggregated forms of Aβ, seems promising in the treatment of early AD (Malik and Robertson, 2017). The usage of aducanumab (doses $\leq$30 mg/kg) has been proved to be safe in humans (Ferrero et al., 2016). In another study, the same group showed that aducanumab could penetrate the brain and reduce the soluble and insoluble Aβ in a transgenic mouse model of AD (Sevigny et al., 2016). Interim analyses of a phase 1b clinical trial showed that administration of aducanumab in prodromal or mild AD patients reduces Aβ in the brain in a dose- and time-dependent manner (Sevigny et al., 2016). The reduction of brain Aβ was accompanied with a clinical decline (Sevigny et al., 2016). Most recently, Ksenia et al. demonstrated a murine analog of aducanumab could clear amyloid plaques and restore calcium homeostasis in an AD mouse model (Kastanenka et al., 2016). Together, these results indicate aducanumab has the

potential for treatment of AD and the phase 3 clinical trials are currently ongoing.

Since the limited value for immunogen selection in AD transgenic mouse models, the use of validated antibodies and biophysical methods are required to explore the antigens that would be most likely recognized by the human immune system and thus capable to stimulate a protective antibody response (Marciani, 2016).

Another immunotherapeutic technique is through active immunization with Aβ or Tau peptides, i.e., through active immunity, to elicit antibodies from patients themselves. Therapeutic vaccination takes advantage of the immune response against a harmful self-antigen, but the reaction should not cause adverse autoimmunity. Active immunization with Aβ 1–42 peptide for AD immunotherapy induced the onset of meningoencephalitis in 6% of treated patients (Schenk, 2002) leading to premature termination of the study in 2002. So this technique needs to be improved. The adjuvants or immune modulators are critical for the success use of AD vaccine through active immunity. Adjuvants exert their immune modulatory activities by using specific receptors to stimulate immunity. However, most adjuvants induce the pro-inflammatory Th1 response and rare adjuvants induce anti-inflammatory Th2 response. QS-21, as a Th1 adjuvants, could induce Th2 response in phase 1 study of AN1792 vaccine but induce a pro-inflammatory in phase 2 study (Zotova et al., 2013). Interestingly, the de-acylated derivative of QS-21 named QT-0101 is an effective Th2 adjuvants and have the ability to induce strong systemic Th2 immunity (Marciani, 2015). Alum is a safe but weak Th2 adjuvant (Bozorgomid et al., 2016). Long-term vaccination studies with canine model using Aβ 1–42 showed that the role of alum is effective in the young but efficacy is low in the elderly which may be due to immunosenescence with aging (Head et al., 2008). Thus, an AD vaccine would benefit from strong adjuvants like QT-0101.

More efforts were put to explore effective immunogens for vaccination to minimize autoimmune reactions and switch immune response type in AD. For example, many studies used non-viral DNA vaccines without any adjuvant (Okura and Matsumoto, 2008), which may elicit a Th2-type immune response in the hosts (Ghochikyan et al., 2003; Kim et al., 2007). The Th2-type immune response was demonstrated to play a beneficial role in neuroregeneration without generating autoimmune CNS inflammation after the injury (Hendrix and Nitsch, 2007).

Tau hyperphosphorylation in AD are also induced by human oligomers, causing the neuric dystrophy in cultures neurons. Tau-positive neurotoxicity will be increased by crossing human amyloid precursor protein with human tau transgenic mice (Selkoe and Hardy, 2016). Tau accumulation was regarded as a downstream effect of Aβ protein in AD. Recent work reveals the possible link between tau and Aβ in the promotion of cognitive decline. After removing tau oligomers, memory deficits were reversed and plaque deposition was promoted in the brain, accompanying with the most surprising observation, that Aβ*56 levels decreased (Castillo-Carranza et al., 2015). These findings shed lights on the tau oligomerization which acts not only as the consequence of Aβ pathology but also as a toxic mediator in AD, supporting the potentially therapeutic role of tau oligomers for AD treatment. Recently, Eva et al. demonstrated that an active vaccine, AADvac1, could specifically recognize pathological Tau oligomers (Kontsekova et al., 2014). Active immunotherapy with this vaccine reduced the levels of tau oligomers and the extent of neurofibrillary pathology in the brains of transgenic rats (Kontsekova et al., 2014).

Immunotherapy for PD patients has made a great progress in recent years. PD pathology in the brain is characterized by Lewy bodies, in which the major constituent is the accumulated and aggregated misfolded synaptic protein α-synuclein (α-Syn). Therefore, cerebral α-Syn protein was selected as the target immunogen and the aim was to reduce its levels. So far, targeting α-Syn for PD immunotherapy has been still encouraged. However, recent work comes up with several problems which we should face with. The pathological aggregation of α-Syn originates from a monomeric, natively unfolded form rather than an α-helical multimeric, membrane-bound form (Burre et al., 2015). Intervention with the physiological function of α-Syn should be replaced with the conformation-specific antibodies for the “pathogenic” forms of α-Syn in PD immunotherapy (Lee and Lee, 2016). Taken safety and efficacy into consideration, non-human primate models should be used to validate the antibodies for PD immunotherapy.

8. Conclusions

Our understanding of neural-immune crosstalk and mutual regulation in aging and age-related diseases progressed greatly over the decades. Although all aged persons have some levels of chronic inflammatory conditions, not all elderly individuals suffer from age-related neurodegenerative diseases like AD or PD. Thus, inflammaging is necessary but not sufficient to cause age-related neurodegenerative diseases. Additional triggers are clearly required for disease onset. Although enormous progress on the etiology of neurodegenerative diseases has been made, further investigation is critically needed. Detailed uncovering the impact of immune system aging and inflammation on neurodegenerative diseases, offered the great promise for immunotherapy strategies to prevent and/or treat these diseases in elderly individuals at risk for chronic inflammation-associated neurodegenerative diseases.

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