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REVIEW

Inflammation in Alzheimer's Disease and Molecular Genetics: Recent Update

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Abstract Alzheimer's disease (AD) is a complex age-related neurodegenerative disorder of the central nervous system. Since the first description of AD in 1907, many hypotheses have been established to explain its causes. The inflammation theory is one of them. Pathological and biochemical studies of brains from AD individuals have provided solid evidence of the activation of inflammatory pathways. Furthermore, people with long-term medication of anti-inflammatory drugs have shown a reduced risk to develop the disease. After three decades of genetic study in AD, dozens of loci harboring genetic variants influencing inflammatory pathways in AD patients has been identified through genome-wide association studies (GWAS). The most well-known GWAS risk factor that is responsible for immune response and inflammation in AD development should be APOE ε4 allele. However, a growing number of other GWAS risk AD candidate genes in inflammation have recently been discovered. In the present study, we try to review the inflammation in AD and immunity-associated GWAS risk genes like *HLA-DRB5/DRB1*, *INPP5D*, *MEF2C*, *CR1*, *CLU* and *TREM2*.

Keywords Inflammation · Alzheimer's disease · Genetics · GWAS · TREM2

Introduction

Alzheimer's disease (AD), firstly described by Alois Alzheimer in 1907 (Avramopoulos 2009), is an irreversible neurodegenerative disease and the most common cause of dementia in elderly adults. In the United States, more than 5.4 million people are affected by AD now (Alzheimers Association 2012). Approximately 35.6 million people are currently diagnosed with AD in the world (Alzheimers Association 2013). It is estimated that, as the population lifespan increases, the number of AD affected patients will triple by 2050 (Hebert et al. 2003).

Alzheimer's disease is clinically characterized by progressive loss of the ability of learning and memory, and a decline in other cognitive functions, ultimately resulting in dementia and death. Histopathologically, there are two principal hallmarks in AD: (1) extracellular amyloid deposits that primarily consist of amyloid beta (Aβ) peptides and (2) neurofibrillary tangles resulting from the intracellular accumulation of hyper-phosphorylated microtubule-associated protein tau (Huang and Mucke 2012). To date, the mechanisms leading to the formation of these lesions and their underlying association with AD are still not adequately understood. Nevertheless, several competing theories have been proposed trying to explain the cause of AD, including Aβ hypothesis, tau hypothesis, cholinergic hypothesis and inflammation hypothesis. Due to unsuccessful experimental and clinical results, cholinergic theory has not been widely accepted. On the contrary, the Aβ and tau theories are well-known hypotheses due to their capability to explain most AD pathogenesis.

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However, it is insufficient for Aβ plaques and hyperphosphorylated tau to explain all the features of AD. In 2008, a study discovered that significant burden of Aβ deposition found in elderly persons did not necessarily cause clinically cognitive impairments (Aizenstein et al. 2008). Moreover, clinically reduced Aβ in the brain through immune-therapeutics did not improve the AD patients' cognitive functions (Holmes et al. 2008). These studies suggest that some other factors might have involved in AD pathogenesis.

Genetic efforts through the employment of large-scale genome-wide association studies (GWAS) to search for AD susceptibility genes in the inflammatory process have never stopped. *APOE* is supposed to be the original gene found to have a genetic linkage with AD (Strittmatter et al. 1993). Several years after this discovery, *APOE* was reported to play an essential role in AD inflammation (Guo et al. 2004). Most recently, in 2012, APOE was found to trigger an inflammatory cascade that weakens the blood–brain barrier (BBB) through an inflammatory molecule known as cyclophilin A (CypA) (Bell et al. 2012). The researchers observed that APOE significantly raises levels of CypA. The increased CypA, in turn, activates a pro-inflammatory pathway that ultimately leads to the breakdown of the BBB. This is a typical case in which an AD susceptible gene is involved in the inflammatory process associated with AD pathogenesis. Over 20 years has passed since the discovery of an association of *APOE* with AD in 1993, and numerous genetic association studies have been published since then. In this review, we will not put emphasis on the results of all GWAS risk genes in AD [which have been extensively reviewed previously (Bettens et al. 2013; Guerreiro et al. 2012; Medway and Morgan 2014; Tanzi 2012; Tosto and Reitz 2013)], but rather on the most recently implicated GWAS risk genes proved or expected to be involved in the inflammatory process of AD pathogenesis.

Inflammation in AD

Inflammation is a systematic and complicated immune response to clear an invading pathogen, a traumatic event, or generally, an injurious agent. The agent may be from the organism itself (such as a necrotic cell) or foreign, for example, viruses and bacteria. The inflammation can be acute or chronic. The inflammatory reaction that involves in most neurodegenerative diseases (Craft et al. 2006; Liu et al. 2013; Pizza et al. 2011; Sudduth et al. 2013; Varnum and Ikezu 2012), is often termed "neuroinflammation". Microglia, which is supposed to be the resident macrophages of the brain, and atrocities are the main cells that involve in this process. In the brains of both AD individuals and transgenic animal models, it was found that Aβ plaques are surrounded by activated glial cells (Bauer et al. 1991; Cagnin et al. 2001; Fillit et al. 1991; Liu et al. 2013; Varnum and Ikezu 2012). Activated microglia and astrocytes strongly secrete inflammatory components such as pro-inflammatory cytokines, chemokines, complement, macrophage inflammatory proteins, monocyte chemoattractant proteins, reactive oxygen species (ROS), nitric oxide (NO) prostaglandins, leukotrienes, thromboxanes and so on (Akiyama et al. 2000; Griffin et al. 1998; Mrak et al. 1995; Town et al. 2005; Tuppo and Arias 2005). The released inflammatory molecules, especially some cytokines such as interleukin (IL)-18, IL-1β and tumor necrosis factor (TNF)-α, impair the balance of normal neurophysiologic condition that correlates with cognition and learning and memory (Fillit et al. 1991; Gemma and Bickford 2007; Jankowsky and Patterson 1999; Liu et al. 2013; Varnum and Ikezu 2012). These secreted inflammatory mediators, in turn, activate more microglia and astrocytes to produce inflammatory molecules. In addition, immune cells including, T cells, B cells and monocytes are found to migrate from the periphery through the BBB and present in the brains of AD individuals (Conductier et al. 2010; Ruan et al. 2010; Savarin-Vuaillat and Ransohoff 2007).

Microglia and Astrocytes

Microglia are derived from monocyte precursor cells during embryonic development. They are generally considered to be the main resident macrophage species in the brain. Microglia are recognized as the key players in the innate immune/inflammatory responses against the injury that occurs in AD (Mandrekar-Colucci and Landreth 2010). In the central nervous system (CNS), approximately 10 % of the total cells are microglia (Benarroch 2013). Microglia are inactive under physiological condition. However, they can be stimulated by many factors including Aβ. Activated microglia changes the morphology; for instance, the branching and soma growth decreases, an amoeboid form appears as well as various specific markers on the cellular surface (Town et al. 2005). Activated microglia are phagocytic and able to migrate to clear the damaged cells or debris. They can also release inflammatory molecules such as ROS, cytokines, chemokines and some growth factors (Fig. 1).

Over two decades have passed, it is still impossible to make a conclusion about whether microglia should be considered as a friend or an enemy to CNS (Wyss-Coray and Rogers 2012). It was reported that, when microglia were moderately stimulated by low levels of Aβ, they had a strong capability to clear Aβ through phagocytosis. However, if microglia were strongly activated by high concentration of Aβ, they tended to enhance the generation

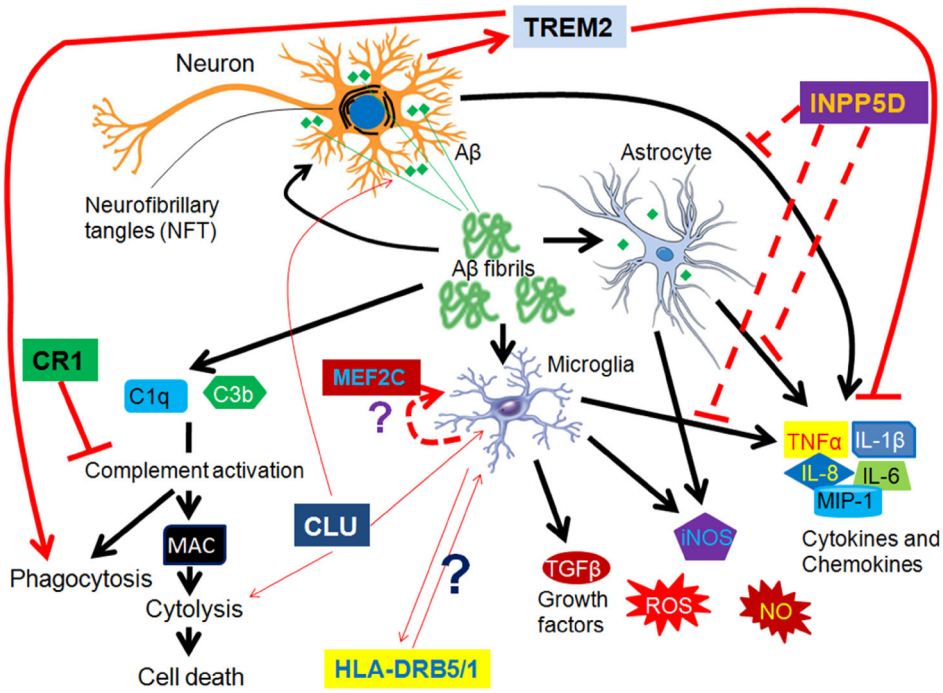

Fig. 1 Scheme of inflammation in Alzheimer's disease. Aβ peptides released by neurons, oligomerize and form Aβ fibrils that activate microglia and actrocytes. Activated glia cells produce inflammatory cytokines and chemokines, iNOS, some growth factors, ROS and NO. In response to the fibrillar Aβ stress, the complement system is also activated, resulting in enhanced phagocytosis or even cytolysis induced cell death

of pro-inflammatory molecules, such as IL-1β and TNF-α, resulting in neuronal damage and compromised ability of Aβ clearance (Liu and Chan 2014). Therefore, it seems that microglia in AD is like a double-edged sword. It can be either beneficial or detrimental, but not both at the same time.

Unlike microglia, astrocytes are generally treated to be the most abundant cells that support neurons in the brain (Sofroniew and Vinters 2010). They interact with neurons and are known to be involved in regulating the secretion and recycling of neurotransmitters, synaptic remodeling, energy metabolism, ion homeostasis as well as oxidative stress (Halassa and Haydon 2010; Henneberger et al. 2010). In AD, though the mechanisms are still elusive, it has been demonstrated that astrocytes can be activated in the presence of Aβ. Compared with quiescent astrocytes, reactive astrocytes can encircle senile plaques and form a cell barrier between the plaques and healthy neurons (Sofroniew and Vinters 2010). However, although astrocytes activation has a protective role for the brain, the role of astrocytes may not be beneficial under certain conditions. Several reports suggested that reactive astrocytes could be a producer for low amount of Aβ in addition to neurons, which are the major source of Aβ (Liu and Chan 2014). In vitro studies showed that, in response to Aβ, cultured astrocytes significantly overexpress a number of inflammatory related factors such as IL-1β, TNF-α, inducible NO synthase (iNOS), and NO (Fig. 1; White et al. 2005).

Neuron

As the core components of the brain, neurons were traditionally not treated as a part of neuroinflammation. However, some interesting evidence suggests that neurons also participate in the inflammatory response in the CNS. For examples, neurons can produce COX-2-derived prostanoids (Davis and Laroche 2003; Natarajan and Bright 2002; Pavlov and Tracey 2005), several cytokines such as IL-1β and IL-18 (de Rivero Vaccari et al. 2008; Fann et al. 2013; Zou and Crews 2012), complement and macrophage colony-stimulating factor (Du Yan et al. 1997). Moreover, in the brain of AD individuals, an inflammation-induced enzyme named iNOS has been reported to be expressed by degenerating neurons (Heneka et al. 2001; Lee et al. 1999; Vodovotz et al. 1996).

On the other hand, it has been noted that neurons are able to generate various molecules that are demonstrated to suppress inflammation, such as TREM2, CD22, CD200, CD59 and fractalkine (Hsieh et al. 2009; Mott et al. 2004; Ransohoff 2007; Singhrao et al. 1999; Walker et al. 2009). Interestingly, several of these molecules have been found to be deficient in AD. For instance, the expression of CD200 and CD59 was reported to be down-regulated in neurons of AD brain (Walker et al. 2009; Yang et al. 2000). Generally, studies in the expression of inflammatory molecules in neurons of AD individuals are still not fully explored, and more investigations into this area are needed.

The Complement System

The complement system is an essential part in activating and executing of immune responses (Wyss-Coray and Rogers 2012). This system consists of around 30 cell-membrane-associated and cytosolic proteins that are activated in cascade (Forneris et al. 2012). The factors of this system mainly have four biological functions, namely, recognition, opsonization, inflammatory stimulation through anaphylatoxins and direct killing through the membrane attack complex (MAC) (McGeer and McGeer 2002). Generally, certain molecular patterns on pathogens are recognized either by C1q molecule, mannose-binding proteins containing collagen-like receptor binding domains, or through the interaction with the C3 multifunctional protein (Sahu and Lambris 2001; Tenner 1999). Activated C3 recruits immune cells, amplifies antigen-specific immune responses, promotes phagocytosis, forms MAC by binding C5, C6, C7, C8 and C9 to facilitate complement-mediated cytolysis, and executes the cell death (Ricklin et al. 2010).

Complement proteins and receptors are mostly generated in the liver and have high concentrations in serum. However, many of them can be synthesized locally in the brain as well (Barnum 1995; Gasque et al. 1995; Morgan and Gasque 1996; Nataf et al. 1999). The abnormality of the complement system has been reported in brain injury and neurodegenerative disease (D'Ambrosio et al. 2001; Gasque 2004), including AD. In the brain of AD patient, it has been observed that the expression of C1q, C3b, C4d and C5b-9 is elevated, and the MAC colocalizes with senile plaques and tangle-positive neurons (Blalock et al. 2004; Fonseca et al. 2004; Katsel et al. 2009; Shen et al. 2001). In addition, in the microvasculature, microglia are reported to surround the fibrillar Aβ deposits (Fan et al. 2007). In vitro studies demonstrated that Aβ aggregates activated the complement system by binding C1q or C3b (Jiang et al. 1994; Rogers et al. 1992). Neurofibrillary tangles or aggregated tau were also observed to activate the classical pathway (Shen et al. 2001). In conclusion, both of Aβ and tau in AD can activate the complement system. Activated complement system is essential for the elimination of cell debris and the clearance of protein Aβ and/or tau aggregates, though it also promotes unwanted inflammation (Shen and Meri 2003).

Inflammatory Cytokines and Chemokines

Cytokines, mainly produced by immune system cells, are nonstructural soluble proteins with low molecular weights (8–40 kDa). They can be synthesized by a variety of immune cells including macrophages, T lymphocytes, natural killer (NK) cells and some non-immune cells as well, such as fibroblasts and Schwann cells. In the CNS, however, cytokines are secreted by microglia and astrocytes and have been linked to CNS development. Moreover, enhanced expression of pro-inflammatory cytokines, such as IL-6, IL-10, IL-1β, TNF-α, are observed in the brain and cerebrospinal fluid (CSF) of Alzheimer's patients (Blum-Degen et al. 1995; Jiang et al. 2011; Mrak and Griffin 2005; Tarkowski et al. 2002). In the animal models of AD, the expression level of TNF-α, IL-1α and IL-1β was also reported to be elevated (Apelt and Schliebs 2001; Benzing et al. 1999; Matsuoka et al. 2001; Sly et al. 2001). The production of these pro-inflammatory cytokines leads to microglial activation, astrogliosis, and induce the release of other pro-inflammatory molecules, amplifying the cytokine effects. The exact consequences of altered cytokines on brain function and neurodegeneration related to AD are still elusive, but growing evidence in AD model mice suggests that these inflammatory molecules may have potent effects on neurodegeneration, amyloidosis and learning and memory (Wyss-Coray 2006; Wyss-Coray and Mucke 2002). For example, in AD transgenic animals, cytokines are found to increase the susceptibility to Aβ deposition (Games et al. 1995; Guo et al. 2002) and upregulate beta-secretase 1 both at mRNA and protein level, as well as its enzymatic activity (Sastre et al. 2003).

Chemokines are the largest family of cytokines in human immunology. Their major function is to recruit immune cells, such as macrophages, lymphocytes, monocytes, neutrophils, basophils and dendritic cells toward sites where an inflammatory response is required (Meraz-Rios et al. 2013). Chemokines exert their biological effects through association with specific G-protein-coupled receptors called chemokine receptors which can be divided into four families, CXCR, CCR, CX3CR1 and XCR1 (Azizi et al. 2014). Growing evidence has shown that chemokines and their receptors are increased in the CNS, which may play important roles in neuroinflammation of neurodegenerative diseases, including AD, Parkinson's disease, multiple sclerosis, human immunodeficiency virus-associated dementia, and stroke (Duan et al. 2008; Ruan et al. 2010). In the brain of AD patients, monocyte chemotactic proteins, like MCP-1 or CCL2, and chemokine receptors including CCR3 and CCR5 are found to be present in activated microglia surrounding amyloid deposits. Even in the prodromal stage of AD, the expression of several chemokines such as inducible protein 10, CCL2, and CXCL8 are elevated both in brain tissue and CSF. In vitro studies demonstrated that Aβ peptide stimulated human monocytes to release chemokines such as IL-8 (CXCL8), macrophage inflammatory protein (MIP)-1α, MIP-1β and MCP-1. Moreover, it is observed that the

expression of IL-8, MIP-1α and MCP-1 after exposure to Aβ is upregulated in cultured microglia from rapid autopsies of AD patients and control individuals.

Molecular Genetics

It has been widely accepted that genetic factors play a key role in AD. It is estimated that approximately as much as 80 % of the phenotypic variability in AD is genetically caused (Cruchaga et al. 2012). The search for genes involved in AD has been ongoing for over two decades since 1987 (Tanzi 2012). It did not bring much reward until the application of GWAS which has revolutionized genetics research. Currently, GWAS has been the most common strategy to evaluate genetic variants in the genome using single nucleotide polymorphism (SNP) arrays to study the association with AD (Sherva and Farrer 2011). It can assess over one million SNPs in a single individual, genotype large number of populations (over 1000 subjects) and identify candidate genes in an unbiased manner (Mullane and Williams 2013). In 2009, the first replicable GWAS confirmed *APOE* as the first genetic risk factor for late-onset AD (LOAD). Since then, as a result of European and international genome-wide association collaborations, at least nine novel risk loci have been reported, including *CR1*, *BIN1, CD2AP, EPHA1, CLU, MS4A6A, PICALM, ABCA7* and *CD33* (Harold et al. 2009; Hollingworth et al. 2011; Lambert et al. 2009; Naj et al. 2011; Seshadri et al. 2010). Recently, a meta-analysis by the International Genomics of Alzheimer's Project found 11 new AD risk genes, including *CASS4, CELF1, FERMT2, HLA-DRB5/DRB1, INPP5D, MEF2C, NME8, PTK2B, SLC24A4/RIN3, SORL1* and *ZCWPW1*. Additionally, it confirmed 8 (*CR1, BIN1, CD2AP, EPHA1, CLU, MS4A6A, PICALM and ABCA7*) of the nine previously reported AD associated genes, in which *CD33* was ruled out due to the failure to replicate (Lambert et al. 2013). At the same time, two independent groups revealed *TREM2* as a rare but significant risk for AD through exome sequencing (Guerreiro et al. 2013; Jonsson et al. 2013). Not surprisingly, several of these AD risk molecules are involved in immune and inflammatory process (Bagyinszky et al. 2014). In this review, due to limitations of space, we mainly focus on these six genes: *CR1, CLU, HLA-DRB5/DRB1, INPP5D, MEF2C,* and *TREM2*.

Complement Receptor 1

The complement receptor 1 (CR1, also referred as CD35) is the receptor for the activated form of C3b and C4b complement components (Iida et al. 1982). The *CR1* gene is located on chromosome 1 at the locus 1q32 in a genetic cluster of complement activation genes (de Cordoba and Rubinstein 1986). CR1 is a multifunctional protein, which is widely expressed on the extracellular membrane of, B lymphocytes, monocytes, macrophages, erythrocytes, eosinophils, some CD4-positive T cells, dendritic cells, Langerhan cells in the skin glomerular podocytes and microglia as well (Crehan et al. 2013; Klickstein et al. 1988, 1997; Korotzer et al. 1995; Liu and Niu 2009). CR1 has two isoforms: CR1-F and CR1-S, where the F means the "fast" isoform with a smaller molecular weight while the S refers to "slow" isoform (Aiyaz et al. 2012). In addition, the expression of CR1-S isoform is lower than CR1-F in the brain of AD patients, compared with controls (Hazrati et al. 2012). CR1 acts as an inhibitor of complement activation through two pathways that lead to the dampening of the immune response and limiting surrounding tissue damage. The first one is that CR1, by reversibly binds binding to C3b and C4b, inactivates the C3 and C5 convertases, the multi-protein complexes including C3b and C4b. The second mechanism is that CR1 can promote the dissociation of the catalytic subunits C2a or Bb leading to acceleration of the decay of the C3 convertase (Liu and Niu 2009). In the brain, the exact mechanisms of how CR1-mediated complement regulates AD pathogenesis are elusive. However, it is speculated that CR1 is likely to be beneficial to AD through C3b-mediated clearance of Aβ deposits from the brain and/or protecting healthy neurons from inflammation-mediated impairment (Fig. 1). Several interesting hypotheses have been proposed, for example, the deficiency in C3b-mediated clearance of neurotoxic Aβ deposits from the brain and the potential beneficial effect through minimizing inflammation-mediated impairment of healthy neurons (Aiyaz et al. 2012; Thambisetty et al. 2013).

Clusterin

Clusterin (CLU), also known as apolipoprotein J, is a multifunctional glycoprotein, which was originally described because of its capability to induce cell aggregating in vitro (Blaschuk et al. 1983). *CLU* mRNA is widely expressed (de Silva et al. 1990) and the mature CLU product is secreted out of the cell to serve as an extracellular chaperone (Carver et al. 2003; Wyatt et al. 2009). Secreted CLU is a heavily glycosylated, 75–80-kDa heterodimeric protein that is linked by five disulfide bonds (Choi-Miura et al. 1992). *CLU* is reported to participate in numerous biological processes including roles in sperm maturation (Blaschuk et al. 1983), complement-mediated cell lysis (Hochgrebe et al. 1999), lipid transport (Jenne et al. 1991) and apoptosis (Kim et al. 2010; Scaltriti et al. 2004). The association between *CLU* and AD has been well demonstrated. Initially, the expression level of CLU was found to

be significantly elevated in the AD brain regions than compared with control subjects (May et al. 1990). Moreover, CLU was reported to be present in amyloid plaques (Giannakopoulos et al. 1998). In addition, recent studies have revealed that the concentration of CLU in the CSF and plasma of AD patients is significantly elevated (Sihlbom et al. 2008; Thambisetty et al. 2010). Interestingly, as a chaperone protein, CLU has been proven to interact with Aβ peptides and this interaction plays an important role in Aβ aggregation, toxicity and clearance (Baig et al. 2012; DeMattos et al. 2002; Narayan et al. 2012; Yerbury et al. 2007). Also, several studies have suggested that *CLU* is a potential modulator of inflammation in AD pathogenesis. Besides its role in complement-mediated cell lysis (which has been mentioned before), *CLU* has been shown to involve in complement activation (Urbich et al. 2000). In 2005, one study showed that CLU could activate microglia both in vivo and in primary rat microglia in vitro (Fig. 1; Xie et al. 2005). Most recently, CLU was reported to participate in astrocyte and microglia mediated Aβ clearance in vitro (Mulder et al. 2014). Moreover, *CLU* is suggested to indirectly regulate several inflammatory cytokines such as TNF-α and IL-6 (Yu and Tan 2012). In summary, though more evidence is needed, it seems that *CLU* might be involved in AD pathogenesis though facilitating Aβ aggregation, modulating astrocyte and microglia mediated Aβ clearance and complement activation, and stimulating microglia activation (Fig. 1).

HLA-DRB5/DRB1

The human leukocyte antigen (*HLA*) region is located on chromosome 6p21.3 and encodes proteins for the major histocompatibility complex (MHC). In human, HLA is the name of MHC. HLA and MHC are often used interchangeably in the literature (Torres et al. 2012). The proteins encoded by HLA play an important role in immune response, including antigen processing and presentation, and self-recognition by immune cells. Genes in this region are involved in a variety of pathways such as inflammation, the complement cascade, histocompatibility, and ligands for immune cell receptors (Downs-Kelly et al. 2007). The MHC complex can be divided into three subgroups: MHC classes I, II, and III, in which the class II MHC locates at the centromeric end and encodes genes including *HLA-DRA, -DRB1, -DRB3, -DRB4*, *-DRB5, -DQA1, -DQB1, -DPA1* and *-DPB1*. The class II HLA-DR antigens are expressed by antigen-presenting cells, including microglia in the brain and they can interact with T cell receptors. It has been reported that HLA-DR positive activated microglia are found in the substantia nigra of Parkinson's disease individuals (McGeer et al. 1988; Orr et al. 2005) and animals with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism (Hirsch and Hunot 2009). The experimental evidence of how HLA-DR associates with AD is extremely limited, but it is reasonable to speculate that, as another important neurodegenerative disease, the situation of HLA-DR in AD (Fig. 1) is probably similar to that in Parkinson's disease.

INPP5D

As a member of the inositol polyphosphate-5-phosphatase (INPP5) family, *INPP5D* is better known as SH2 domain containing inositol-5′-phosphatase, SHIP (also SHIP1 or SHIP1α). The human SHIP protein, encoded by the *INPP5D* gene located on chromosome 2q37.1, is an enzyme that hydrolyses the 5′-phosphate of phosphatidylinositol (PI)-3,4,5-triphosphate (PI(3,4,5)P3) to generate PI-3,4-bisphosphate (PI(3,4)P2) (Arijs et al. 2012). SHIP is expressed predominantly by cells in the hematopoietic compartment (Kerr 2011). SHIP it is also found to be present in osteoblasts, mature granulocytes, monocyte/macrophages, mast cells, platelets and NK cells (Cox et al. 2001; Geier et al. 1997; Giuriato et al. 1997; Hazen et al. 2009; Maresco et al. 1999; Trotta et al. 2005). As for the biological functions of SHIP, it was discovered to be the key negative regulator of IgE + Ag-generated PI(3,4,5)P3 levels in murine bone marrow derived mast cells (Huber et al. 1999). Also, SHIP negatively regulates IgE- or IgE + Ag-induced inflammatory cytokine release from mast cells, as well as B cell proliferation, chemotaxis and activation (Kalesnikoff et al. 2002; Kim et al. 1999; Sly et al. 2003, 2007). The function of SHIP in immune response and inflammation in the brain is still poorly understood. However, according to current knowledge about SHIP, it is possible that SHIP can suppress the release of various inflammatory cytokines from microglia, astrocytes or even neurons (Fig. 1).

MEF2C

The myocyte enhancer factor-2 (*MEF2*) proteins are members of the MADS (MCM1, agamous, deficiency, serum response factor) family of transcription factors (Naya and Olson 1999; Yu et al. 1992). In mammals, MEF2 proteins are encoded by four genes MEF2A, B, C, and D. The four *MEF2* isoforms are expressed in overlapped, however, with different patterns, both in the tissues of embryos and adults (Potthoff and Olson 2007). *MEF2C* is more widely expressed and regulates diverse transcriptional events such as the development and differentiation of many tissues (Potthoff and Olson 2007). In addition, *MEF2C* is found to be highly expressed in B cells of the spleen and lymph node (Swanson et al. 1998), and plays a critical role in B cell proliferation upon antigen stimulation (Khiem et al. 2008; Wilker et al. 2008). Recently, MEF2 is

reported to be a central transcriptional component of the innate immune response in the adult fly (Clark et al. 2013). In the adult brain of human and rodent, *MEF2C* is highly expressed in the regions closely associated with learning and memory, for instance, frontal cortex, entorhinal cortex, dentate gyrus, and amygdala (Leifer et al. 1994; Lyons et al. 1995). Recently, MEF2 is reported to be a central transcriptional component of the innate immune response in the adult fly (Clark et al. 2013). Therefore, it is a plausible possibility that MEF2 is also involved in the inflammatory process in the brains of individuals with AD through maybe regulating microglia proliferation (Fig. 1).

TREM2

Triggering receptor expressed on myeloid cells 2 (*TREM2*) is a member of the innate immune receptor TREM family, which is predicted to result in a R47H substitution that causes an ~3-fold increase in the susceptibility to LOAD. *TREM2* gene is located on chromosome 6p21.1 and encodes a 26-kDa transmembrane glycoprotein that consists of an extracellular immunoglobulin-like domain, a transmembrane domain, and a short cytoplasmic tail (Colonna 2003). It is an innate immune receptor expressed on the extracellular membrane of activated macrophages, osteoclast, immature dendritic cells, and microglia in the brain (Takahashi et al. 2005). Its signaling capacity is carried out through forming a complex with the TYRO protein tyrosine kinase binding protein (TYROBP, also known as DAP12) (Paloneva et al. 2002). The TREM2/TYROBP complex is reported to regulate key signaling pathways involved in differentiation of dendritic cells and osteoclasts, phagocytic activity in microglia and immune responses (Bouchon et al. 2001; Hsieh et al. 2009; Otero et al. 2012). In the CNS, it is revealed that TREM2 negatively regulates inflammatory responses by repression of cytokine production and secretion in response to both TLR2 and TLR4 ligands zymosan and LPS (Hamerman et al. 2006; Sessa et al. 2004; Turnbull et al. 2006). Therefore, TREM2 is speculated to be beneficial in AD pathogenesis (Fig. 1); its anti-inflammatory properties could reduce inflammation-induced innocent bystander neuronal damage (Boutajangout and Wisniewski 2013). In addition, *TREM2* is also known to participate in the regulation of phagocytosis that responsible for removing damaged or apoptotic neurons (Fig. 1), which promote tissue repair in response to AD-related pathology (Jiang et al. 2013). People with a loss-of-function mutation of *TREM2* have high risk to develop a chronic neurodegenerative disease (Nasu-Hakola disease) which is most probably due to the deficiency in eliminating tissue debris (Neumann and Takahashi 2007). Interestingly, it has been demonstrated that TREM2 is upregulated in AD mice (Fig. 1; Frank et al. 2008), possibly in a failed compensatory attempt by the mice to keep the inflammatory response in check (Hickman and El Khoury 2014).

Are These AD Risk Inflammation Associated Factors Potential Therapeutic Targets for AD?

On the basis of amyloid and tau hypothesis, a variety of therapeutic approaches and compounds have been developed for AD. Almost all of these strategies have focused on reducing of Aβ generation, aggregation, facilitating Aβ clearance, or inhibiting the level of phosphorylated tau or total tau or their fibrillization. Despite the unsuccessful results of extensive basic and clinical trials (Giacobini and Gold 2013; Yoshiyama et al. 2013), we have learned much valuable experience and lesson from the failure. Although it has limitations for the Aβ and tau cascade hypothesis, it is still a critical and useful theory to find novel potential therapeutic targets for AD. For example, just as what has been mentioned before, *CR1* and *CLU* have been suggested to participate in Aβ aggregation and clearance. For *HLA-DRB5/DRB1, INPP5D, MEF2C,* and *TREM2*, due to the limited basic research on their biological function in Aβ and/or tau associated metabolism, it is too early to speculate whether they are part of this process. However, we cannot rule out the possibility that these four candidates may be potential targets for AD treatment, either. Up to now, one fact that should not be bypassed is, the only approved pharmacological agents for AD treatment are *N*-methyl-D-aspartate receptor antagonist memantine and the cholinesterase inhibitors (donepezil, rivastigmine, galantamine) (Giacobini and Gold 2013). And none of these compounds act through mechanisms that can be explained by Aβ or tau cascade hypothesis. This interesting fact suggests that reduced level of Aβ or hyper-phosphorylated tau, though they are still very useful, should not be treated as the only criterion in searching new therapeutic targets for AD. These AD risk genes from GWAS should always be on the list of potential candidates for AD treatment, though the current evidence is too far from enough.

Conclusion

To date, the field of inflammation in AD has come a long way from its first discovery. Although a lot of evidence is tempting to conclude that inflammatory processes are the driving force of AD pathogenesis and that inhibiting inflammation would be beneficial, caution must be taken in deciding inflammation as the therapeutic target to prevent or treat the disease. Convincing data have demonstrated that many inflammatory molecules are like a double-edged

sword, and it may cause more problems than it can solve by simply suppressing them. Despite the complexity of the mechanism involved in AD pathology, inflammatory pathway is worth considering as a potential candidate for therapeutic interventions.

Genetic research in AD has broadened our understanding of the causes of AD. GWAS has become the most common method for identifying novel AD genes. Tens of AD risk genes have been identified in recent years. Several newly confirmed genes provide more clues about the involvement of inflammation in AD. Although the mechanism of how inflammation in AD is influenced by these genes (*CR1*, *CLU*, *HLA-DRB5/DRB1*, *INPP5D*, *MEF2C*, and *TREM2*) is still poorly known, these genes add new knowledge to our understanding of AD and may act as promising therapeutic targets to improve the prevention and treatment of AD.

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