■ Review ■

Importance of Microglial Cytoskeleton and the Actin-interacting Proteins in Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disorder and is expected to become more and more widespread as life expectancy increases. New therapeutic target, as well as the identification of mechanisms responsible for pathology, is urgently needed. Recently, microglial actin cytoskeleton has been proposed as a beneficial role in axon regeneration of brain injury. This review highlights in understanding of the characteristics of microglial actin cytoskeleton and discuss the role of specific actin-interacting proteins and receptors in AD. The precise mechanisms and functional aspects of motility by microglia require further study, and the regulation of microglial actin cytoskeleton might be a potential therapeutic strategy for neurological diseases.

Key Words: Alzheimer's disease, Microglia, Cytoskeleton, Actin filaments, Ionized calcium binding adapter molecules (Iba1), Cofilin 1 (CFL1)

INTRODUCTION

Alzheimer's disease is the most common neurodegenerative disorder and is characterized. Alzheimer's disease is expected to become more widespread as life expectancy increases, so urgent need for new therapeutic targets as well as the identification of mechanisms responsible for pathology. Over the past decade, two major functions of AD, early amyloid-β (Aβ) plaques and nerve fiber tangles (NFT), have been intended to provide insight into AD etiology. However, a number of investigations initially demonstrated that in addition to Aβ plaques and NFT, the brains of patients with AD showed evidence of a persistent inflammatory response (Akama et al., 2000; Akiyama et al., 2000; Combs et al., 2000; Tuppo and Arias, 2005; Mrak and Griffin, 2007). Several studies have shown an inflammatory response in post-mortem tissue samples of AD patients (Cribbs et al., 2012; Sudduth et al., 2013; Gomez-Nicola and Boche, 2015; Janssen et al., 2016; Knezevic and Mizrahi, 2018). Unlike acute inflammation, the anti-inflammatory and pre-inflammatory responses of AD are characterized by chronic inflammation, which occurs when the signal transmission balance is broken (Grammas, 2011; Rubio-Perez and Morillas-Ruiz, 2012; Meraz-Ríos et al., 2013; Ferreira et al., 2014). This chronic inflammation is due to the activation of microglia, moves and accumulates at the site of injury (Mittelbronn et al., 2001; Nimmerjahn et al., 2005; Ginhoux et al., 2010).

Recently, a number of papers have focused on microglial function of inflammatory cytokines, and chemokines. How-

1. Uropod

3. Lamelipodia
: branched actin filaments
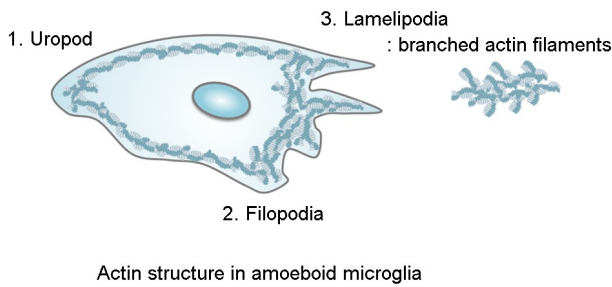
2. Filopodia

Actin structure in amoeboid microglia

Fig. 1. Representation of the vairous actin structures present in microglia. The cells reconstruct the actin filaments to form structures such as urapods (1), filopodia (2), and lamelopodia (3). Lamellipodia is containing branched actin filaments, which form the the mechanism of the actin network to easily connect with each other forming an intricate and highly plastic network.

ever, studies on dynamics of microglial actin cytoskeleton are rare. Recently, microglial actin cytoskeleton has been proposed as a beneficial role in brain injury through axon regeneration. This review highlights in understanding of the characteristics of microglial actin cytoskeleton in AD and discuss the factors that influence receptors and signaling pathways. In addition, the relative contribution by resident microglia during disease processes is also considered.

Morphological change for the mobility of microglia

Microglia has the ability to change shape. The ability allows for high mobility in tight spaces within the brain parenchyma and the feeding of various particles to adapt to the environment. The morphological change is the result of rearrangement of cytoskeletal proteins, in particular actin filaments. For motility and mobility, the cells reconstruct the actin filaments to form structures such as lamelopodia, filopodia and urapods (Fig. 1).

Lamellipodia is a very thin cytoplasmic membrane, containing a densely packed actin filament network arranged below the membrane. "Filopodia" plays an important role in intercellular signal transduction, chemical attraction and adhesion to the extracellular matrix. The structure called "uropod" attracts the rest of the cell body. The uropod is the posterior part of the cell formed by contractile trailing protrusions (Gupton and Gertler, 2007; Lai et al., 2008; Blanchoin et al., 2014; Hind et al., 2016; Franco-Bocanegra et al., 2019).

Actin filaments (F-actin) are the basic components of the actin cytoskeletal structure formed by the polymerization of spherical actin monomers (G-actin). The mechanism of F-actin formation in microglia is assembly, branching, cross-linking and degradation with other proteins. Actin polymers are produced by combinations of complex branch networks. Branching of F-actin plays an essential role in motility and mobility for the actin network (Vinzenz et al., 2012).

Mechanisms of microglial actin network

Polymers of F-actin interact with other proteins through crosslinking mechanisms to control motility and mobility. The crosslinking mechanism is a more complex structure than the actin network and is formed of actin filaments that allow for adaptability. Several crosslinked proteins have been reported that are specifically expressed depending on the cell type. The microglia involved in actin bundling and membrane ruffling with ionized calcium binding adapter molecules (Iba1) (Ohsawa et al., 2000). Actin bundles support the structures, such as lamellipodia and filopodia, which are structures essential for migration and phagocytosis of microglia (Bartles, 2000; Sasaki et al., 2001; Ohsawa et al., 2004).

Other cross-linking protein expressed by microglia, Cofilin 1 (CFL1) which serves as disassembly machinery in microglia. In order to respond to changes in the environment, the cross-linked proteins continue to carry out the mechanism of assembly as well as degradation. CFL1 is an actin-binding protein that cleaves the polymerization of actin filaments, and in this way produces G-actin monomers for filament elongating and branching. CFL1 is an important regulator of actin dynamics and is highly expressed in the human brain (Niwa et al., 2002; Samstag et al., 2013). A study has shown that CFL1 knockdown inhibits activation and migration of microglia (Alhadidi and Shah, 2018), which highlights the importance of CFL1 in microglial function.

Association with signaling pathways of phagocytosis

Specific receptors and signal transduction pathways contribute to the reconstitution of actin proteins are utilized for microglial phagocytosis (Fig. 2). In addition, phagocytosis of microglia may require several types of receptors to function (Fu et al., 2014). In general, there are highly affinity recep-
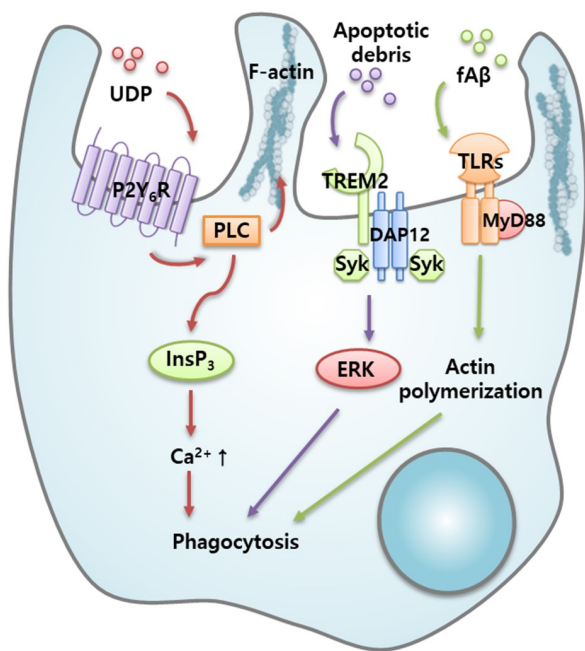
Fig. 2. Microglial phagocytosis and signal pathways associated with actin cytoskeleton in Alzheimer's disease. UDP trigger microglial phagocytosis through $P2Y_6R$/PLC/InsP3 pathway. Apoptotic debris induces phagocytosis via TREM-2/DAP12/ERK pathway. f-Aβ provokes phagocytosis by microglia via TLRs through activation of MyD88-dependent actin polymerization.

tors that bind to external microbial pathogens, such as Toll-like receptors (TLRs) and recognized apoptotic cell substances, such as Trigger Receptors Expressed on Myeloid cells 2 (TREM-2).

TREM-2 is located primarily on the cell surface of microglial cells of bone and central nerve system (CNS), up-regulating chemokine synthesis and mediating protective phagocytosis of apoptotic cell debris (Klesney-Tait et al., 2006; Napoli and Neumann, 2010). TREM-2 in microglial cells leads to the reconstitution of F-actin and phosphorylation of extracellular signal regulated kinase (ERK) / mitogen activated protein kinase (MAPK) through binding to DNAX activating protein 12 (DAP12) to mediate the removal of apoptotic neurons (Takahashi et al., 2005; Piccio et al., 2007). Clinical observation shows that TREM-2 / DAP12 aberrant signal transmission due to genetic mutations of TREM-2 and DAP12 results in Nasu-Hakola disease, a systemic osteocystic disease with progressive sporadic dementia and extensive sclerosis in the systemic frontal and basal ganglia

(Satoh et al., 2012).

Besides these two receptors, some receptors, including the complement receptor (Veerhuis et al., 2011), scavenger receptor, pyriminergic receptor P2Y G-protein binding 6 ($P2Y_6$), macrophage antigen complex 2, mannose receptors (Lucin and Wyss-Coray, 2009), and low density lipoprotein receptor-related protein receptors are involved in phagocytosis in brain inflammatory responses (Smith, 1999).

In particular, research on the $P2Y_6$ receptor has attracted attention over the past few years since the demonstration that $P2Y_6$ receptors induce uridine diphosphate (UDP)-induced microglial phagocytosis (Koizumi et al., 2007; Uesugi et al., 2012). $P2Y_6$ receptors actively respond to UDP and activate phospholipase C to induce the synthesis of inositol 1,4,5-triphosphate and to release Ca^{2+} (Koizumi et al., 2007). In addition to causing intracellular Ca^{2+} overloading, the $P2Y_6$ receptor dependent signaling pathway promotes actin cytoskeletal polarization to form filopodia-like protrusions, thereby promoting cell phagocytosis.

The role of actin-interacting protein in AD progression

Overall, the changes in microglial morphology have been noted presence of AD pathology, as evidenced in post mortem human brain. To observe the relationship between phenotype of microglia and disease progression in AD, the post mortem human brain study compared with morphology and number of microglia in various brain areas including the temporal cortex, and frontal cortex (Hopperton et al., 2018). The author of the study considered that the temporal cortex affected early AD, after which the frontal cortex was affected.

A reduced number of Iba1-positive microglia was observed in the temporal cortex, as well as an overall lower number of microglia. The activated form of ramified microglia was reported only in the visual cortex, indicating that microglia was activated during the early stages of AD. Therefore, it can be seen that microglia in the visual cortex are associated with tau pathology and have an inverse relationship between ramified microglia and arborized area.

In microglia, actin-interacting proteins can potentially play a role in aging and AD progression. Phosphorylated tau and co-localized CFL1-actin rods caused abnormal accu-

mulation and aggregation of F-actin (Fulga et al., 2007). Because tau is also a microtubule protein, tau hyperphosphorylation causes cytoskeletone dysfunction, which can also cause difficulties in regulating actin dynamics. In animal study, a reduction in levels of activated CFL1 was observed in an age-dependent manner in APPPS1 mice and exceeded those seen in aging in wild-type mice. This suggests that AD progress is associated with an increase in phosphorylated CFL1 (Hinman et al., 2004).

Microglial receptors and signaling pathways in AD disease

AD pathology utilized the APP/PS1 and 5XFAD transgenic mouse models of Aβpathology along with human AD brain tissues (Ulrich et al., 2014; Jay et al., 2015). Initial characterization of TREM2 in AD revealed the contribution of tau pathology using hTau mice (Bemiller et al., 2017). This exacerbation is accompanied by morphological dystrophy and extensive neurological stress kinase hyperactivation including ERK, c-Jun N-terminal kinase (JNK) and Glycogen synthase kinase 3β (GSK3β)-related pathways. TREM2 signal transduction in the context of amyloid pathology appears to have a disease-specific contribution of TREM2. Generally, they are protected at an early stage of the disease by promoting the removal of intracellular and extracellular pathological tau species and damaged neuronal debris. Inflammation and abnormal synapse and neuron swallowing, however, become pathogenic during the neurodegenerative stage of the prevailing disease (Leyns et al., 2017). In the study, the authors further emphasized the heterogeneity of TREM2 involved in the neurodegenerative process by the stage-specific response to pathology.

The role of the P2Y$_6$ receptor, a member of the G-protein-coupled receptor family, in AD has been investigated recently in several studies using animal models and post-mortem human brain (Lai et al., 2008; Ajit et al., 2013). Deletion of the P2Y$_6$R in a mouse model of AD increases the mortality, enhances neurological deficits and Aβ accumulation in the brain and decreases the migration of microglia to Aβ plaques (Ajit et al., 2013). Similarly, reduced P2Y$_6$R expression in microglia but also in astrocytes has been observed in post-mortem brain samples from AD patients, as compared to normal controls, suggesting that loss of P2Y$_6$R expression in microglia correlates with the AD progression in humans (Lai et al., 2008). These results suggest that P2Y$_6$R in microglia can prevent the progression of AD, particularly under neuroinflammatory conditions (Elliott et al., 2009).

CONCLUSIONS

Microglia, resident macrophages of the CNS, plays an important role in the pathological and physiological processes of the AD disease. Microglial cells are involved in several functions of the brain. Changes in cell motility and shape are associated with functional changes in the cell. Motility and mobility are determined by a number of actin interacting proteins and membrane receptors. AD has been found to change actin-interacting proteins, likely reflecting changes in motility of microglia, which may contribute to the development and progression of the AD disease. The current collected research has clearly identified the relationship between actin protein and tau. However, due to the relative lack of research on microglia motility proteins in AD, related studies are needed. This review also highlights in understanding of the role of specific actin-interacting proteins and receptors in aging and AD. The precise mechanisms and functional aspects of motility by microglia require further study, and the regulation of microglial actin cytoskeleton might be a potential therapeutic strategy for neurological diseases.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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