Invited Review Article

Neuroinflammation in motor neuron disease

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ABSTRACT

Increasing evidence suggests that the pathogenesis of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) is not restricted to the neurons but attributed to the abnormal interactions of neurons and surrounding glial and lymphoid cells. These findings led to the concept of non-cell autonomous neurodegeneration. Neuroinflammation, which is mediated by activated glial cells and infiltrated lymphocytes and accompanied by the subsequent production of proinflammatory cytokines and neurotoxic or neuroprotective molecules, is characteristic to the pathology in ALS and is a key component for non-cell autonomous neurodegeneration. This review covers the involvement of microglia and astrocytes in the ALS mouse models and human ALS, and it also covers the deregulated pathways in motor neurons, which are involved in initiating the disease. Based on the cell-type specific pathomechanisms of motor neuron disease, targeting of neuroinflammation could lead to future therapeutic strategies for ALS and could be potentially applied to other neurodegenerative diseases.

Key Words: neuroinflammation, glia, ALS, neurodegenerative disease.

INTRODUCTION

Neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), are characterized by the selective death of certain group of neurons. Therefore, for a long time, exploring the cause of selective neuronal death in these neurodegenerative diseases has been central to such research. In contrast, activation of glial cells located in the vicinity of degenerating neurons is observed in almost all neurodegenerative diseases. For many years, glial activation was regarded as a secondary phenomenon and as a consequence of neurodegeneration, since glial cells, named after the Greek word for "glue," were previously thought to do nothing more than holding the neurons together. However, recent research using genetic and chimeric mouse models elucidated an active role of glial cells in neurodegenerative diseases, and the term "neuroinflammation" has been used to describe the key phenomenon involved in the glia-mediated pathology of these diseases. Neuroinflammation, which is mediated by activated glial cells and infiltrated T lymphocytes and accompanied by the subsequent production of proinflammatory cytokines and neurotoxic or neuroprotective molecules, is a characteristic of many neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS).[1, 2] In this review article, we will review the evidence from animal and human studies that describe the

contribution of glia and neurons to ALS pathology.

ALS AND SOD1

ALS is an adult-onset, fatal neurodegenerative disease, characterized by the selective degeneration of both upper and lower motor neurons. Dysfunction and, ultimately, death of motor neurons result in the progressive paralysis of skeletal muscles and respiratory failure within 2–5 years of disease onset. Most cases of ALS occur sporadically; however, 10% of the cases are familial, and more than 20 causative genes have been identified. Among them, dominant mutations in the gene for copper/zinc superoxide dismutase (SOD1) are a frequent cause of inherited ALS.[3] Since its identification as a causative ALS gene in 1993, ALS research has advanced substantially by studying rodent models that overexpress the human SOD1 gene with ALS-linked mutation. Ubiquitous overexpression of the mutant human SOD1 protein in mice leads to progressive motor neuron degeneration. The degeneration seen in these mice resembles the pathology seen in humans, which includes selective motor neuron death and gliosis with abnormal accumulation of misfolded SOD1 proteins. SOD1 is a ubiquitously expressed enzyme that catalyzes the reaction of converting reactive superoxide to oxygen and hydrogen peroxide. It is now generally recognized that all SOD1 mutant proteins (both enzymatically active and inactive) uniformly provoke unidentified toxicities in degenerating neurons.[3, 4] To date, many hypotheses have been proposed to explain the link between mutant SOD1 and ALS, including damage to mitochondria, ER stress, defects in protein degradation machinery, axonal transport dysfunction, excitotoxicity from excess glutamate at synapse, and overproduction of neurotoxic molecules through neuroinflammation.[4, 5] It is likely that the combination of the above mechanisms, rather than a single mechanism, contributes to neurodegeneration in ALS.

NON-CELL AUTONOMOUS NEURODEGENERATION IN ALS

The selective death of motor neurons in ALS led researchers to focus on the pathomechanism within motor neurons, namely cell autonomous mechanisms. However, recent studies, including ours, indicate that non-cell autonomous processes also contribute to motor neuron degeneration in certain rodent models and may also contribute to the sporadic form of ALS. Restricted expression of SOD1 mutations in neurons in mice did not lead to neurodegeneration.[6, 7]; however, one case produced very late onset of moderate neurodegeneration.[8] Subsequently, wild-type neurons in chimeric mice consisted of both wild-type and mutant SOD1 expressing cells, acquired an ALS phenotype when surrounded by glial cells carrying the SOD1 mutation.[9] This is further validated by our study using chimeric mice derived from SOD1[G37R] mice. SOD1[G37R] mice ubiquitously express human SOD1 transgene with ALS patient-derived mutation at codon 37, which replaces glycine with arginine in the SOD1 protein.[10] Olig^{−/−} mice are a useful model since they are not able to generate motor neurons and oligodendrocytes.[11] In SOD1[G37R]:Olig^{−/−} chimeric mice, all motor neurons are derived from mutant SOD1-expressing embryonic cells, and they express the transgene at the same level as the mice with ubiquitous expression of mutant SOD1. In contrast, the cell types other than motor neurons and oligodendrocytes are mixture of wild-type and SOD1[G37R] cells. Despite high levels of mutant SOD1 expression in all motor neurons, SOD1[G37R]:Olig^{−/−} chimeric mice did not show motor neuron degeneration and had a longer survival time than SOD1[G37R] mice.[12] Thus, the concept of non-cell autonomous neurodegeneration is well established based on the findings from these genetic models of ALS.

Following these studies, a major unanswered question remained: precisely, which cell types contribute to motor neuron degeneration? We and others have engineered mouse models of ALS in which the mutant SOD1 transgene can be deleted in a cell type-specific manner using Cre-loxP system. Ablation of the mutant SOD1 transgene in either astrocytes or microglia using floxed SOD1[G37R] (loxSOD1[G37R]) or SOD1[G85R] mice with Cre recombinase significantly slowed the disease progression and extended survival times of mice.[13-16] Subsequently, using the loxSOD1[G37R] mice, oligodendrocytes were shown to be also involved in the non-cell autonomous neurodegeneration,[17] whereas mutant SOD1 expression in Schwann cells and skeletal muscle had little impact on the course of the disease.[18, 19] In summary, glial cells, such as microglia, astrocytes, and oligodendrocytes, are actively involved in the course of motor neuron disease.[5] Furthermore, since becoming established in ALS research, non-cell autonomous neurodenegeration has also been demonstrated in other neurodegenerative diseases, including polyglutamine diseases such as Huntington's disease and spinocerebellar ataxia, Alzheimer's disease, and Parkinson's disease.[20] Although these findings do not detract from understanding the pathomechanism within degenerating neurons, exploring the pathomechanism within glial cells will provide us a new direction of research and the potential for designing novel candidate therapeutics for those diseases.

MECHANISMS OF GLIA-MEDIATED NEUROINFLAMMATION IN ALS

Astrogliosis and microgliosis are pathological hallmarks of neuroinflammation in ALS.[21, 22] (Figure 1). Below, we have summarized the roles of microglia and astrocytes in the pathology of ALS as reported in studies of rodent models and humans with ALS.

1. Microglia as innate immune cell in CNS

Microglia, derived from the hematopoietic cell lineage, are generally considered to be the primary innate immune cells of the central nervous system (CNS). Progenitor cells for microglia develop in the embryonic yolk sac and then migrate into the CNS during embryogenesis. At present, many researchers agree that under normal conditions, monocytes and macrophages are not likely to infiltrate into the CNS and become microglia, except when the blood–brain barrier is damaged such as in experimental autoimmune encephalitis, following irradiation, or other brain
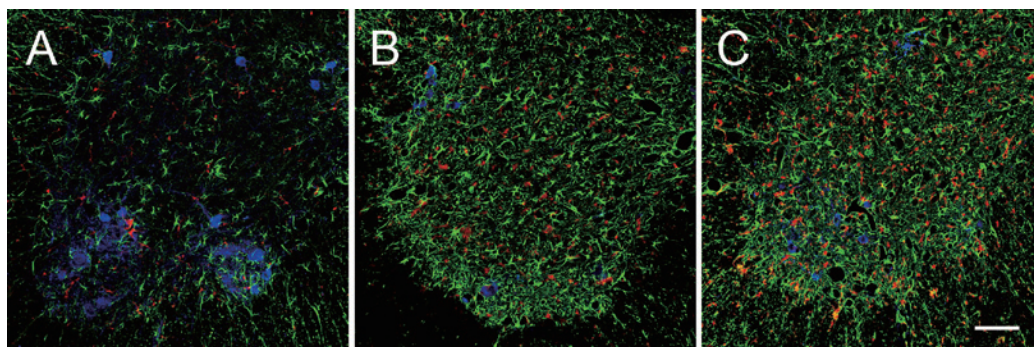

Fig. 1 Activated microglia and astrocytes in the lumbar spinal cord of mutant SOD1 mice.
Lumbar spinal cord sections from SOD1[G93A] mice at pre-onset (A), symptomatic stage (B), and end-stage (C) were stained with antibodies for ChAT (cholinergic motor neuron, blue), GFAP (astrocytes, green), and Iba-1 (microglia, red). Anterior horn regions were shown. Prominent activation of microglia and astrocytes with motor neuron loss were observed (B and C). Scale bar: 100 µm.

inflammatory diseases. Microglia, along with their dynamic arborizations of cellular processes, are continuously surveying the CNS environment. Under normal conditions, these cells are called as "resting microglia," a term recently called into question because we now recognize that microglia are continuously surveying the nervous system.[23] As innate immune cells, microglia sense and react to many types of damage, including microbial infection, microhemorrhage of blood vessels, immunoglobulin–antigen complexes, and abnormal, misfolded proteins in the neurodegenerative diseases. In response to such stimuli, microglia change their morphology from ramified to amoeboid form, migrate to the damaged cells, and clear the debris of the dead cells by phagocytosis. Through such processes, microglia release reactive oxygen species, proinflammatory cytokines, complements, and other toxic molecules, leading to the acceleration of neuronal dysfunction and death, which is the vicious cycle recognized as neuroinflammation.[2]

2. Microglia and neuroinflammation

Gliosis has long been known as a component of ALS pathology, with microgliosis being recognized in the past 20 years.[24] Research using positron emission tomography provided direct evidence of microglial activation in the brains of living patients with ALS. The intensity of microglial activation was correlated with the severity of disease, suggesting active involvement of microglial activation in ALS.[25] Microgliosis and inflammation have been demonstrated multiple times in lesions of mutant SOD1 mice and human with ALS. These lesions contain elevated levels of proinflammatory molecules such as cytokines (TNF-α: tumor necrosis factor-α, IL-1β: interleukin-1β, IL-12: interleukin-12, IFN-γ: interferon-γ, and others), reactive oxygen species (superoxide, nitric oxide, and its derivatives), chemokines, and glutamate.[26-29] Microglia also produce mitogenic factors (macrophage colony stimulating factor), anti-inflammatory cytokines (TGF-β: transforming growth factor-β), and neurotrophic factors (IGF-1: insulin-like growth factor-1), suggesting that there is a neuroprotective component in neuroinflammation (Figure 2).

3. M1/M2 hypothesis in microglia

In periphery, activated macrophages are categorized into two distinct phenotypes: classically activated (M1) and alternatively activated (M2) phenotypes. M1 macrophages secrete proinflammatory molecules (TNF-α, IL-1β, IL-12, nitric oxide, superoxide, etc.) with impaired phagocytic activity hence considered as cytotoxic, whereas M2 macrophages secrete anti-inflammatory molecules (IL-4: interleukin-4, IL-10: interleukin-10, TGF-β) and trophic factors (IGF-1) with increased phagocytic property, therefore regarded as cytoprotective.[30] As an analogy to macrophages, polarization of M1/M2 microglia *in vitro* was induced by the addition of LPS (lipopolysaccharide) or IFN-γ for M1 and IL-4 for M2.[31] In mutant SOD1 mice, a phenotypical shift from M2 microglia to M1 microglia during disease progression was proposed.[32] Although it is an intriguing hypothesis that may explain the pathomechanism of neurodegenerative diseases from a view of microglial polarity, increasing evidence suggests that microglial activation status cannot be explained by just two populations and is more complex and distinct among the diseases.[2]

4. Microglia as determinant of disease progression in ALS

The active role of microglia in disease progression was demonstrated by three lines of evidence. Selective reduction of mutant SOD1 from microglia/macrophages in mice using the Cre-LoxP system slowed disease progression in SOD1^{G37R} and SOD1^{G85R} mice.[13, 15] A complimentary approach in which microglia/macrophage was replaced via bone marrow transplantation demonstrated that wild-type microglia/macrophage slowed disease progression in SOD1^{G93A} mice.[33] Subsequently, non-cell autonomous effects of mutant microglia *in vitro* were also demonstrated by showing reduced survival of the primary cultured motor neurons cocultured with mutant-
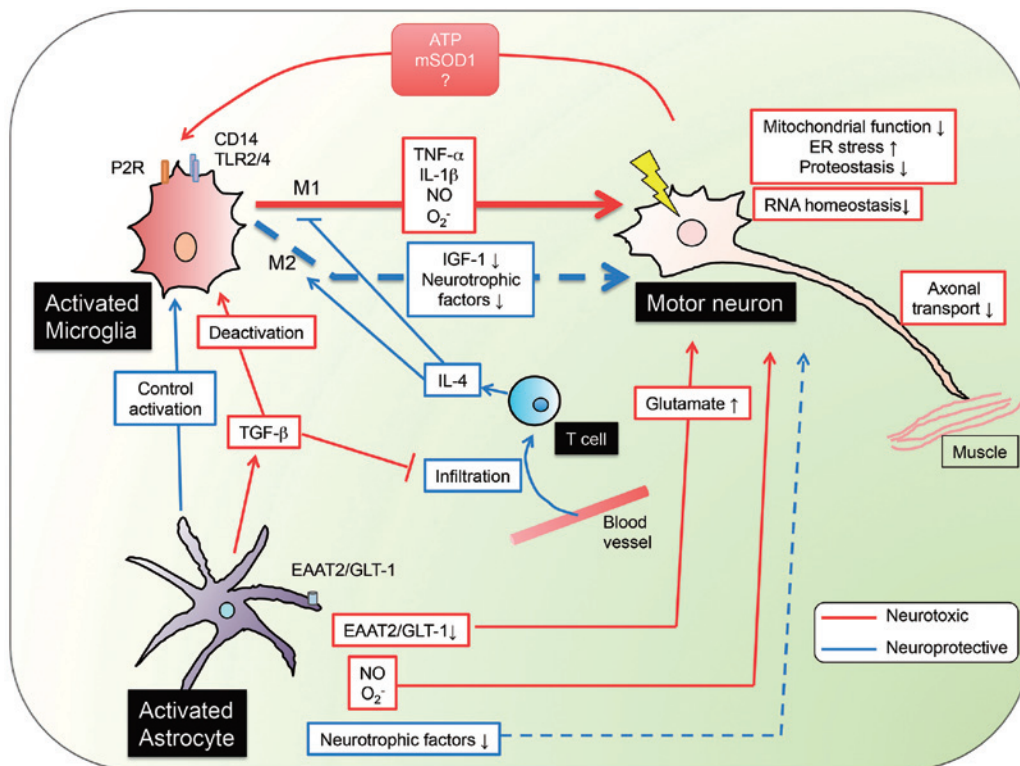
Fig. 2 Cell and non-cell autonomous neurodegeneration in ALS.
Age-dependent accumulation of damage within motor neurons initiates motor neuron disease. Unidentified factors derived from damaged motor neurons cause microglial activation. Astrocytes and infiltrated T lymphocytes also regulate activation status of microglia. Abnormally activated microglia and astrocytes produce high levels of proinflammatory molecules, together with losses of neuroprotective properties from those glial cells, cause further damage to motor neurons, hence, driving rapid disease progression. Among the numerous factors secreted from diseased astrocytes, we identified TGF-β1 as one of the exacerbation factors to drive disease progression through interfering the neuroprotective reaction mediated by microglia and T lymphocytes.

expressing microglia.[34]

5. Innate and acquired immunity in ALS

The identity of factors that activate microglia release has been explored. The innate immune system is the first line of defense against invading pathogens, which are recognized mainly through Toll-like receptors (TLRs). Elevated levels of innate immune receptors such as TLR2 and CD14 were described in mutant SOD1 mice. Furthermore, transplanting bone marrow deficient in MyD88 (myeloid differentiation factor 88), an essential adaptor protein responsible for most TLR signaling, accelerated disease progression in SOD1[G37R] mice.[35] This outcome is likely related to the effect of irradiation in the process of chimeric mice generation.[36, 37] Indeed, genetic ablation of MyD88 had no effect on disease course in SOD1[G37R] mice,[35] although inactivation of NFκB, a transcription factor downstream of MyD88, seems to be effective in controlling the disease. Recent work demonstrated that selective inhibition of NFκB signaling in microglia prolongs the survival time of mutant SOD1 mice.[38] Till date, factors known to be released from

damaged neurons in ALS models are ATP and extracellular SOD1, which activate microglia *in vitro* through purinergic receptors and CD14, respectively.[39, 40] Other factors central to damaged motor neuron-microglial communication and the role of innate immune system in ALS should be explored further (Figure 2).

In contrast to the innate immune system, the role of acquired immunity in ALS has recently been investigated. The presence of T lymphocytes in spinal cord lesion of ALS mice and sporadic ALS patients suggested the involvement of acquired immunity in ALS.[41] Genetic ablation of CD4+T cells or functional total T cells (through RAG2 gene deletion) accelerated disease progression in ALS mice.[42, 43] In cited studies, CD4+T cells were considered to stabilize microglial activation status with a decreased level of proinflammatory cytokines and an increased level of the neurotrophic factor IGF-1. Another study showed that transferring CD4+CD25+ cells (regulatory T cells) extended the life span of ALS mice.[44, 45] These studies support the idea that a specific population of T lymphocytes plays a protective role through controlling microglial activation. These studies also provide the basis for intriguing immunological research about motor neuron disease that can be done in the future.

6. Targeting microglia to control neuroinflammation in ALS

Several approaches to controlling neuroinflammation by targeting microglia have been successful in ALS mouse models. For example, eliminating microglia-derived superoxide by administration of apocynin significantly slowed disease progression in mutant SOD1 mice,[46] however, other group failed to reproduce the efficacy of this compound.[47] Alternatively, glutamate secreted from microglia seems attractive targets for treatment. Blocking excess glutamate secretion from microglia either by pharmacological blockade of gap-junction[48] or by genetically eliminating the system xC-transporter[49] slowed disease progression in mutant SOD1 mice. Moreover, recent study demonstrated that miR-155, one of the micro RNAs, was elevated in human ALS and mutant SOD1 mice. Eliminating miR-155 through genetic ablation[50] or administration of antisense oligonucleotide[51] extended survival time of SOD1^{G93A} mice, partly through restoring microglial functions and controlling neuroinflammation.

7. Astrocytes in ALS

Astrocytes have many important functions in maintaining and supporting CNS neurons. One of their important functions is to maintain low extracellular concentrations of glutamate. Excess glutamate in the synaptic cleft results in excessive neuronal firing and increased influx of calcium and can be toxic to neurons. Astrocytes clear excess glutamate from the synaptic cleft predominantly through the EAAT2/GLT-1 glutamate transporter. Evidence suggests that defects in clearing glutamate by astrocytes are due to a loss of EAAT2/GLT1 transporter in sporadic and familial ALS human cases as well as SOD1 mice.[52-54] Riluzole is a pharmacological agent that reduces glutamate release from nerve terminals and is the only approved drug for ALS, supporting the idea that excitotoxicity is implicated in ALS. A second role that can be attributed to deleterious astrocyte behavior in ALS is the insufficient release of neurotrophic factors that are important in maintaining neuronal health. Glial-derived neurotrophic factor, brain-derived neurotrophic factor, and ciliary neurotrophic factor are all released by astrocytes and support the survival of motor neurons.[55] A loss of neurotrophins from astrocytes might indirectly be involved in neuronal death. In contrast, ALS astrocytes may release neurotoxic factors. *In vitro* studies confirm that factors released by SOD1 astrocytes in culture media can induce apoptosis in motor neuron cultures. One of the identified toxic factors is neurotrophic growth factor.[56] Similarly, embryonic stem (ES) cell derived motor neurons cocultured with mutant SOD1-expressing astrocytes survive for a shorter period than the neurons cultured with wild-type astrocytes, supporting the mechanism

of non-cell autonomous neurodegeneration.[57-59]

8. *Targeting neuroinflammation in ALS astrocytes*

Astrocytes have been recognized as a promising therapeutic target, and new studies of intervention are coming to attention. We have demonstrated that selective ablation of the mutant SOD1 gene from GFAP-positive astrocytes slows disease progression and extends lifespan in ALS mice.[14] In this study, mutant astrocytes were prone to enhanced microglial activation, suggesting a potential role for astrocytes in controlling microglial activation. Alternative approaches for targeting diseased astrocytes include selective activation of antioxidant genes through the Nrf2-ARF system[60] and transplanting glia-restricted stem cells.[61] Subsequently, we have recently identified TGF-β1 as a key factor upregulated in astrocytes of ALS mice and patients with ALS. TGF-β1 is known as an inhibitory cytokine that is implicated in homeostasis of the immune system, microglial development, and neuroprotection. Astrocyte-specific overproduction of TGF-β1 in SOD1^{G93A} mice accelerated disease progression resulting in reduced IGF-1 production in deactivated microglia and fewer infiltrating T cells with an IFN-γ-dominant milieu, while astrocyte-specific gene ablation of mutant SOD1 resulted in lower levels of TGF-β1 in astrocytes and slowed disease progression. Moreover, expression levels of endogenous TGF-β1 in SOD1^{G93A} mice negatively correlated with lifespan. Furthermore, administration of a TGF-β signaling inhibitor after disease onset extended survival time in SOD1^{G93A} mice. These findings indicate that astrocytic TGF-β1 determines disease progression by inhibiting the neuroprotective inflammatory response mediated of microglia and T cells, suggesting that targeting astrocytic TGF-β1 is a promising candidate for the therapy of ALS (Figure 2).[62]

MOTOR NEURON AS A KEY COMPONENT OF DISEASE

The increasing number of studies that describe the role of glial cells in ALS should not undervalue the role of the motor neuron in the pathomechanism of ALS. Indeed, our cell type-specific gene excision approach demonstrated that mutant SOD1 toxicities in motor neurons determine the time of disease onset in mice.[13, 14] Numerous studies have shown that pathogenic changes in motor neurons might trigger ALS. Based on research on SOD1-linked ALS, defects in mitochondrial function, ER stress, proteostasis, and axonal transports have been suggested as plausible pathomechanisms in motor neuron degeneration (Figure 2).[3, 4] There are many reports to reduce proteotoxicities in ALS models by activating chaperone system and protein degradation machineries, such as ubiquitin-proteasome pathway and autophagy-lysosomal pathway. For example, to reduce the toxic effects of misfolded mutant SOD1, we have found that inducing the chaperone system through activating sirtuin 1, a longevity-related gene, or inducing autophagy, and inhibiting cathepsin B through administration of cystasin C, an endogenous cysteine protease inhibitor, protected motor neurons from mutant SOD1 toxicities.[63, 64]

In addition to the mechanisms mentioned earlier, the recent discovery of ALS genes related to RNA metabolism, such as TAR-DNA-binding protein-43 (TDP-43), fused in sarcoma, and C9Orf72, illuminates a novel important pathway: abnormal RNA homeostasis.[65] Abnormal accumulation of the TDP-43 protein was identified in the lesions of almost all cases of sporadic ALS and a subgroup of patients with frontotemporal dementia (FTD). In addition, missense mutations of TDP-43 gene were found in familial and sporadic ALS and FTD.[66] Evidence from genetics and pathology indicate that misregulation of TDP-43 is central to neurodegeneration in sporadic ALS. Multifunctional roles of TDP-43 in RNA homeostasis have been reported. These include regulating transcription, splicing, transport, and stabilizing mRNAs as well as micro

RNA biogenesis, regulating non-coding RNAs and cytosolic RNA granules, and spliceosomal integrity.[65, 67, 68] Furthermore, aggregate-prone properties of the TDP-43 protein suggest a role for abnormal proteostasis in neurodegeneration. In contrast to SOD1-ALS, the pathomechanism for TDP-43 mediated ALS is considered as both a loss of TDP-43 function and a gain of toxicities.[65, 68] Dominant mutations of TDP-43 lead to ALS with a pathology closely resembling sporadic ALS. One of the mechanisms to explain disrupted proteostasis by TDP-43 mutation is increased stability of protein. Mutant TDP-43 proteins uniformly exhibit longer half-lives in cells, and accelerated disease onset is correlated with longer half-lives of mutant proteins.[69-71] In sporadic ALS, multiple events including non-genetic factors such as aging may initiate deregulation of TDP-43 through compromised protein degradation machinery. Once the TDP-43 protein starts to accumulate with disrupted autoregulation to control its own RNA level, then it causes a vicious cycle for further accumulation, misfolding, and aggregation of TDP-43 proteins to disrupt homeostasis in motor neurons.[65] On the other hand, the mechanisms to cause deregulation of TDP-43 should be explored as an upstream pathway in ALS. While yet to be solved, the pathomechanism for ALS motor neurons is a key element in initiating disease in ALS.

GLIAL ALTERATION IN TDP-43-LINKED FAMILIAL ALS

The recent discovery of new ALS genes, including TDP-43, provides researchers with the opportunity to develop new animal models, however, no standard ALS models of TDP-43-linked or sporadic ALS have been established yet. Beside of prominent TDP-43 accumulation in ALS motor neurons, TDP-43 has also been identified as a key protein component of glial cytoplasmic inclusion (GCI) mainly found in the oligodendrocytes of ALS tissue.[72] Less frequently, TDP-43 deposition is also found in ALS astrocytes. In TDP-43 mouse models, several reports suggested involvement of the glial cells in disease. Involvement of microglial NFκB in neuroinflammation of TDP-43-linked ALS was demonstrated in the mice ubiquitously expressing mutant TDP-43.[73] Moreover, an inducible robust expression of mutant TDP-43^{M337V} transgene in astrocytes led to progressive neurodegeneration in the rat model, indicating that non-cell autonomous pathomechanism might also be involved in TDP-43-linked ALS.[74] On the other hand, transplanting astrocytic precursor cells derived from disease-causing mutant TDP-43^{A315T} mice in the cervical spinal cord of wild-type rat did not produce pathological changes in the motor neurons.[75] Discrepancy among these studies might be attributed to the expression levels of mutant TDP-43 in astrocytes. Other study pointed out the role of astrocytes in neurodegeneration in mice with chronic depletion of TDP-43 predominantly in astrocytes.[76] Although the molecules in glial cells responsible for the neurodegeneration of TDP-43 linked-ALS need to be identified, glial dysfunction is likely to be involved in TDP-43 linked ALS.

TARGETING NEUROINFLAMMATION IN SPORADIC ALS

Most of the studies cited here that aim to control neuroinflammation used inherited ALS mouse models to verify their effects. It should be noted that the disease mechanisms of mutant SOD1-mediated familial ALS could be different from sporadic ALS. In addition, the molecules deregulated in glial cells in mutant SOD1-mediated ALS should be re-evaluated in human sporadic ALS cases to validate the usefulness of SOD1 mouse models for research regarding the control neuroinflammation. Alternatively, to explore the therapeutic targets in glial cells of sporadic ALS, researchers recently established glial progenitor cells isolated directly from post-

mortem spinal cords of patients with sporadic ALS. Despite limited resources, technical hurdles, and ethical hurdles, they found that astrocyte-like cells from patients with sporadic ALS showed an inflammatory phenotype with elevated levels of chemokines, proinflammatory cytokines, and components of the complement cascades and were toxic to ES-cell derived motor neurons.[77, 78] Another approach is to generate astrocytes from iPS cells of ALS patient with TDP-43 mutation. Although there are no reports to study iPS cell-derived glial cells from sporadic ALS patients, one study described that iPS-derived astrocytes from a single ALS case with TDP-43 mutation showed abnormality in themselves and decreased survival *in vitro*.[79] To date, only a few tools are available for studying the role of glial cells in sporadic ALS; therefore, more tools need to be established and validated.

CONCLUSION AND PERSPECTIVE

Active contributions of neuroinflammation in ALS pathology have been extensively demonstrated and are summarized in this review (Figure 2). It should be also considered whether it is feasible to translate the research results from ALS rodent models to development of treatments for sporadic ALS. To date, many clinical trials based on the research using mutant SOD1 mice have been conducted for patients with sporadic ALS; however, hardly any drugs were demonstrated efficacy for sporadic ALS. Failure to translate results of rodent models to sporadic human patients was mainly attributed to two reasons: (1) insufficient protocols in rodent study, including the timing of drug administration (Drugs should be administered after the disease onset) and small sample sizes and (2) differences in the mechanisms of the disease between SOD1-linked ALS and sporadic ALS.[80, 81] We would like to emphasize that more work is necessary to test whether there is a common mechanism for neuroinflammation in SOD1- or TDP-43-linked ALS and sporadic ALS. Controlling neuroinflammation has also been the focus in other neurodegenerative diseases including Alzheimer's and Parkinson's diseases.[2, 82] Further understanding of molecular pathology within glial cells will contribute to developing therapies that will slow the progression of ALS, benefiting patients with sporadic and familial ALS.

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