Nagoya J. Med. Sci. **85**. 30–32, 2023
doi:10.18999/nagjms.85.1.30

Neuroinflammation in neurodegenerative disease

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Komine O, Yamanaka K. Neuroinflammation in motor neuron disease. *Nagoya J Med Sci*. 2015;77(4): 537–549.

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.

Keywords: neuroinflammation, glia, ALS, neurodegenerative disease

Neuroinflammation is mediated by activated glial cells and infiltrated lymphocytes, leading to the subsequent production of proinflammatory cytokines and related molecules. It is associated with the pathomechanism of various neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). The term "neuroinflammation" first appeared in the research articles in 1995 to refer to the glial response and lymphocyte infiltration in the central nervous system (CNS) of patients with infectious and autoimmune neurological diseases such as multiple sclerosis. This term appears only in ≈ 300 articles during initial 10 years (1995–2004), and subsequently in more than 10,000 articles during a few years after we published the review

Received: October 16, 2022; accepted: November 10, 2022
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article in *Nagoya Journal of Medical Science* in 2015.[1] This clearly suggests the development of this concept in the neuroscience research field, owing to its significance in the various aspects of CNS diseases.

The role of neuroinflammation in neurodegenerative diseases has substantially expanded. In ALS, an adult-onset motor neuron disease, the role of microglia and astrocytes in disease progression has been identified in Cu/Zn superoxide dismutase (SOD1)-mediated ALS mouse model.[2,3] Moreover, astrocytic TGF-β1 has been identified as a key regulator that inhibits the neuroprotective inflammatory response mediated by microglia and T cells in ALS mice, suggesting that targeting astrocytic TGF-β1 has a promising potential for ALS treatment.[4]

More recently, the phenotypic heterogeneity of reactive astrocytes has been described and extensively analyzed. A subset of activated astrocytes in ALS-SOD1 mice was immunopositive for ubiquitinated-SOD1 aggregates, suggesting that they are defective in proteostasis. These reactive astrocytes have atypical shape, and are immunopositive for ubiquitin and cleaved caspase-3, suggesting they are degenerating and aberrantly activated astrocytes. The novel role of TRIF, an innate immune adaptor protein essential for the toll-like receptor signaling, has been identified in eliminating such aberrantly activated astrocytes.[5] However, the phenotypic heterogeneity of astrocytes is not limited in ALS. One study demonstrated that the toxic reactive astrocytes, referred to as A1 astrocytes, were induced by the specific sets of cytokines released from activated microglia in vitro and were present in the lesions of various neurodegenerative diseases including ALS with a specific marker of complement C3. Although A1 astrocytes are toxic to cultured neurons, the detailed molecular basis of toxic properties of A1 astrocytes remains unknown, and whether the mechanism of A1 astrocytes-mediated toxicities is common to diverse neurodegenerative diseases should be determined.

With regard to the polarity of microglial activation, M1/M2 microglia define detrimental/beneficial activation phenotype, in analogy to macrophage activation. However, recent studies questioned the existence of such polarization of microglia. More recently, disease-associated microglia (DAM) have been proposed as an activation phenotype defined by a subset of deregulated genes and are found in the various neurodegenerative diseases in common.[6] The association between DAM with the severity and progression of neurodegenerative diseases is unclear. Thus, in this study, we compared the gene expression profiles of isolated microglia from a diseased brain or spinal cord of three mouse models for AD and ALS: $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice with an amyloid pathology, rTg4510 mice with tauopathy, and $SOD1^{G93A}$ mice with motor neurodegeneration by RNA-sequencing.[7] Despite robust neuroinflammation with microglial responses in all mouse models, $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice do not show neuronal death, whereas rTg4510 and $SOD1^{G93A}$ mice show a substantial loss of neurons. Moreover, we found that the reduction of homeostatic microglial genes, which are linked to physiological microglia function, was correlated with the severity of neurodegeneration, whereas the DAM genes were uniformly upregulated in all mouse models. Moreover, in human precuneus with early AD pathology, gene expressions of microglia and oligodendrocytes were reduced, although the DAM genes were not upregulated. The glial phenotypes were correlated with the severity of neurodegeneration, hence provides insights to better understand the role of glial dysfunction in the progression of Alzheimer's disease.[7]

Oligodendrocytes are less explored in neurodegenerative diseases. In ALS, abnormal accumulation of TDP-43, an RNA binding protein, in motor neurons and oligodendrocytes is recognized as a pathological hallmark. The mechanisms through which oligodendrocytes with TDP-43 aggregation play a detrimental role in ALS require further investigation, that may provide a clue to identify the novel therapeutic targets for this devastating disease.

ACKNOWLEDGMENTS

This study is partly supported by Grants-in-Aid for Scientific Research (A) JP22H00467 from the Japan Society for the Promotion of Science (JSPS), AMED (grant number: JP22wm0425014), and JST (grant number: JPMJMS2024).

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