Novel therapeutic strategy for NMO: RGMa-mAb found effective against CNS inflammation

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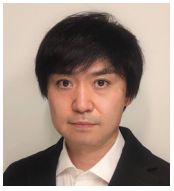


Abstract

Neuromyelitis optica (NMO) is a currently incurable immune-mediated inflammatory disorder of the central nervous system (CNS). In the present study, using a clinically relevant NMO rat model and an NMO-autopsied human samples, we provide new insights on the pathophysiological mechanism of NMO, and show that an antibody against repulsive guidance molecule-a (RGMa) can ameliorate NMO-associated motor deficit and neuropathic pain by interrupting the interplay between immune cells, specifically macrophages and neutrophils.

Background & Results

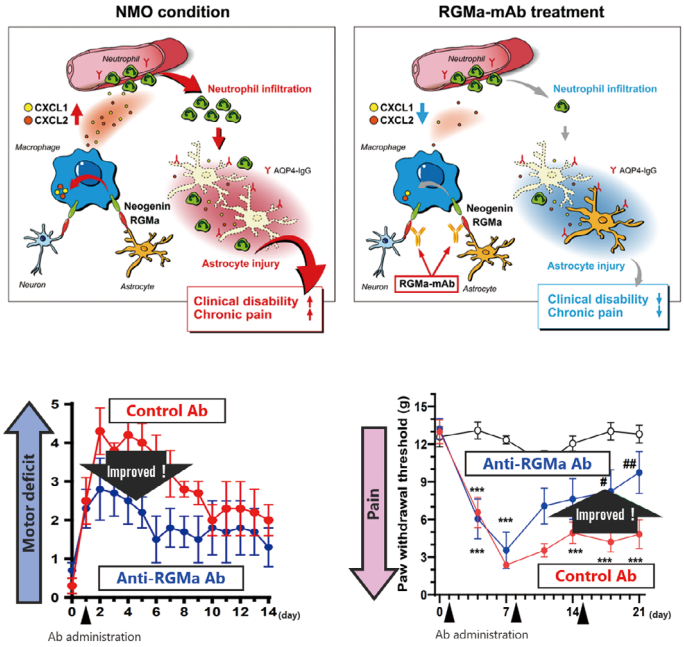
A key feature of NMO is “perivascular astrocytopathy”, that is caused by the leakage of pathogenic autoantibodies against the water channel protein aquaporin-4 (AQP4) into the CNS. Acute NMO attacks are frequently severe, causing visual loss, paraplegia, intractable neuropathic pain, and death.

RGMa is a membrane-associated glycosylphosphatidylinositol-anchored glycoprotein which has multiple functions including neurite growth inhibition and immune regulation, and has been implicated in various central nervous system (CNS) disorders such as multiple sclerosis and spinal cord injury.

In the present study, we investigated the possible involvement of RGMa signaling in the pathology of CNS inflammation under NMO condition. We found that, both in NMO rats and NMO-autopsied human samples, RGMa is expressed by neurons and astrocytes, whereas its receptor neogenin is expressed by infiltrating macrophages. Exploiting their contribution, we treated the NMO rats with anti-RGMa neutralizing antibody and evaluated the therapeutic effect by behavioral testing (motor symptom and neuropathic pain), immunohistochemistry, and gene expression study. Anti-RGMa antibody treatment resulted in less astrocytic death and decreased clinical symptoms. Interestingly, we found that RGMa-mAb treatment clearly suppressed neutrophil infiltration along with decreased expression of neutrophil-attracting chemokines. We then found that neogenin-expressing macrophages accumulated in the lesion site expressed strong neutrophil chemoattractants. Further analysis revealed that RGMa directly regulated the expression of chemoattractants in macrophages. Therefore, RGMa signaling in infiltrated macrophages is considered as a critical driver of neutrophil-related astrocytopathy in NMO lesions.

Significance of the research and Future perspective

Our findings revealed a new molecular mechanism of NMO pathophysiology in which RGMa stimulates macrophages to attract neutrophils to the lesions, that lead to the exacerbation of CNS inflammation. The interplay between macrophages and neutrophils revealed by our present study is possibly shared by a variety of CNS inflammatory conditions. Therefore, RGMa-mAb treatment may provide an efficient therapeutic strategy for treating wide range of CNS diseases.



Patent Japanese Patent Application No. 2021-567731

Treatise Iwamoto, Shosuke; Itokazu, Takahide; Yamashita, Toshihide et al. RGMa signal in Macrophages Induces Neutrophil-related Astrocytopathy in NMO. Annals of Neurology. 2022, 91, p. 532-547, doi: 10.1002/ana.26327

URL https://www.med.osaka-u.ac.jp/pub/molneu/index_e.html

Keyword neuromyelitis optica, macrophage, RGMa