

INTRODUCTION

Neuromyelitis Optica (NMO), or Devic's Syndrome, is an inflammatory autoimmune disease that causes damage to the cells of the central nervous system. NMO is a relapsing-remitting disease, characterized by recurrent and severe episodes of optic neuritis and transverse myelitis. Damage to the optic nerve leads to vision loss and eye pain, while damage to the spinal cord leads to weakness and paralysis of limbs, loss of sensation, and issues with bladder and bowel function. Until recently, NMO was classified as an acute form of multiple sclerosis. However, in 2003, data from the Mayo Clinic confirmed the presence of a disease-causing antibody, NMO-IgG. Various studies have shown that NMO-IgG binds to aquaporin-4 (AQP4) found in high concentrations on the foot processes of astrocytes in the central nervous system. This binding causes astroglia to produce classical and alternative complement factors with a convergence at C3, which is hypothesized to recruit of other cells to complete the lytic cascade.

To understand the role of C3 in NMO pathology, we elucidated the relationship between C3 and other immune cells present, with particular focus on neutrophil activation and recruitment.

MECHANISM OF DISEASE

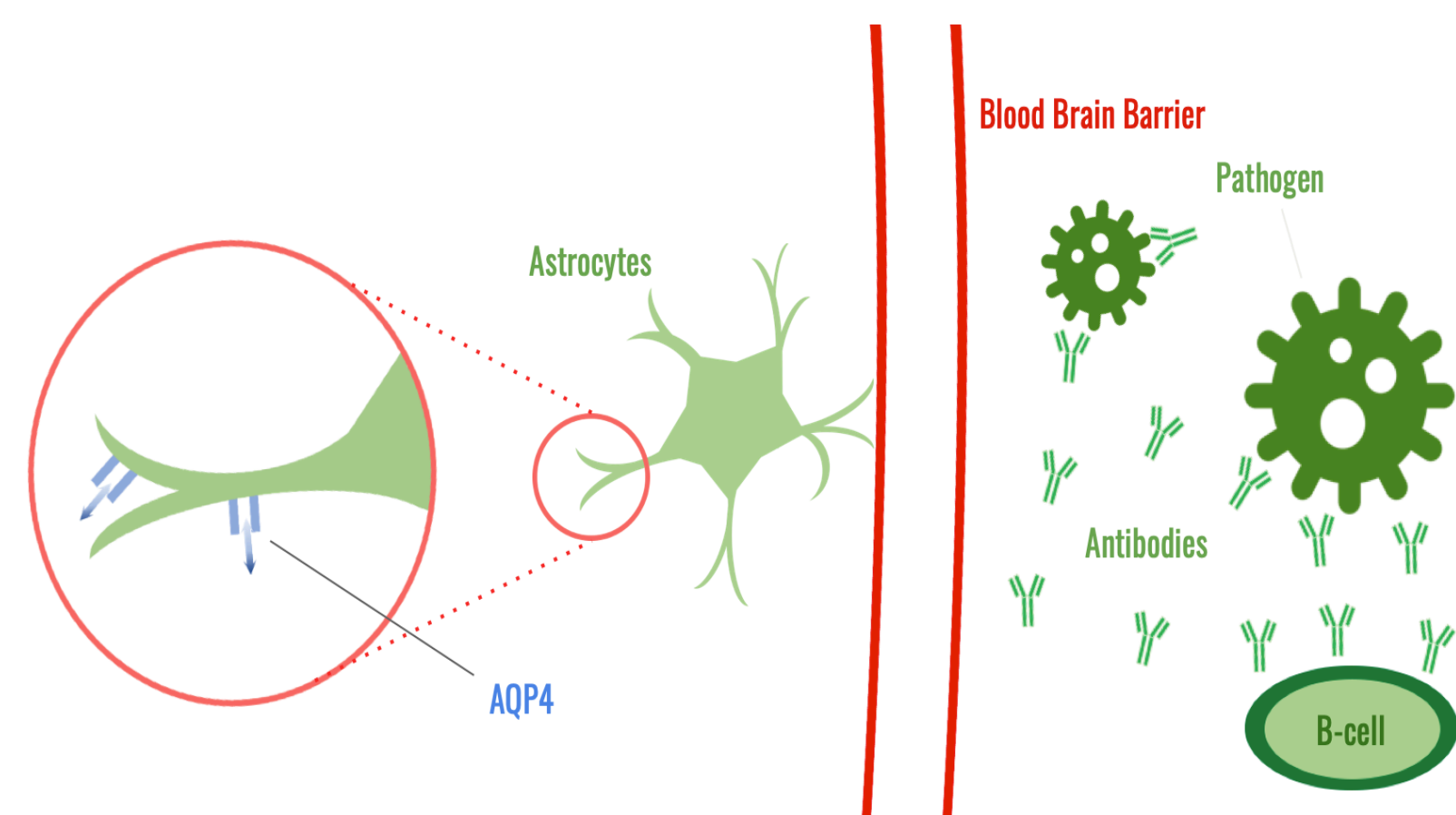


Figure 1 Healthy astrocytic function maintained by AQP4 channels within the central nervous system

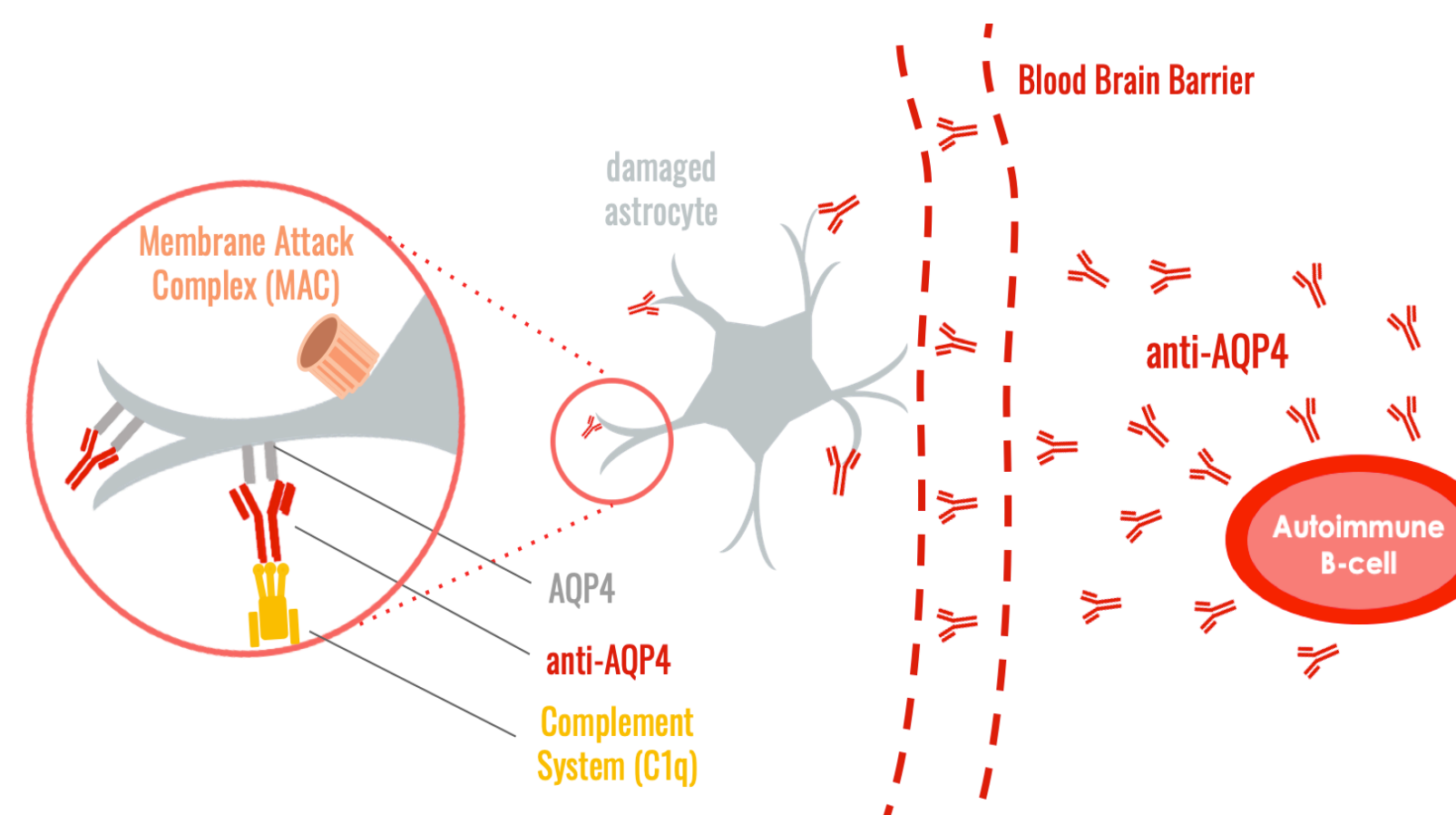


Figure 2 The classical and alternative pathways of the complement system activated by the binding of anti-AQP4 to AQP4

In the disease model, autoimmune B-cells produce NMO-IgG, an antibody selectively binds to AQP4 channels expressed on the foot processes of astrocytes in the CNS. Reactive astroglia produce classical and alternative complement factors, resulting in a high concentration of C3. The rapid, proinflammatory response by astroglia which demyelinates particular regions of the spinal cord and optic nerve. Lesions also form in these areas, causing optic neuritis and transverse myelitis in affected patients. While AQP4 is concentrated within the CNS, this protein is also present in other regions in the body, particularly in the kidneys. These proteins are also affected by this disease, leading to bladder and bowel problems as well.

PROJECT DATA

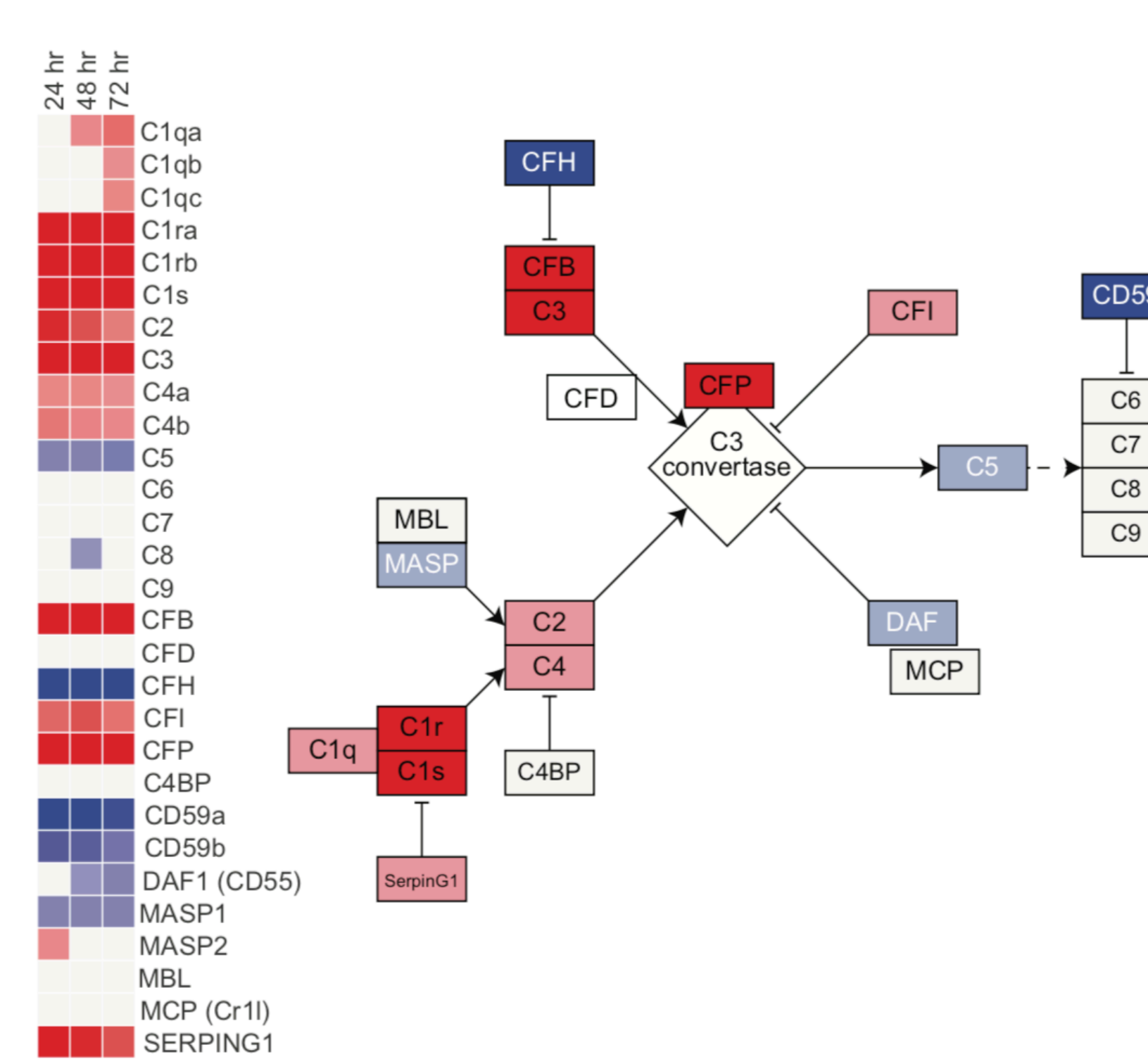


Figure 3 Activated astroglia produce complement factors of the classical and alternative pathways. Astroglia stimulated with NMO-IgG produced mRNA transcripts associated with early complement factors from the classical and alternative pathways (red). The lectin pathway showed no increase in mRNA transcript production, and various downstream transcripts from C3 also showed no increase (blue). Data was collected using a microarray. *Unpublished data*

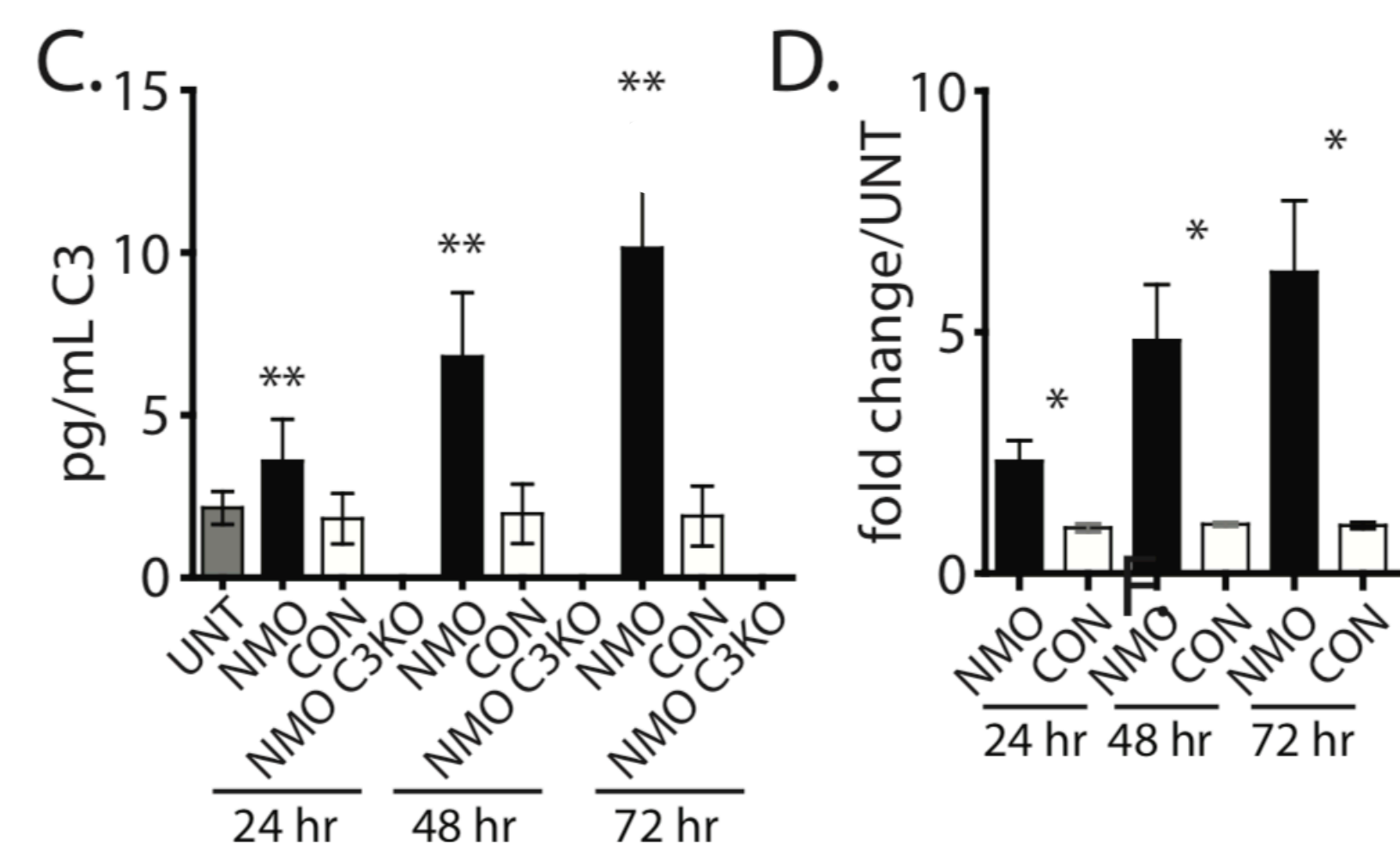


Figure 4 C3 production by mixed astroglia cultures when stimulated by NMO-IgG repeatedly every 24 hours over a 72 hour period. *Unpublished data*

FUTURE DIRECTIONS

The presence of early, non-lytic complement products provide possible therapeutic targets.

C3 appears to be activating neutrophils, however, they do not appear to be involved in trafficking neutrophils into the central nervous system. Future experiments are needed to discover the driving mechanism for recruitment of neutrophils.

When C3 is cleaved, it produces C3a and C3b. However, C3a was not discovered. This chemokine may be interacting with other immune cells. Further investigation may provide insight into its role in the NMO model.

REFERENCES

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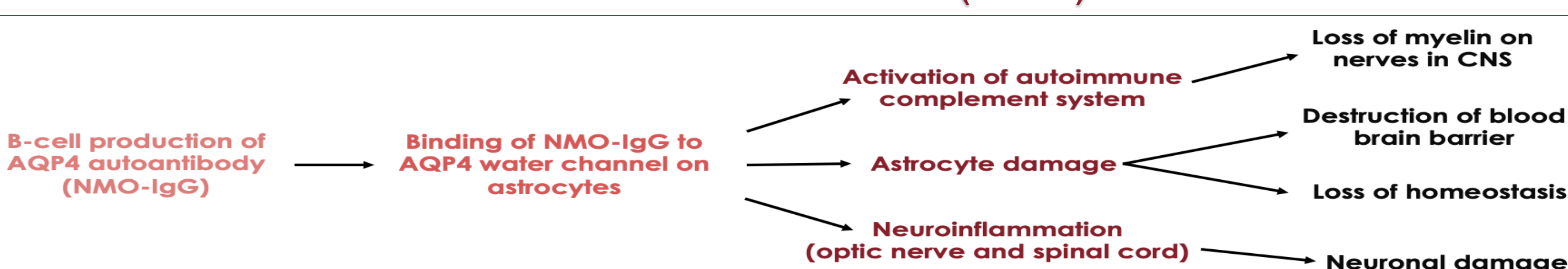
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DIAGNOSTIC CRITERIA

- I. Patient must present core clinical symptoms
 - i. Optic neuritis
 - ii. Acute transverse myelitis
 - iii. Area Postrema syndrome (hiccups, nausea and vomiting)
 - iv. Brain lesions or spinal cord lesions (visible on MRI scan)
- II. Positive test for NMO-IgG antibodies
- III. Exclusion of alternative diagnoses

MECHANISM OF DISEASE (cont.)



CONCLUSIONS

- Astroglia and pure astrocytes produce large amounts of functional complement molecules in vivo when stimulated with NMO-IgG.
- The classical and alternative complement pathways are shown to be upregulated, with convergence at C3.
- Quantitation of C3 shows an increase with sustained stimulation by NMO-IgG.
- C3 produced by astroglia is shown to activate neutrophils, but C3 is likely not driving trafficking of neutrophils.

RESOURCES

