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Update on NMOSD and MOGAD

cGAS-STING-IFN-I Signaling Pathway Promotes Autoreactive T cells and Aggregates Neuromyelitis Optica Spectrum Disorder

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease characterized by anti-aquaporin 4 (AQP4) antibody-mediated astrocyte damage and subsequent demyelination. The abnormal type I interferon (IFN-I) production influences the differentiation of B cells and T cells, and exacerbates the disease in NMOSD patients. This study aims to examine the contributions of IFN-I to NMOSD, its molecular mechanisms, and clinical implications.

Methods

We used single-cell RNA sequencing data analysis to illustrate the responses of cGAS-STING-IFN-I signaling pathway in myeloid cells in both the periphery and central nervous system (CNS) in NMOSD patients. NMO-IgG intracerebral injection mouse model (NMO-IgG model) and Th17-AQP4p135-153 specific passive transfer mouse model (Th17-AQP4 model) were established to verify the activation of the IFN-I signaling. The STING$^{-/-}$ mice and STING inhibitor H-151 were used to observe the effects of inhibiting the signaling pathway on above models.

Results

Figure 1. Augmentation of cGAS-STING-IFN-I responses in the NMOSD CSF monocytes/microglia and blood monocytes.

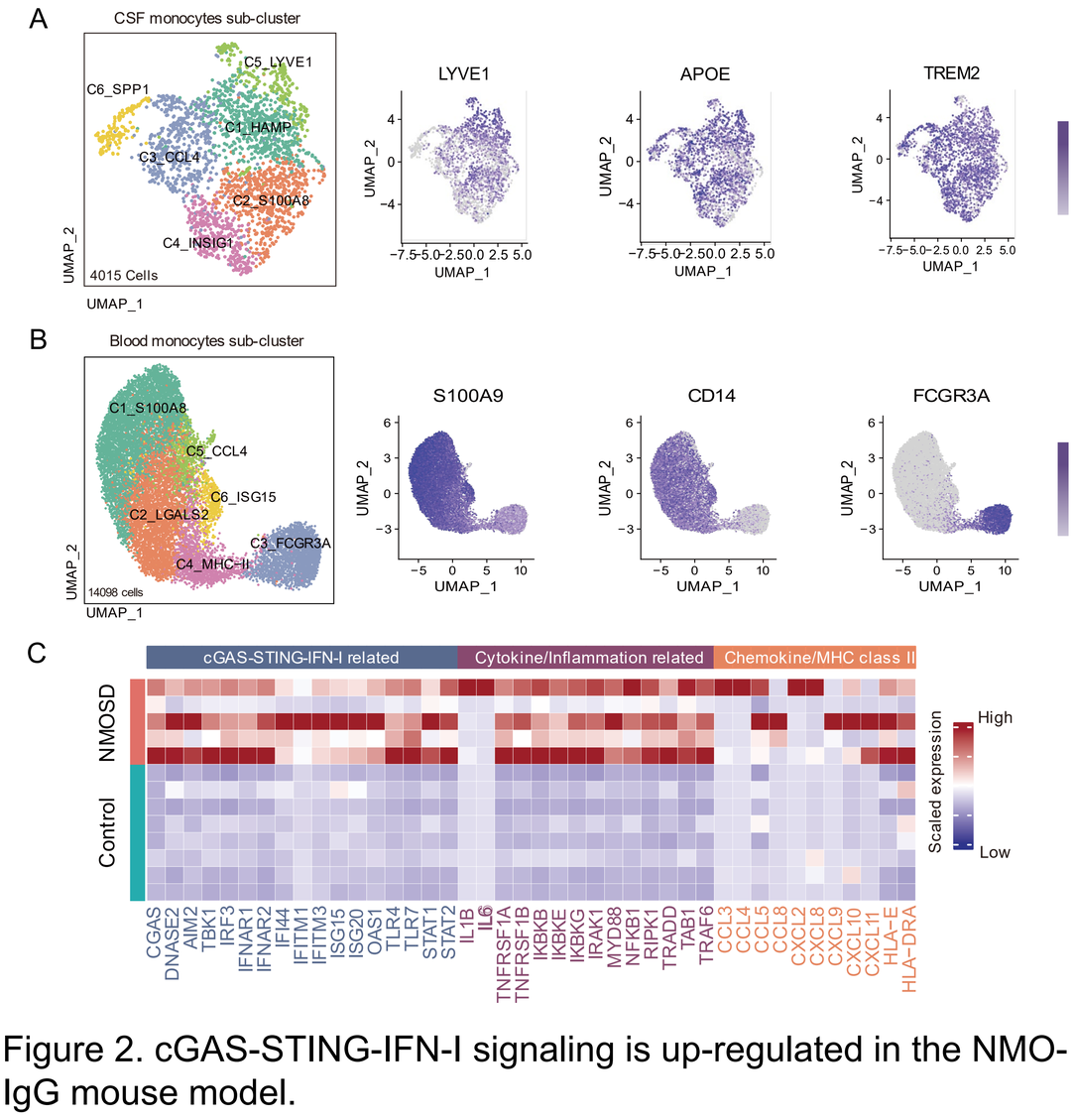


Figure 2. cGAS-STING-IFN-I signaling is up-regulated in the NMO-IgG mouse model.

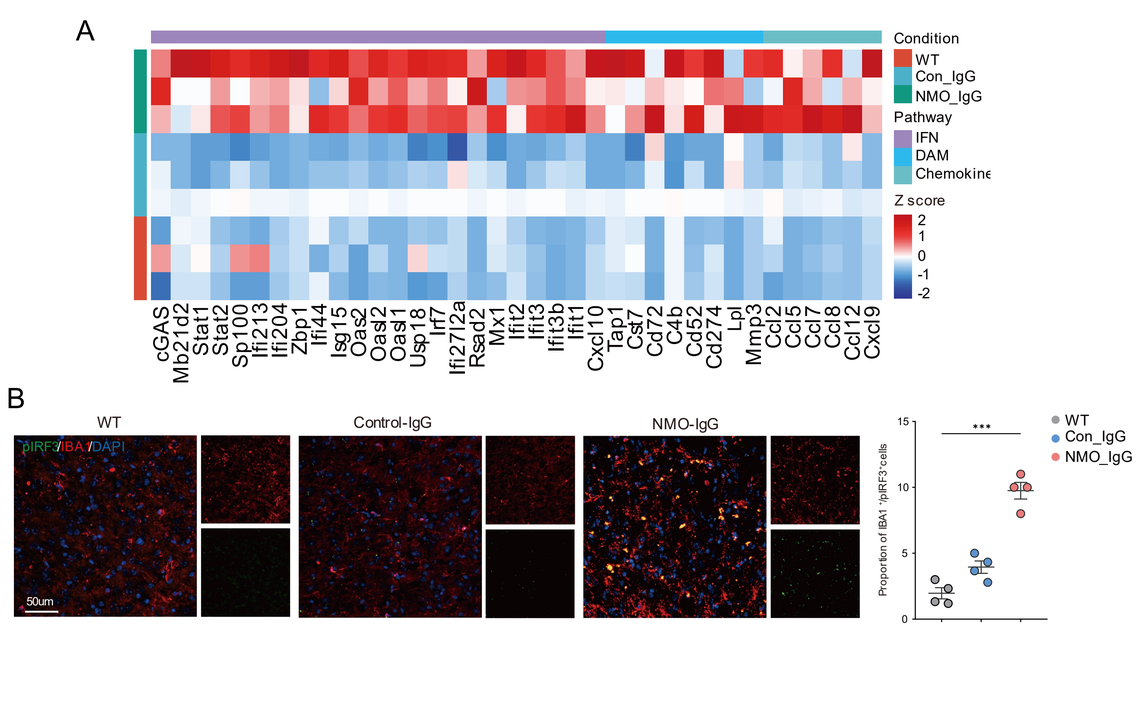


Figure 3. STING$^{-/-}$ mice exhibited improved immunopathology in the NMO-IgG model.

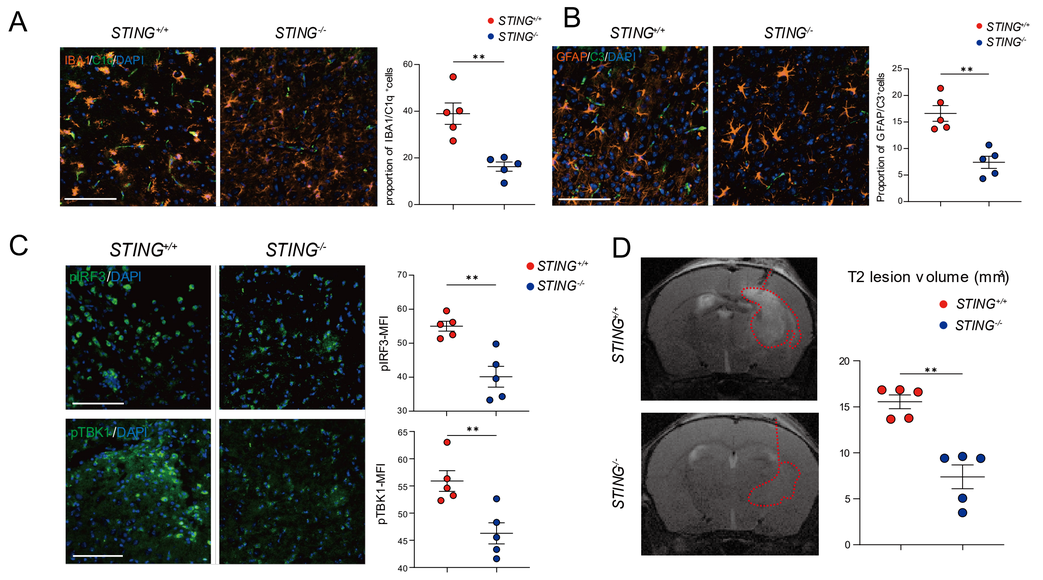


Figure 4. STING$^{-/-}$ deficiency reduced the injury of the Th17-AQP4 mouse model and hindered the activation of AQP4-specific Th17 and B cells.

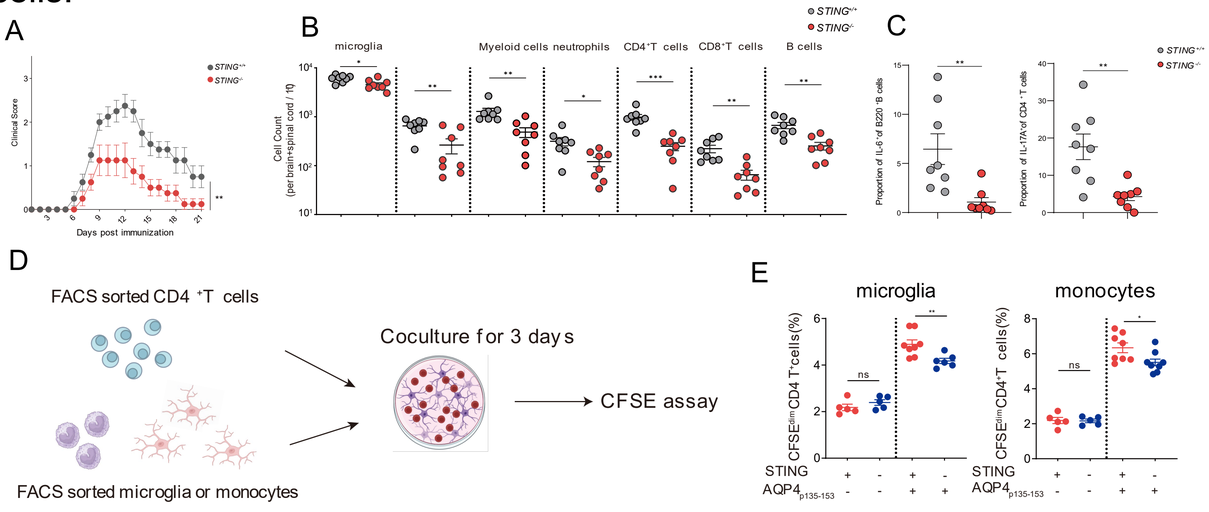
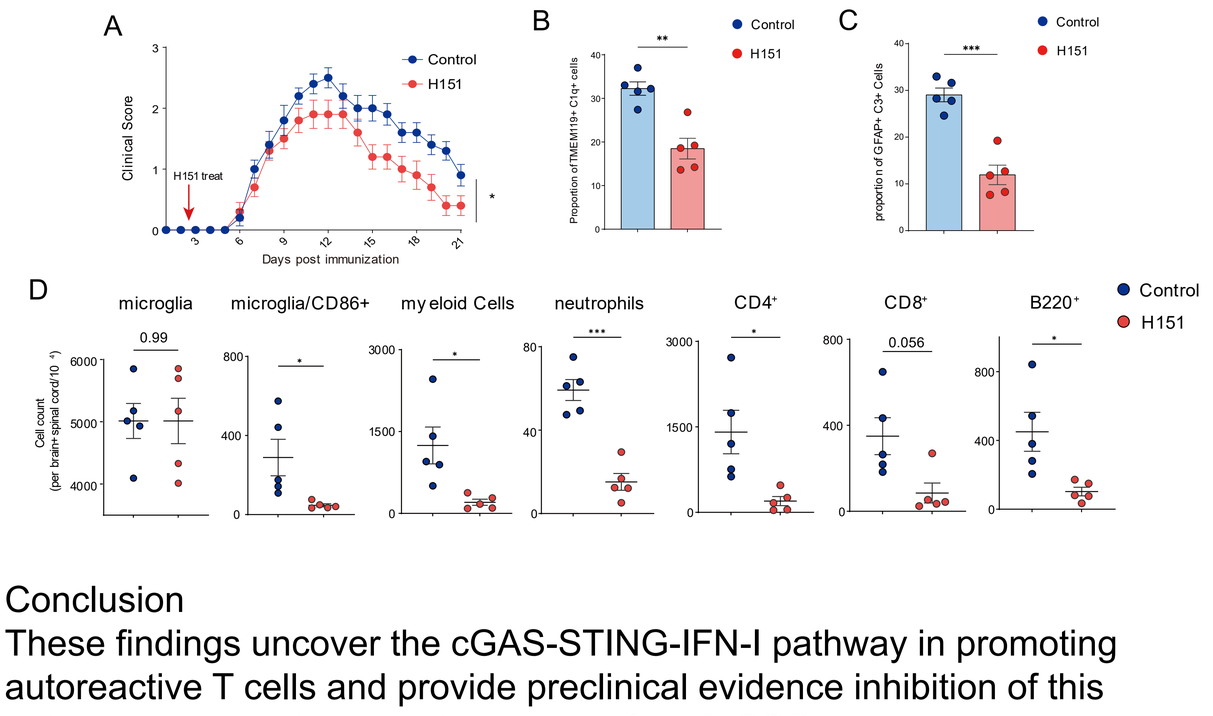


Figure 5. STING inhibitor H-151 effectively improves the Th17-AQP4 mouse model.



Conclusion

These findings uncover the cGAS-STING-IFN-I pathway in promoting autoreactive T cells and provide preclinical evidence inhibition of this pathway is a new therapeutic revenue for NMOSD.

References

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