

4-Octyl itaconate inhibits inflammation via the NLRP3 pathway in neuromyelitis optica spectrum disorders

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Introduction

NMOSD are rare inflammatory astrocytic diseases of the central nervous system. Previous studies have shown the pathogenic role of the AQP4 autoantibody, which binds to AQP4 on the foot process of astrocytes, causing astrocyte damage and inducing inflammatory reactions and granulocyte and macrophage infiltration. NLRP3 inflammasome activation and IL-1 β and IL-18 overproduction in response to pathogen-associated molecular patterns and damage-associated molecular patterns have been linked to inflammatory and autoimmune disorders. Itaconic acid, produced by the immune response gene-1 (IRG1) enzyme, is the most important metabolite from the tricarboxylic acid cycle and an important regulator of immunity and inflammation. Itaconic acid and its derivative 4-OI specifically block NLRP3 inflammasome activation by reducing the interaction between NLRP3 and serine/threonine protein kinase. This study aimed to determine the role of IRG1 and the activation status of the NLRP3 inflammatory pathway in acute-onset NMOSD and to investigate the inhibitory effects of 4-OI on NLRP3 inflammasome activation via the IRG1–itaconic acid–NLRP3 pathway in monocytes and macrophages by using in vitro models.

Results

1. Patients with acute NMOSD exhibit prominent upregulation of IRG1 expression and upregulation of the NLRP3 inflammasome, IL-1 β , IL-6, and tumor necrosis factor (TNF)- α in monocytes.

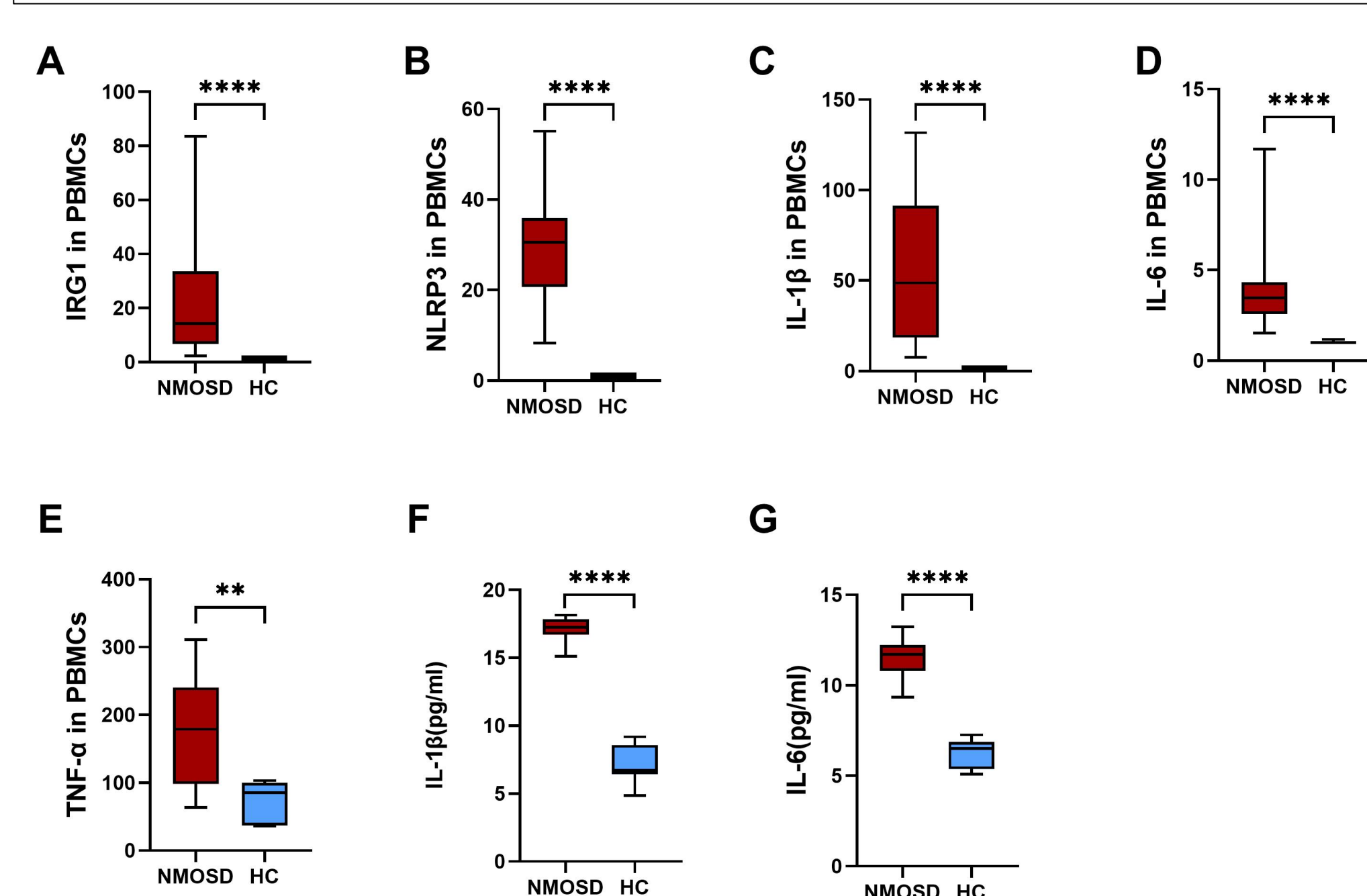


Figure 1. Real-time PCR results for 15 patients with untreated NMOSD and age- and sex-matched HC subjects.

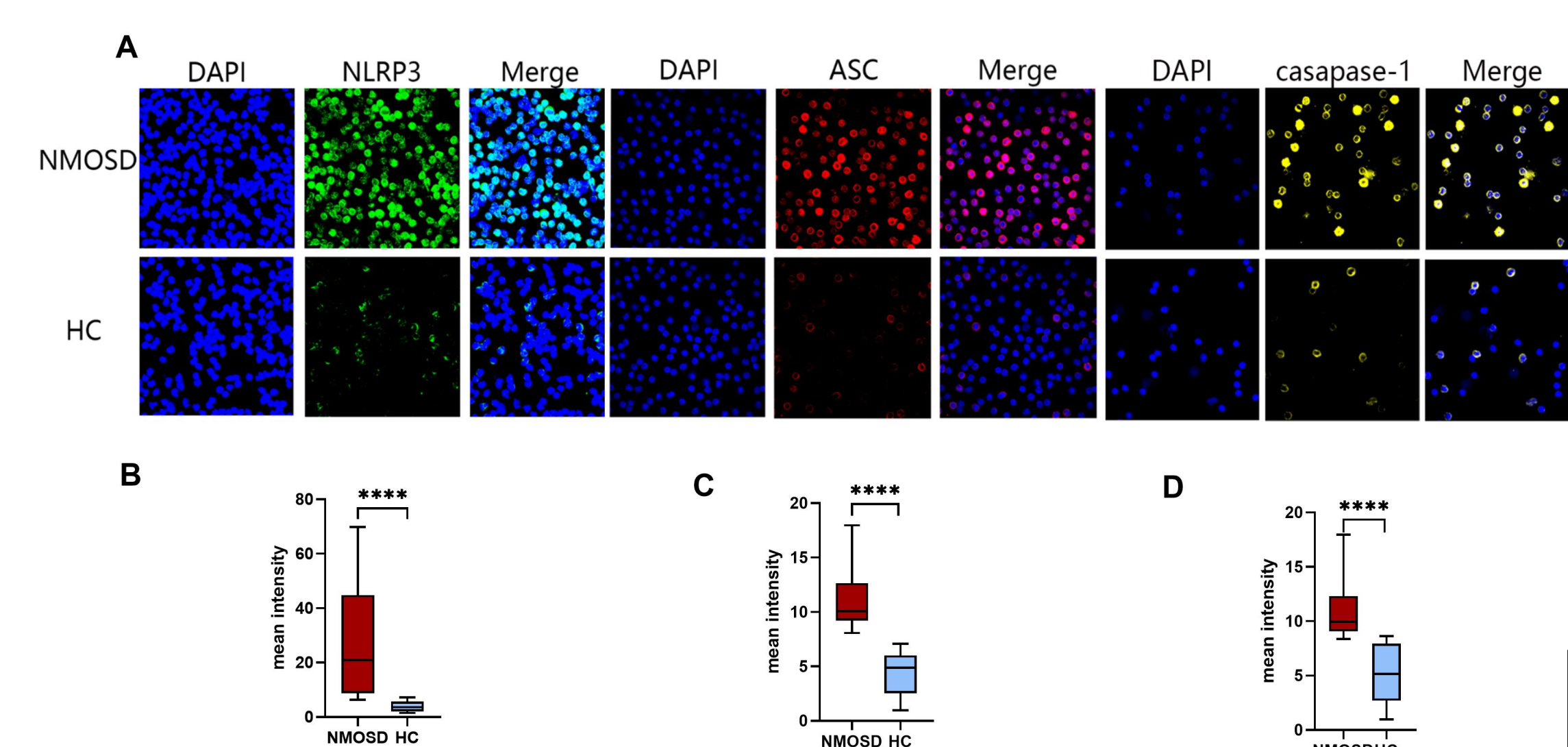


Figure 4. The synthesis and expression of the NLRP3 protein, ASC and caspase-1 in monocytes were greater in CD14 monocytes from patients with NMOSD than in those from healthy controls.

2. 4-OI inhibited the activation of the IRG1 – itaconic acid–NLRP3 inflammatory pathway in the PBMCs of patients with NMOSD.

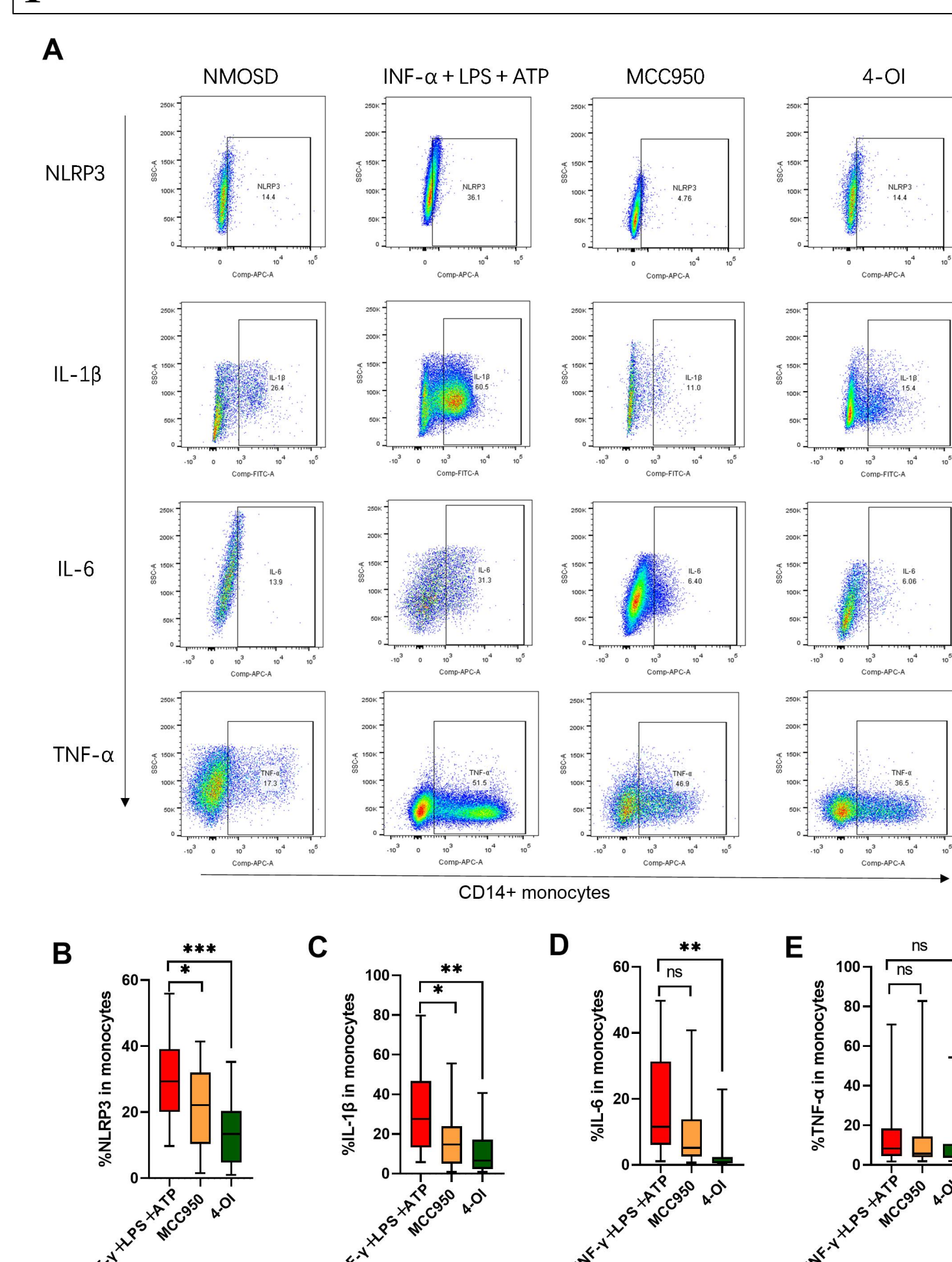
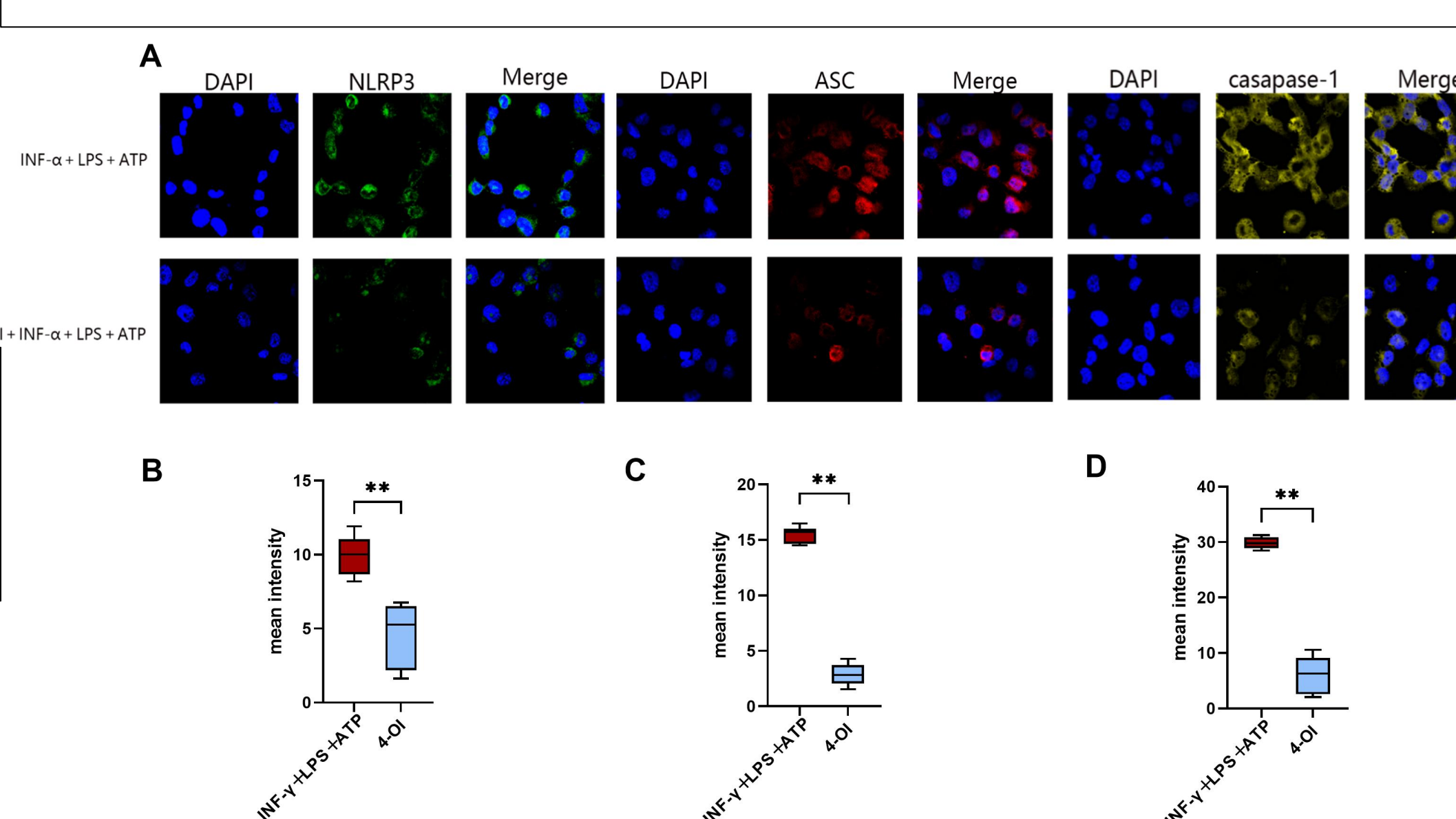


Figure 2. The flow cytometry results of CD14 monocytes, monocyte subtypes, and HLA-DR between NMOSD patients and HC.

3. 4-OI inhibited the IRG1–itaconic acid–NLRP3 inflammatory pathway in THP-1-derived macrophages.



Discussion

We proposed that inflammation induced IRG1 expression, thereby establishing a positive autocrine feedback loop, reducing the release of proinflammatory mediators and macrophage activation by inhibiting the NLRP3 inflammatory pathway. These results showed the inhibitory effect of 4-OI on the NLRP3 inflammatory pathway in monocytes and macrophages in NMOSD, indicating that 4-OI might be a therapeutic direction for NMOSD.

Literature

- [1]Takai Y, Misu T, Suzuki H, et al. Staging of astrocytopathy and complement activation in neuromyelitis optica spectrum disorders. *Brain*. 2021;144:2401-2415.
- [2]Jarius S, Paul F, Franciotta D, et al. Mechanisms of disease: aquaporin-4 antibodies in neuromyelitis optica. *Nat Clin Pract Neurol*. 2008;4:202-214.
- [3]Pittock SJ, Zekeridou A, Weinshenker BG. Hope for patients with neuromyelitis optica spectrum disorders - from mechanisms to trials. *Nat Rev Neurol*. 2021;17:759-773.

Figure 3. Flow cytometry revealed a significantly greater proportion of the NLRP3 pathway in monocytes from patients with NMOSD than in monocytes from healthy controls.

