The COMMD3/8 complex: a novel therapeutic target for autoimmune diseases

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Abstract

The immune system depends on cell migration among various anatomical sites, which is orchestrated by chemoattracting molecules and their receptors. We previously identified a protein complex consisting of copper metabolism MURR1 domain-containing (COMMD) 3 and COMMD8 (COMMD3/8 complex) as a signaling adaptor for chemoattractant receptors that controls B cell migration and promotes humoral immune responses. In our recent study, the COMMD3/8 complex was shown to play an important role in the pathogenesis of autoimmunity. Moreover, celastrol, an anti-inflammatory compound with a poorly defined mechanism of action, was found to exert the immunosuppressive activity by inhibiting the COMMD3/8 complex. Our study suggests that the COMMD3/8 complex is a potentially druggable target in autoimmune diseases, and points to celastrol as a lead pharmacologic candidate in this capacity.

Background & Results

Based on the essential role of the COMMD3/8 complex in humoral immune responses, we tested whether deficiency of the COMMD3/8 complex alleviates collagen-induced arthritis, a B cell-dependent mouse model of rheumatoid arthritis. COMMD3/8 complex deficiency inhibited the progression of arthritis, which was accompanied by reduced production of autoantibodies. These findings suggested that the COMMD3/8 complex contributes to the pathogenesis of rheumatoid arthritis.

Prompted by this finding, we performed a chemical screen to identify inhibitors of the COMMD3/8 complex that could be used for the treatment of autoimmune diseases. Since the function of the COMMD3/8 complex depends on the association between COMMD3 and COMMD8, we sought for compounds that disrupt the physical interaction between the two COMMD proteins. After screening of chemical libraries, we identified celastrol as the most potent compound. Celastrol is thought to be a major bioactive constituent of a medicinal herb, *Tripterygium wilfordii*, but its mechanism of action had been poorly understood.

Using site-directed mutagenesis, molecular dynamics simulations and liquid chromatography-tandem mass spectrometry, we revealed that celastrol dissociates the COMMD3/8 complex by covalently binding to C170 on COMMD3. Celastrol inhibited B cell migration, suppressed humoral immune responses and blocked progression of arthritis, recapitulating deficiency of the COMMD3/8 complex. The immunosuppressive effects of celastrol were abolished in mice carrying a mutation substituting C170 on COMMD3 to alanine, which rendered the COMMD3/8 complex resistant to celastrol. These findings established that the COMMD3/8 complex is the major target of celastrol.

Significance of the research and Future perspective

Having established the involvement of the COMMD3/8 complex in a mouse model of rheumatoid arthritis, we demonstrated that celastrol exerts disease-ameliorating effects by targeting the COMMD3/8 complex. These findings provide a proof of concept that disrupting the interaction between COMMD3 and COMMD8 may be a useful strategy for the treatment of autoimmune diseases and support the consideration of celastrol as a lead candidate in that endeavor.

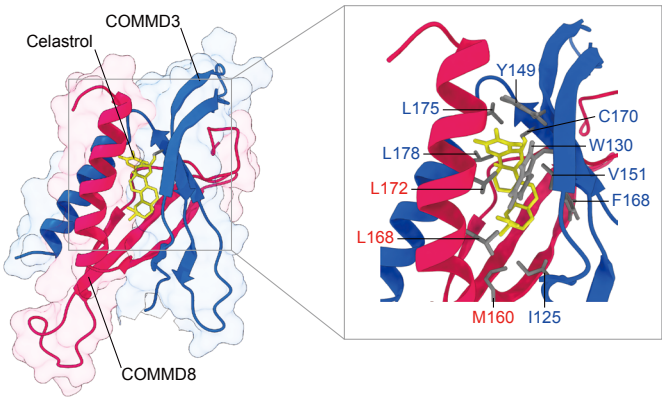

Fig.1 A model of the celastrol bound COMMD3/8 complex.

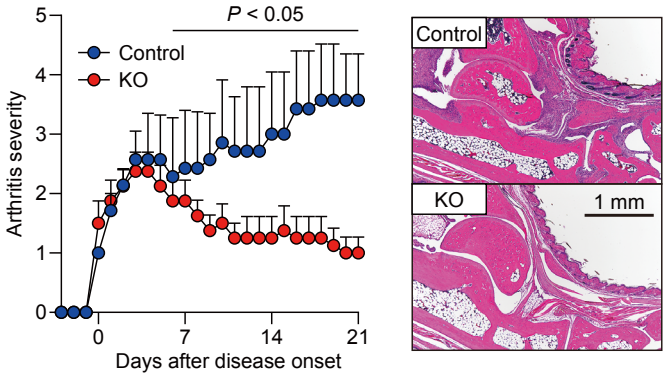

Fig.2 Effects of CMMD3/8 complex deficiency on arthritis.

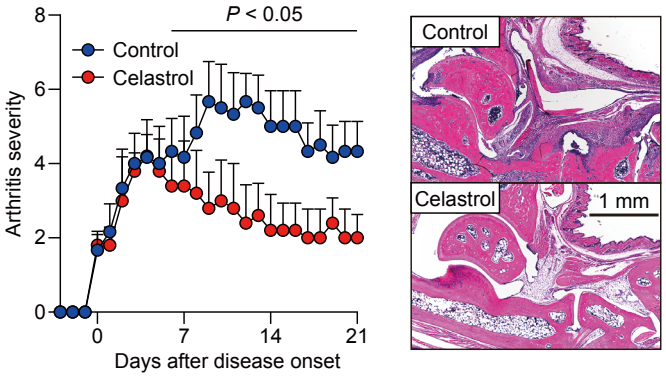

Fig.3 Effects of celastrol treatment on arthritis.

Patent

Treatise Shirai, Taiichiro; Nakai, Akiko; Ando, Emiko et al. Celastrol suppresses humoral immune responses and autoimmunity by targeting the COMMD3/8 complex. Sci. Immunol. 2023, 8 (81), eadc9324. doi: 10.1126/sciimmunol.adc9324
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Keyword autoimmunity, rheumatoid arthritis, B cell, COMMD3/8 complex, celastrol