Acute phase response is a systematic reaction of organisms. It can directly function as an immunomodulator. Orosomucoid-2 (ORM2) is an acute phase reactant mainly synthesized in the liver, directly contributes to chronic inflammation.

Background: ORM2 expression was determined by ELISA and immunostaining. Fibroblast-like synoviocytes (FLSs) and macrophages were cultured in the presence of recombinant ORM2. NF-κB and p38 MAP kinase expression levels were assessed by Western blot analysis. Knockdown experiments were carried out using siRNAs for NF-κB p65, p38, and glucocorticoid C (GyPC). Proximity ligation assay was performed to test the molecular interaction between ORM2 and GyPC. Recombinant ORM2 was injected into the affected joints of mice with IL-1β-induced arthritis.

Methods: ORM2 expression was measured in the sera, synovial fluids, and synovia of patients with rheumatoid arthritis (RA). Major cell types producing ORM2 were synovial macrophages and FLSs. Recombinant ORM2 robustly upregulated IL-6, TNF-α, IL-8, and CCL2 produced by macrophages and/or FLSs of RA patients via NF-κB and p38 MAPK pathways. GyPC was the receptor of ORM2 on synovial macrophages and FLSs. Such an increase by ORM2 was reproduced in mouse macrophages and FLSs. Intra-articular injection of ORM2 promoted the severity of arthritis in mice and accelerated the infiltration of macrophages in affected joints. Moreover, in RA patients, circulating ORM2 levels correlated with disease activity assessed by DAS28 and well represented radiographic progression in 2 years.

Conclusion: Acute phase protein ORM2 can directly increase the production of pro-inflammatory cytokines/chemokines by macrophages and FLSs and promote chronic arthritis in mice, suggesting that it could be a new therapeutic target for RA.

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ORM2 in synovial macrophages can directly promote the secretion of pro-inflammatory cytokines and chemokines. ORM2 expression was correlated with disease activity and radiographic progression in RA patients.

Keywords:

Rheumatoid arthritis, Cytokines and chemokines, Synovium

References:


Figure 1. Hypothetical model for ORM2-dictated reciprocal activation of macrophages and FLSs in RA. Under high inflammatory conditions, ORM2 is actively produced from arthritic joints, particularly by stimulation of synovial macrophages and fibroblasts with TNF-α, IL-1, and Toll-like receptor-4 agonists, as well as from the liver. The secreted ORM2 in turn binds to a functional receptor GyPC on RA-FLSs, activates NF-κB and p38 MAP kinase pathways, and then directly induces production of pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-8), and chemokines (e.g., IL-8, CCL2) via the two signaling pathways. Resultant cytokines and chemokines can amplify chronic inflammation by further activating macrophages and FLSs and by facilitating recruitment of monocytes and neutrophils to inflamed joints. As a result, more activated macrophages and FLSs can secrete greater amounts of ORM2 and thereby lead to ORM2-centered mutual activation of macrophages and FLSs, constructing a feed-forward cycle of rheumatoid inflammation.

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