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A Competitive Inhibitor of MOART Showed Potent Therapeutic Effects in a Mouse Model of Collagen-induced Arthritis

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Abstract

Background/Purpose:

Despite tumor necrosis factor (TNF) inhibitors and Jak kinase inhibitors (JKI) have shown a significant advance in the treatment of rheumatoid arthritis (RA) however, only 20 to 30% of patients experience remission. Recently, we identified a novel membrane organizer of osteoclast multinucleation, which we named Macrophage Osteoclast Adipocyte Regulating Tetraspanin, also known as TM4SF19 (Transmembrane 4 L6 family member 19). Knockout mice lacking the entire *moart* gene dramatically reduced a bone loss in an ovariectomized mouse model. In this study, we investigated the therapeutic effects of MP2021, a competitive inhibitor of MOART, in a mouse model of collagen-induced arthritis (CIA).

Methods:

To induce CIA, DBA/1J mice (n = 10 per group) were immunized subcutaneously at the tail with chicken type II collagen on days 0 and 14 ~18. Mouse MP2021, human MP2021, control IgG-Fc or TNFR2-Fc fusion protein (etanercept) were injected subcutaneously twice or three times a week before/after the onset of CIA. Clinical arthritis scores were measured by summing the scores of all four paws. Disease progression was monitored daily, and cytokines and histologic analysis (synovial inflammation, joint damage, and bone loss) were measured by H&E, IHC, and μCT at the end of the study.

Results:

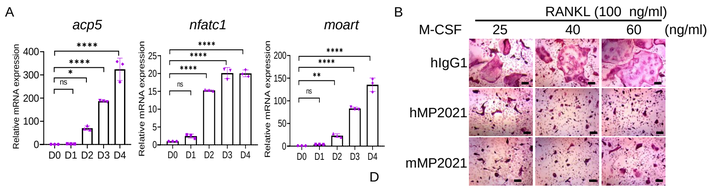
Clinical arthritis scores and morphological signs of bone destruction improved in the mMP2021-treated group compared to IgG-Fc. Expression levels of *il1β*, *il6*, *tnfα*, *comp*, *mmp3*, and *mmp13* were significantly reduced in the articular bones of mice treated with mMP2021. Histologic analysis also showed that mMP2021 inhibited bone damage by inhibiting synovitis, synovial formation, and chondrolysis, and significantly reduced the number of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts. hMP2021 administered subcutaneously to CIA mice also showed more inhibitory effects on clinical arthritis scores than etanercept. The hMP2021 showed equivalent effects when administered intravenously or subcutaneously, which is a promising result for the clinical application of this molecule.

Conclusion:

We found that human MP2021 as well as mouse MP2021 significantly inhibited cartilage damage and bone erosion in established mouse CIA models, along with a reduction in multinucleated osteoclasts. These findings suggest that MP2021 has potential as a novel therapeutic agent that can be effectively applied to various bone and joint diseases, including rheumatoid arthritis.

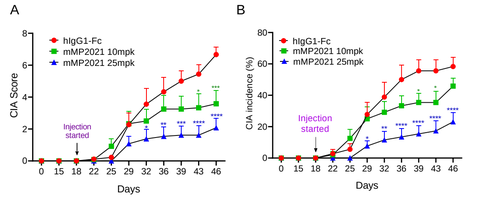
Background

✓ Targeting LEL region of Moart inhibited osteoclast differentiation.

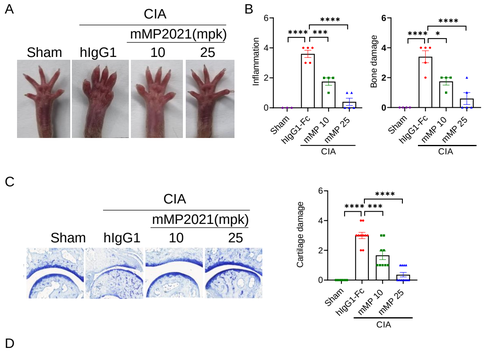


Results

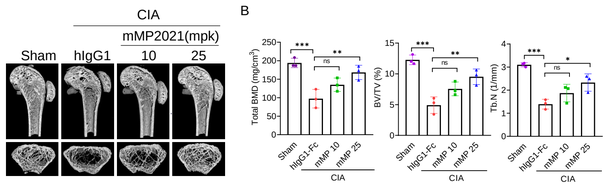
1. mMP2021 suppresses the collagen induced arthritis (CIA) in mice.

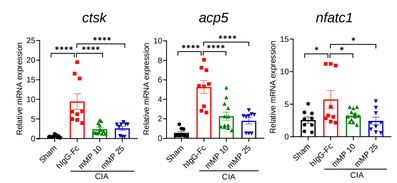


2. mMP2021 suppresses CIA induced inflammation, bone erosion, and cartilage damage in a dose dependent manner.

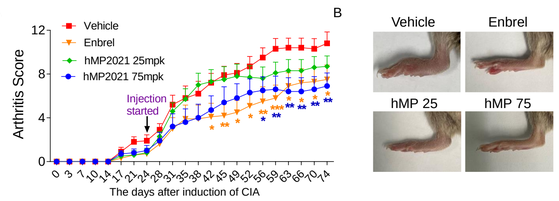


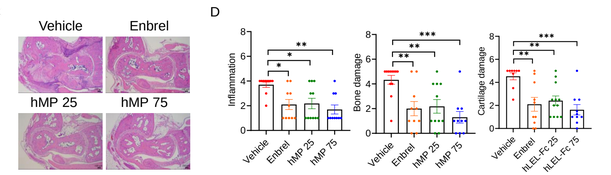
3. mMP2021 inhibits inflammatory bone loss in mice with collagen induced arthritis by activating osteoclast differentiation..



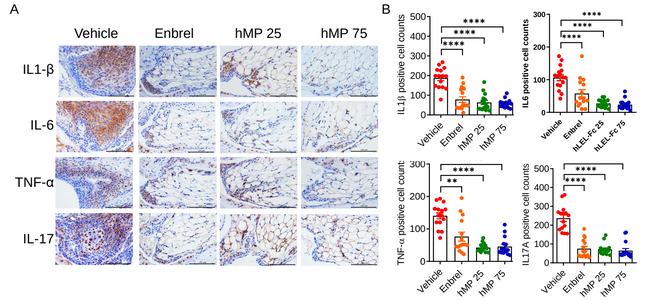


4. hMP2021 treatment showed therapeutic effect on CIA mice

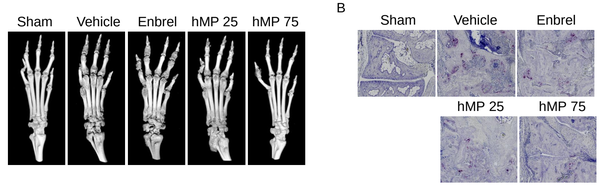




5. hMP2021 suppresses inflammatory cytokines induced by CIA.



6. hMP2021 inhibit inflammatory bone destruction by abnormal osteoclast activation in CIA mice.



Summary

- ✓ MP2021 inhibited multinucleated osteoclast formation and bone resorption activity of bone marrow derived macrophage.
- ✓ Histological analysis showed that MP2021 effectively suppressed inflammation, cartilage damage and bone erosion in collagen induced arthritis mice.
- ✓ MP2021 treatment significantly reduced the expression of inflammatory genes and mmps in the articular bones of CIA mice.
- ✓ μCT analysis showed that the decreased inflammatory bone loss in CIA mice were complemented by administration MP2021.
- ✓ MP2021 suppressed bone destruction by blocking osteoclast hyperactivation in CIA mice.

Conclusion

- ✓ Moart is a possible therapeutic target for osteoclast-related bone diseases
- ✓ MP2021 could be a promising novel therapeutic agent to target osteodestructive diseases caused by osteoclast hyper-differentiation, including rheumatoid arthritis.

References

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