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THE ROLE OF *MID1-PP2A AXIS* IN INFLAMMATION-INDUCED JOINT DAMAGE IN ANTIGEN-INDUCED ARTHRITIS

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INTRODUCTION: Rheumatoid arthritis (RA) is a chronic autoimmune joint disease which often causes structural joint damage not reversible by currently available therapeutics, urging discovery of new molecular mediators for therapeutic targeting. In a murine model of RA, antigen-induced arthritis (AIA) we have previously shown that destructive AIA is characterized by accumulation of synovial myeloid cells which up-regulate *Mid1* gene. Due to the previously described involvement of *Mid1* in pathogeneses of immune-mediated diseases, the objective of this study was to evaluate the role of *Mid1* in AIA.

MATERIALS AND METHODS: AIA was induced in C57BL6 mice by immunization with methylated bovine serum albumin (mBSA) and subsequent intra-articular injection of mBSA. Expression of *Mid1* and pro-inflammatory cytokines was assessed by qRT-PCR. Mice were treated with metformin, which prevents Mid1-mediated ubiquitinilation of PP2A, and thus has an anti-inflamatory effect, at a daily dose of 1g/kg, to evaluate the effects of blocking the Mid1-mediated inflammation on arthritis development and subchondral bone resorption (assesed by μ-CT).

RESULTS: *Mid1* was up-regulated in knee joints early after arthritis induction. Its expression positively correlated with severity of arthritis assesed by knee diameter measurement and levels of pro-inflammatory cytokines, IL-1, IL-6 and TNF. Although Mid1 is positioned on the X-chromosome, its expression was up-regulated in arthritic joints of both male and female mice. Metformin treatment ameliorated the severity of arthritis and arthritis-induced subchondral bone resorption.

CONCLUSION: Inhibition of Mid1-mediated PP2A degradation by metformin might aid to therapeutic management of inflammatory arthritides.

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