

Persistent global inflammation caused by the loss of SIRT1 protects against experimental osteoarthritis

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Purpose: Inflammatory pathways have been attributed to play a central role in the pathogenesis of osteoarthritis (OA). However, most previous studies using knockout (KO) mice to inactivate inflammatory genes have showed no significant protection in experimental OA. In addition, biologic treatments targeting cytokines in OA have showed poor efficacy in clinical studies. This raises the question whether persistent inflammation has a central role in driving disease. The histone deacetylase Sirtuin 1 (SIRT1) has potent anti-inflammatory effects, thought in part, by decreasing NF- κ B translocation into the nucleus. In this study, we examine the disease outcome in mice in which SIRT1 has been deleted globally or just in the cartilage.

Methods: Post-natal deletion of SIRT1 in a pan tissue or a cartilage specific manner was achieved by crossing SIRT1^{fl/fl} mice x ROSA CreER^{T2} mice (SIRT1^{ROSA}) or SIRT1^{fl/fl} mice x Aggrecan CreER^{T2} mice (SIRT1^{Agg}) respectively. Destabilisation of the medial meniscus (DMM) was used as a model of injury induced OA. The effect of SIRT1 deletion 24 hours, 8 weeks and 12 weeks post DMM was examined by RT-PCR (gene expression) and histology (disease scoring and synovitis). Bone marrow chimera experiments were conducted to evaluate the role of infiltrating cells and chronic inflammation post injury. Assessment of protein levels was conducted by either ELISA or western blot from serum or avulsed femoral heads respectively.

Results: Joints obtained from SIRT1^{ROSA} mice 24hrs post DMM displayed increased joint synovitis score ($p < 0.001$), inflammatory response genes including IL-1 β ($p < 0.0001$), TNF- α ($p < 0.0001$), IL-6 ($p < 0.0001$), CCR2 ($p < 0.001$), MMP-13 ($p < 0.01$), and ADAMTS-4 ($p < 0.001$). Increased in inflammatory gene expression and synovitis were not observed in joints obtained from SIRT1^{Agg} mice. Serum levels of pro-inflammatory cytokines (IL-1 β ($p < 0.05$), TNF- α ($p < 0.05$), IL-6 ($p < 0.01$)) were only elevated in SIRT1^{ROSA}.

Surprisingly, SIRT1^{ROSA} mice, despite increased early inflammatory gene expression and synovitis, were protected from disease 8 and 12 weeks post DMM compared to control mice ($p<0.01$). Conversely, SIRT1^{Agg} mice with reduced early inflammatory gene expression and synovitis displayed increased disease 8 and 12 weeks post DMM compared to wild type mice ($p<0.01$). Joints of SIRT1^{ROSA} mice also displayed increased gene expression of fibrosis markers including TGF- β ($p<0.05$), COL2A1 ($p<0.05$) and CTGF ($p<0.01$).

SIRT1^{ROSA} mice engrafted with WT bone marrow continued to display an increase in early synovitis and inflammatory gene expression (24h post DMM). Conversely, wild type and SIRT1^{Agg} mice engrafted with SIRT1^{ROSA} deficient bone marrow had no increased inflammation indicating that inflammatory change post DMM is largely independent of the bone marrow cells.

Conclusions: These results show that SIRT1 has a mixed role in the joint; having both protective and pro-disease functions depending on its tissue expression. This study also highlights the fact that inflammation in the joint, which is largely bone marrow independent, may be associated with chondro-protection rather than worsening of disease. We speculate that this may be due to its effect on joint repair.