# Transferrin-1 receptor (TfR1) as a potential therapeutic target in synovitis

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**Introduction:**
Inflammatory cytokines and proteolytic enzymes derived from synovial tissue play central roles in joint diseases such as rheumatoid arthritis and osteoarthritis. Among the signaling pathways that regulate these mediators, NF-κB is one of the most critical. Activation of NF-κB requires formation of the IKK complex and phosphorylation of IκBα, leading to transcription of inflammatory genes. Recent studies have identified transferrin-1 receptor (TfR1), originally known as a receptor for cellular iron uptake, as an essential component of IKK complex assembly [1]. This raises the possibility that TfR1 may act as a regulator of NF-κB–mediated synovial inflammation. In this study, we investigated whether TfR1 could serve as a potential therapeutic target for synovitis.

**Methods:**
The synovial fibroblast-like cell line SW982 was used to model synovitis and stimulated with IL-1β (10 ng/ml). TfR1 was silenced using small interfering RNA (siRNA), and cellular responses were evaluated by Cell Counting Kit-8 (CCK-8) assay, reverse transcription-quantitative PCR (RT-qPCR), and Western blotting. To assess the impact of TfR1 knockdown on cartilage, the immortalized normal human chondrocyte cell line C28/I2 was examined using CCK-8 assay and RT-qPCR. Statistical analyses were performed with Welch's t-test, with $p < 0.05$ considered significant.

**Results:**
TfR1 knockdown significantly reduced the viability of SW982 cells (Fig. 1). IL-1β stimulation increased the expression of inflammatory cytokines (IL-1β, IL-6, TNFα) and MMP3 in SW982, whereas TfR1 silencing attenuated these responses (Fig. 2). Western blotting demonstrated that TfR1 knockdown suppressed IκBα phosphorylation and subsequent NF-κB nuclear translocation. In contrast, TfR1 knockdown in C28/I2 chondrocytes did not impair cell viability or aggrecan expression (Fig. 3).

**Discussion:**
Our findings indicate that TfR1 regulates synovial inflammation by modulating the NF-κB pathway. Silencing TfR1 reduces synovial cell viability and inflammatory mediator production without adverse effects on chondrocytes. These results suggest that TfR1 may serve as a novel therapeutic target for synovitis and related joint diseases. Further in vivo studies are ongoing to validate its clinical relevance.

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences): Our findings suggest that TfR1 inhibition could represent a novel therapeutic approach for joint diseases such as rheumatoid arthritis and osteoarthritis by suppressing synovial inflammation while sparing cartilage integrity.

REFERENCES: [1] Kenneth NS, Mudie S, Naron S, Rocha S. TfR1 interacts with the IKK complex and is involved in IKK-NF-κB signalling. Biochem J. 2013 Jan 1;449(1):275-84. doi: 10.1042/BJ20120625. PMID: 23016877; PMCID: PMC3537175.

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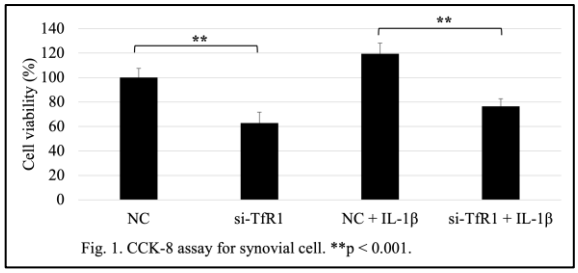

Fig. 1. CCK-8 assay for synovial cell. **p < 0.001.

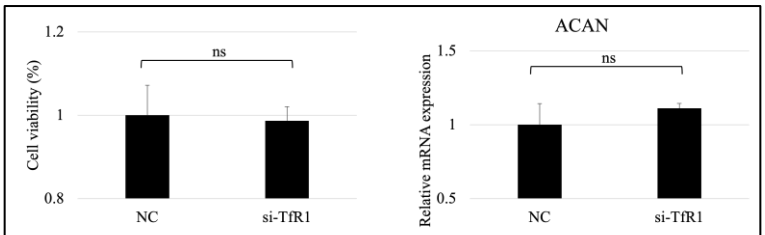

Fig. 3. CCK-8 assay and RT-qPCR for chondrocyte. Ns means no significance.

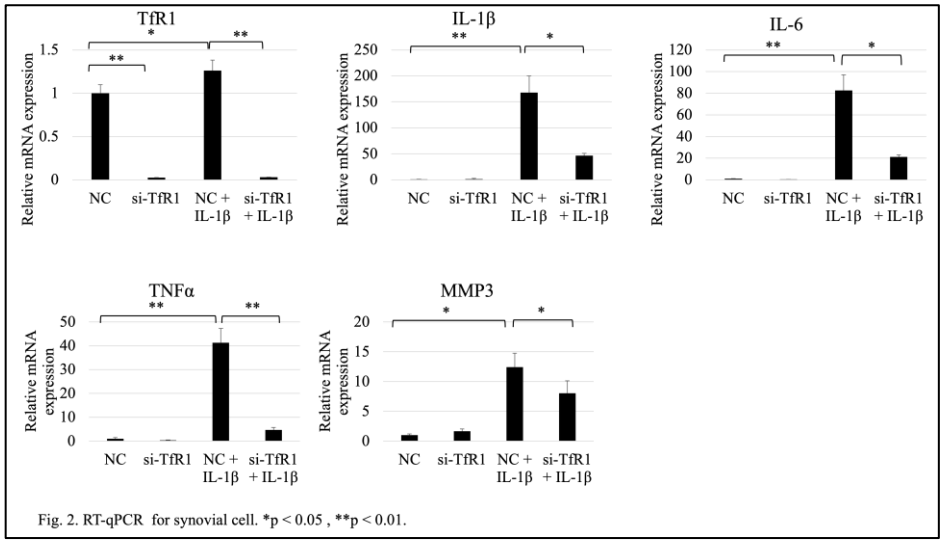

Fig. 2. RT-qPCR for synovial cell. *p < 0.05 , **p < 0.01.