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Background and objectives Pre-B cell colony-enhancing factor (PBEF) is a protein with pro-inflammatory properties elevated in serum, synovial tissue and synovial fluid of patients with rheumatoid arthritis (RA). Levels of PBEF correlate with the degree of inflammation and clinical disease activity in RA patients. Local downregulation of PBEF in the joint can therefore be beneficial. To investigate this approach, an rAAV5 vector encoding PBEF shRNA (rAAV5-PBEFshRNA) was designed to reduce the expression of PBEF. Its capacity to influence arthritis development after local injection in the joint was tested in a murine collagen-induced arthritis (CIA) model.

Materials and methods Murine fibroblast-like synoviocytes (FLS) were transduced with rAAV5-PBEFshRNA or rAAV5-scrambledshRNA. 5 days after transduction, levels of PBEF mRNA and protein were assessed. CIA was induced in male DBA/1 mice on day 0 (intradermal injection of a bovine collagen type II (bCII)/complete Freund's ajuvant (CFA) emulsion at the base of the tail, 12 mice per group) followed by an intraperitoneal boost injection with bCII on day 21. Mice were scored 3× weekly using an established macroscopic clinical scoring system and a calliper to measure paw swelling. At day 21, mice were injected intra-articularly in knee (5 µl) and ankle joints (2.5 µl) of both hind paws with rAAV5-PBEFshRNA, or rAAV5-scrambledshRNA (1.5×10^{10} vp/µl). At day 40, mice were killed and whole ankle joints and synovial tissue from the knee joint were collected. Synovial tissue was analysed for PBEF mRNA expression levels and sections of decalcified ankle joint were stained with H&E and scored for synovitis and cartilage degradation.

Results Transduction of murine FLS with rAAV5-PBEFshRNA resulted in downregulation of PBEF mRNA (61%) and protein (32%) compared to rAAV5-scrambledshRNA after 5 days. In the mice treated locally with rAAV5-PBEFshRNA, the authors observed reduced clinical arthritis scores (53.5% reduction, $p<0.05$) and paw swelling ($p<0.05$) compared to rAAV5-scrambledshRNA treated groups. No delay in onset of disease was found. Expression analysis of PBEF in the knee synovium of rAAV5-PBEFshRNA treated mice showed a decrease in PBEF mRNA levels compared to mice treated with the rAAV5-scrambledshRNA. Histological analysis of the ankle joints showed a decrease in synovitis ($p<0.05$) and cartilage degradation ($p<0.05$).

Conclusions Downregulation of PBEF locally in an inflamed joint using a viral vector results in a decrease in clinical scores and synovial inflammation, as reflected by histological analysis. These data further denote the potential of PBEF as therapeutic target for inflammatory conditions like arthritis.

A180 LOCAL DOWNREGULATION OF PRE-B CELL COLONY-ENHANCING FACTOR/VISFATIN USING AN ADENO-ASSOCIATED VIRUS TYPE 5 VECTOR ENCODING A SPECIFIC SMALL HAIRPIN RNA FOR PBEF RESULTS IN AMELIORATION OF ARTHRITIS

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