Investigation of the role of histone deacetylases in rheumatoid arthritis synovial fibroblasts

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Background:
Fibroblast-like synoviocytes (FLS) are key mediators of tissue destruction in rheumatoid arthritis (RA). Epigenetic changes have been implicated in maintaining the aggressive phenotype of FLS. Histone deacetylases (HDACs) are key enzymes that contribute to the epigenetic signature by affecting the acetylation of histones. Our aim is to determine the role of HDACs in regulating the autoaggressive phenotype of RA FLS.

Methods:
Real time-qPCR was used to measure HDAC1-11 in RA and osteoarthritis (OA) FLS and in RA FLS stimulated with TNF(50ng/ml), LPS(100ng/ml), hypoxia(0.1%) and dexamethasone(1x10^-6 M). OA FLS were used as a control as normal FLS do not proliferate. Joint biopsy samples from patients (n=7/group) treated or untreated with a current RA therapy (anti-TNF) were co-stained with anti-fibroblast and anti-HDAC1. HDAC1 was knocked down in FLS using siRNA transfection and the resulting phenotypes investigated.

Results:
HDAC1 mRNA expression increased (3.9 fold) in RA compared to OA FLS and was not altered by incubation with stimuli. HDAC1 was strongly expressed by FLS in RA but not OA (n=10/group), however the number of HDAC1+ cells was significantly (p=0.05) reduced in RA patients receiving anti-TNF. A 70% knockdown of HDAC1 did not affect cell viability or proliferation.

Conclusion:
HDAC1 is expressed more in RA than OA FLS but is unaffected by stimulation with pro/anti-inflammatory mediators. The influence of HDAC knockdown in FLS using Matrigel invasion assays and gene arrays will be investigated.