A novel Saa3-promoter reporter distinguishes inflammatory subtypes in experimental arthritis and human synovial fibroblasts

ID 2358880
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Year 2011
Title A novel Saa3-promoter reporter distinguishes inflammatory subtypes in experimental arthritis and human synovial fibroblasts
Journal Annals of the Rheumatic Diseases
Volume 70
Number 7
Pages / **Article-Number** 1311-1319
Keywords Adult; Aged; Animals; Arthritis, Experimental/*diagnosis/pathology; Arthritis, Rheumatoid/diagnosis; Cholesterol/pharmacology; Cluster Analysis; Diagnosis, Differential; Dose-Response Relationship, Drug; Feasibility Studies; Fibroblasts/pathology; Gene Expression Profiling/methods; Genetic Vectors; Humans; Lentivirus/drug effects/genetics; Mice; Mice, Inbred C57BL; Middle Aged; Osteoarthritis/diagnosis; Promoter Regions, Genetic; Serum Amyloid A Protein/*genetics; Synovial Membrane/*pathology; Technetium/diagnostic use; Transduction, Genetic
OBJECTIVE: To evaluate the applicability of a lentiviral (LV) serum amyloid A3 (Saa3)-promoter luciferase (Luc) reporter for assessing inflammation in experimental arthritis, synovial fibroblasts (SF) from osteoarthritis (OA) and rheumatoid arthritis (RA) patients. METHODS: In mice, synovium was transduced in vivo by cholesterol optimised LV, and two flares of acute joint inflammation were induced by injection of streptococcal cell wall (SCW) material into the knee-joint cavity. The time course of synovial inflammation was assessed using ex vivo luciferase assays, and histology. Uptake of (99m)technetium (Tc) was used to assess oedema. SF (n=12) of RA and OA patients were stratified by hierarchical clustering of whole genome expression profiles. Relative Saa3-promoter responses were determined in cytokine- or toll-like receptor (TLR)-stimulated SF subgroups. RESULTS: In vivo, the Saa3-promoter reporter activity was strongly upregulated at 1 and 2 days after the first and second SCW challenge. The Saa3-promoter activities during acute inflammation correlated with Tc uptake measurements but were more sensitive and able to respond to the ongoing synovitis in the chronic phase of SCW arthritis. Molecular stratification defined two inflammatory SF subtypes, unrelated to disease classification. Relative Saa3-promoter responses to interleukin 1beta, tumour necrosis factor alpha and TLR4 agonist were significantly increased in OA/RA SF with a high compared to a low inflammatory profile subtype. Serum stimulation of the Saa3-promoter reporter cell-line could distinguish between healthy and RA patients. CONCLUSION: The Saa3-promoter reporter demonstrates a robust and feasible tool for assessing the course and severity of experimental arthritis and for distinguishing molecularly distinct inflammatory SF subtypes from a heterogeneous patient population.
Publisher British Medical Association
ISSN/ISBN 0003-4967 ; 1468-2060
URL http://www.ncbi.nlm.nih.gov/pubmed/21474483
edoc-URL http://edoc.unibas.ch/49999/
Full Text on edoc No;

Digital Object Identifier DOI 10.1136/ard.2010.135665
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/21474483
ISI-Number WOS:000291028800024
Document type (ISI) Article