(n=199 patients), we validated the interaction between anti-CCP and RF with the clinical response to anti-TNF agents. (P=0.044).

Conclusion: The results of this study show that interactions between antibodies are important in the response to anti-TNF therapy and suggest potential pathogenic relationships.

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SAT0007

BLOCKING HISTAMINE-RELEASING FACTOR/TRANSLATIONALLY CONTROLLED TUMOR PROTEIN (HRF/TCTP) ATTENUATES AGGRESSIVENESS OF FIBROBLAST-LIKE SYNOVIOCYTES AND AMELIORATES COLLAGEN-INDUCED ARTHRITIS IN RHEUMATOID ARTHRITIS

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Background: Histamine-releasing factor/translationally controlled tumor protein (HRF/TCTP) stimulates cancer progression and allergic responses. Increased expression of HRF/TCTP occurs in joints of rheumatoid arthritis (RA) patients, but the role of HRF/TCTP in RA remains undefined

Objectives: In this study, we explored the pathogenic significance of HRF/TCTP and evaluated therapeutic effects of HRF/TCTP blockade in RA.

Methods: HRF/TCTP transgenic (TG) and knockdown (KD) mice with collagen-induced arthritis (CIA) were used to determine experimental phenotypes of RA. HRF/TCTP levels were measured in sera and joint fluids in patients with RA and compared to those with osteoarthritis, ankylosing spondylitis, Behcet disease, and healthy controls. HRF/TCTP expression was also assessed in synovium and fibroblast-like synoviocytes (FLS) obtained from RA or OA patients. Finally, we assessed effects of HRF/TCTP and dimerized HRF/TCTP binding peptide-2 (dTBP2), an inhibitor of HRF/TCTP, in RA-FLS and CIA mice.

Results: Our clinical, radiological, histological, and biochemical analyses indicate that inflammatory responses and joint destruction were increased in HRF/TCTP TG mice, and decreased in KD mice compared to wild-type littermates. HRF/TCTP levels were higher in sera, synovial fluid, synovium, and FLS of patients with RA than in control groups. Serum levels of HRF/TCTP correlated well with disease activity in RA. Tumor-like aggressiveness of RA-FLS was exacerbated by HRF/TCTP stimulation and ameliorated by dTBP2 treatment. dTBP2 exerted protective and therapeutic effects in CIA mice, and had no detrimental effect in a murine tuberculosis model.

Conclusion: Our results indicate that HRF/TCTP represents a novel biomarker and therapeutic target for diagnosis and treatment of RA.

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SAT0008

INDIVIDUAL FUNCTIONS OF THE HISTONE-ACETYLTRANSFERASES CBP AND P300 IN REGULATING THE INFLAMMATORY RESPONSE BY AFFECTING HISTONE ACETYLATION AND MRNA STABILITY

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Background: Prolonged TNF-induced H3K27 acetylation (H3K27ac) and increased mRNA stability in rheumatoid arthritis (RA) synovial fibroblasts (SF) are leading to a sustained inflammatory response. Underlying enzymes coordinately regulating these pathways have not been identified so far. The histone acetyltransferases cAMP-response element binding protein binding protein

(CBP) and p300 are writers of activating H3K27ac marks and close homologues with widely accepted redundant functions.

Objectives: To analyze individual functions of CBP and p300 in regulating the inflammatory response of RA SF.

Methods: SF were isolated from patients with RA undergoing joint replacement surgery. The expression of CBP and p300 was silenced by transfection of antisense LNA gapmers (12.5 nM). SF were stimulated with TNF (10 ng/ml) for 24h. Actinomycin D (10 µg/ml) was added 4h after TNF-treatment for 2h and 4h (n=3) to test mRNA stability. Transcriptomes were determined by RNA-seq (Illumina NovaSeq 6000, n=6). We mapped raw reads from RNA-seq reference genome using STAR. Counts for genes were obtained using Feature counts. We searched for differential expression genes (DEG) across experimental conditions using general linear models (glm) implemented in 'edgeR' package of R. Significantly affected genes ($\pm$ fold change > 1.5, FDR < 0.05, top 3000 genes included) entered pathway enrichment analysis for Gene Ontology (GO) biological process, and KEGG pathways in DAVID. Changes in the mRNA (n=12-14) and protein expression (n=6-12) were confirmed by quantitative Real-time PCR and ELISA. The levels of activating histone marks H3K27ac and nuclear localization of p50 and p65 were analyzed by Western blotting.

Results: DEG revealed that silencing of p300 affected the expression of 6026 and 5138 genes in unstimulated and stimulated SF, respectively. In contrast, only 285 and 1911 genes were affected by CBP silencing in unstimulated and stimulated SF, respectively. In TNF-stimulated SF, pathway enrichment analysis of DEG revealed a key role of CBP in regulating the "type I interferon signaling pathway" (p=2.12x10⁻⁶). Both, silencing of CBP and p300 regulated genes enriched in the "TNF signaling pathway" (CBP: p=0.005; p300: p=0.031). In contrast to CBP silencing that had anti-inflammatory effects, silencing of p300 had pro- and anti-inflammatory effects. ELISA experiments suggested that silencing of CBP reduced the secretion of IL6 (p<0.01), CCL2, CXCL31 (p<0.05), and CXCL12 (p<0.001). Silencing of p300 reduced the secretion of CCL2 (p<0.001) and CXCL31 (p<0.05) but increased the expression of IL8 (p<0.001) and CXCL2 (p<0.05). Western blotting revealed that neither CBP, nor p300 silencing affected the nuclear expression of the NF-κB subunits p65 and p50. Silencing of p300 reduced the levels of H3K27ac by 30% in unstimulated SF, and by 61.4% (p<0.05) in presence of TNF. In addition to regulating H3K27ac, silencing of p300 regulated the expression of TNF-induced cytokines by increasing the mRNA stability of IL8, IL6 and CCL2 mRNA but not of CXCL2. Silencing of CBP reduced H3K27ac by 43.5% only in presence of TNF and did not affect TNF-induced mRNA stability of cytokines. This is in line with the enrichment of the GO biological process "regulation of mRNA stability" (p=2.61x10⁻⁸) being enriched only after silencing of p300.

Conclusion: Our results suggested that p300 is the major writer for H3K27ac marks in SF. Additionally, p300 regulated cytokine expression by affecting mRNA stability in a target-specific manner. We identified overlapping and distinct functions for CBP and p300 in regulating the inflammatory response of SF.

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SAT0009

ROLE OF EC-18 IN AUTOIMMUNE ARTHRITIS AND INTERSTITIAL LUNG DISEASE IN CURDLAN-ADMINISTERED SKG MICE

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Background: Although the mortality of patients with rheumatoid arthritis (RA), for which interstitial lung disease (ILD) is one of the major contributors, has still not decreased, new target therapies for RA have shown good response in peripheral arthritis. EC-18 (acetylated diacylglycerol 1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol) is a mono-acetyl-diglyceride that has been isolated from the