and one in each group was receiving bDMARD. M1 circulating monocytes were expanded in RA as compared to HI. This difference was at RA-CV (+) expense. RA monocytes had higher Intracellular levels of IL-1b and IL-6 as compared to HI. M1 from RA-CV (+) had higher intracellular levels of IL-1b and IL-6 than RA-CV (-). M1 monocytes have higher levels of inflammatory cytokines than M2. P-S6R protein, (mTORC activation), was higher in RA patients than HI. The highest levels of P-S6R was observed in M1 monocytes from RA-CV(+) population.

FIGURE 1. Circulating monocytes phenotype, intracellular cytokines and phosphorylated S6R in HI and RA-CV (+), RA-CV (-) and the combined RA patients.

A) *=0,02; B) *=0,016; C) ****=0,0001, **=0,002; D) ****=0,0001, ***=0,0008, **=0,001, *=0,01; E) ****=0,0001, **=0,002; F) ****=0,0001, **=0,001, **=0,003.

Conclusion: RA-CV+ patients, have a significantly higher number of pro-inflammatory circulating monocytes, using a multiparametric classification method. These monocytes also express higher levels of inflammatory cytokines and higher activation of mTORC, which also participate in the development of atherosclerotic plaque, suggesting that these monocytes could be a key element in the non-clarified yet, excess of CV risk of RA patients.

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SAT0005

INHIBITION OF HEPATOCYTE GROWTH FACTOR/C-MET SIGNALING ABROGATES JOINT DESTRUCTION BY SUPPRESSING MIGRATION OF MONOCYTES TO SYNOVIUM IN RHEUMATOID ARTHRITIS

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Background: Hepatocyte growth factor (HGF), originally discovered as a mitogen of hepatocytes, binds to receptor-tyrosine kinase c-Met and has been shown to be a multi-functional cytokine that promotes processes such as cell proliferation, survival, differentiation, migration, and angiogenesis¹. Since HGF/c-Met signaling also leads to tumorigenesis and cancer invasion, that has recently attracted attention as a target for anticancer agents². However, in reports of rheumatoid arthritis (RA), though anti-inflammatory and antiangiogenic mechanisms related to HGF/c-Met signal inhibition have been reported, the role of HGF in RA bone destruction through monocyte migration remains unclear³.

Objectives: To determine the expression of HGF in RA biological fluids, the role it plays in monocyte migration and the therapeutic effect of a savolitinib, a specific c-Met inhibitor, in arthritis model mice.

Methods: HGF/c-Met expression in serum, synovial fluid (SF), and synovial tissues (STs) obtained from RA patients and control subjects, as well as RA fibroblast-like synoviocytes (FLSs) was evaluated by ELISA and immunostaining. To determine the function of HGF in RA SFs, we preincubated RA SFs with a neutralizing anti-HGF antibody and measured the ability of these SFs to induce the human acute monocytic leukemia cell line (THP-1) chemotaxis. Additionally, examinations of SKG mice treated with savolitinib (2.5 mg/kg/day) for 4 weeks were conducted.

Results: HGF level in serum from RA patients was significantly higher as compared to the controls (930 ± 97 vs. 476 ± 97 pg/mL, $p < 0.01$) and decreased by drug treatment for 24 weeks (1147 ± 284 vs. 539 ± 160 pg/mL, $p < 0.05$). Additionally, HGF level in SF from RA patients was higher as compared to SF from osteoarthritis patients (1632 ± 366 vs. 566 ± 140 pg/mL, $p < 0.05$). HGF and c-Met expressions were also noted in RA STs. Stimulation of RA-FLS with TNF- α increased HGF/c-Met expression in a concentration-dependent manner, and c-Met signal inhibition by SU11274 suppressed production of fractalkine/CX3CL1, CXCL16, and MIP-1 α /CCL3 (mean 50%, 56%, 90%, respectively). When HGF was removed by immunoprecipitation, migration of THP-1 in RA-SF was suppressed (mean 23%). In SKG mice, savolitinib significantly suppressed ankle bone damage on μ CT, with an associated reduction in number of tartrate-resistant acid phosphatase-positive osteoclasts.

Conclusion: HGF is produced by inflammation in synovium associated with RA, and then activates monocyte migration to synovium tissue and promotes bone destruction through its own chemotactic effect as well as enhanced chemokine production. These results indicate that a strategy that targets c-Met signaling may be important for resolving bone destruction in RA.

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SAT0006

SIMULTANEOUS ANALYSIS OF ANTI-CCP, RHEUMATOID FACTOR, ANTI-PAD4 AND ANTI-CARBAMYLATED PROTEIN ANTIBODIES REVEALS INTERACTION EFFECTS WITH RESPONSE TO ANTI-TNF THERAPY IN RHEUMATOID ARTHRITIS

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Background: Blocking of the Tumor Necrosis Factor (TNF) activity is a successful therapeutic approach for 2 out of 3 Rheumatoid Arthritis patients. Identifying the patients that will not respond to this therapeutic approach is a major translational goal in RA. Association of seropositivity to rheumatoid factor (RF) or anti-cyclic-citrullinated antibodies (anti-CCP) with anti-TNF response has proven inconclusive, suggesting that other yet unexplored biomarkers could be more informative for this goal.

Objectives: We tested the association of two recently introduced biomarkers in RA: anti-carbamylated protein antibodies (anti-CarP) and anti-peptidylarginine deiminase type 4 (anti-PAD4).

Methods: A prospective cohort of n=80 RA patients starting anti-TNF therapy was recruited and levels for all four autoantibodies -RF, anti-CCP, anti-CarP and anti-PAD4- were measured at baseline. The change in DAS28 score between baseline and week 12 of therapy was used as the clinical endpoint.

Results: Single marker-analysis showed no significant association with drug response. However, when testing for interactions between autoantibodies, we found highly significant associations with drug response. Anti-CCP and RF showed a positive interaction with the response to anti-TNF therapy ($P=0.00068$), and anti-PAD4 and anti-CarP titers showed a negative interaction with the clinical response at week 12 ($P=0.0062$). Using an independent retrospective sample