Results In RA synovial tissue expression of FoxO1 negatively correlated with clinical parameters of disease activity: serum C-reactive protein ($R = -0.771, P = 0.0008$), erythrocyte sedimentation rate ($R = -0.759, P = 0.0003$), and DAS28 ($R = -0.575, P = 0.01$), as well as synovial IL-6 mRNA levels ($R = -0.632, P = 0.004$). In vitro, RA FLS stimulation with IL-1β or TNFα caused rapid down-regulation of FoxO1 mRNA levels, followed by reduction of FoxO1 protein expression and DNA binding. This effect was independent of PKB signalling, and was associated with acceleration of FoxO1 mRNA degradation in the presence of IL-1β. Inhibition of c-Jun N-terminal kinase (JNK), but not other MAPKs, prevented down-regulation of FoxO1 expression and binding by IL-1β, and blocked IL-1β-induced reduction of FoxO1 mRNA stability. Overexpression of constitutively active FoxO1 in RA FLS induced apoptosis associated with altered expression of genes regulating cell cycle and apoptosis: BIM and p27kip1 were induced while expression of Bcl-XL was suppressed in cells expressing active FoxO1.

Conclusions Collectively, our findings suggest that suppressed synovial FoxO1 expression is strongly associated with RA pathology and demonstrate that reduction of FoxO1 expression might contribute to perpetuation of inflammation in RA by promoting FLS survival and proliferation. Our data also identify JNK-mediated modulation of FoxO1 mRNA stability as an important mechanism underlying regulation of FoxO1 by inflammatory cytokines.

Conclusions Here, we describe that the novel cytokine IL-36α, mainly expressed by plasma cells, is upregulated in PsA and RA synovium and leads to IL-6 and IL-8 production by synovial fibroblasts. This finding needs further studies to determine if the IL-36 family can function as a potential target for arthritis therapy.

Background Ankylosing spondylitis (AS) is a clinically well-known chronic inflammatory disease of the axial skeleton and peripheral joints. The pathogenesis of this disease still remains a challenge. Determination of cytokine profile and its role involved in AS pathogenesis give an opportunity to extend the targeted therapeutic approach. Interleukin-17 (IL-17) and interleukin-23 (IL-23) are cytokines of interest in the investigation of the pathogenesis of spondyloarthritis although their importance in AS is not clearly defined.

Objectives to investigate levels of IL-17 and IL-23 in a group of AS and in a demographically matched group of healthy subjects and its association with the disease activity measured by relevant clinical and biochemical parameters.

Materials and Methods 39 AS patients classified by the modified New York and ASAS criteria were assessed clinically and 6 ml of serum were collected from each patient. 39 healthy subjects as control group were included in this study. The serum IL-17 and IL-23 levels were tested using xMAP multiplex immunobead assay technology. At the same time the disease activity was measured by using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

Results The mean serum IL-17 and IL-23 level in AS group was respectively 18.9 (SD 39.6) and 194.6 (SD 261.4) pg/ml. In the healthy control group the mean serum IL-17 level was 15.4 (SD 26.0) and IL-23 level -- 200.3 (SD 256.3) pg/ml. The serum levels of IL-17 and IL-23 were not statistically significantly different from the healthy subjects and the levels did not correlate with the disease activity measured by BASDAI and ASDAS (using the CRP and ESR).

Conclusions These results suggest that IL-17 and IL-23 are not major components of the pathogenesis of inflammation in AS patients. Our data differ from Chen W S et al, in 2012 published data major components of the pathogenesis of inflammation in AS patients. These results suggest that IL-17 and IL-23 are not major components of the pathogenesis of inflammation in AS patients. Our data differ from Chen W S et al, in 2012 published data major components of the pathogenesis of inflammation in AS patients. These results suggest that IL-17 and IL-23 are not major components of the pathogenesis of inflammation in AS patients. Our data differ from Chen W S et al, in 2012 published data major components of the pathogenesis of inflammation in AS patients. These results suggest that IL-17 and IL-23 are not major components of the pathogenesis of inflammation in AS patients. 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patients however show a lack of clinical response to this treatment. The use of robust predictive markers of response to identify individuals who are likely to respond to biological treatments may provide guidance in optimising treatment strategies and lead to lower costs. The ability of MRF8/14 serum complexes, a major granulocyte and monocyte protein associated with inflammation in patients with RA, was tested to differentiate between responders and non-responders to various biological treatments and to monitor disease activity in these RA patients.

Materials and Methods 170 RA patients were treated with adalimumab, infliximab or rituximab and were categorised into responders (n = 125) and non-responders (n = 47) according to the European League Against Rheumatism (EULAR) response criteria. Serum concentrations of MRF8/14 complexes were measured at baseline, week 4 and week 16 and divided in low and high MRF8/14 serum complexes level groups based on the median level for each treatment group. Non-parametric tests were used to analyse the data.

Results Before initiation of adalimumab, infliximab or rituximab treatment, responders showed significantly higher levels of MRF8/14 serum complexes compared to non-responders. (p = 0.010, p = 0.001 and p < 0.001, respectively). Logistic regression analysis showed that a high level of MRF8/14 serum complexes at baseline increased the odds of being a responder by a factor of 3.3 till 55. MRF8/14 serum complexes levels decreased after 4 weeks with respectively 46% and 60% (respectively median delta changes Δ400, IQ160–895 and 840; IQ170–1170) and 16 weeks with 61% and 65% (Δ730, IQ220–1120 and 8970, IQ530–1830) of treatment in responders to adalimumab and infliximab, while MRF8/14 serum complexes levels were stable in non-responders. In patients treated with rituximab, MRF8/14 serum complexes decreased with 61% (Δ1670, IQ959.5–3520) after 16 weeks in responders (p = 0.0009) and increased with 94% (Δ960, IQ405–1155) after 16 weeks in non-responders to treatment (p = 0.0039).

Conclusions MRF8/14 serum complexes can be used as a biomarker predictive of the response to biological therapy in RA patients.

A10.21 TOLL-LIKE RECEPTOR TRIGGERING OF HUMAN BASOPHILS MAY SYNERGISE WITH IG-E-MEDIATED ACTIVATION IN ACPA+ RA

Background Antibodies against citrullinated proteins (ACPA) are highly specific for rheumatoid arthritis (RA). Recently, we described a cellular immune response against citrullinated antigens that was only present in ACPA+ RA patients. This response was mediated via crosslinking IgE-ACPA bound to basophils, and suggests a major role for FcεRI-positive cells in the pathogenesis of RA. However, other mechanisms could also contribute to basophil activation in RA, for example through endogenous TLR ligands present in synovium, which are thought to contribute to chronicity of RA. As only limited information is present on TLR-expression and function in human basophils, it is not known whether such mechanisms could activate basophils. Therefore, we studied the activation of basophils via TLRs in combination with activation via IgE. Because recent studies in mice suggested that Th2-associated immune responses might be protective against arthritis, we also studied the effect of activated basophils on skewing of Th cells.

Materials and Methods Basophils were isolated from healthy donors. Real-time quantitative PCR was used to evaluate RNA expression of TLRs. For TLR-mediated stimulation, basophils were stimulated with pathogen-associated TLR ligands, such as LPS. Activation of basophils was measured using flow cytometry and cytokine assays (multiplex assays and ELISA). Naïve T cells were stimulated in the presence of basophil supernatant to evaluate the effect of TLR- and IgE-mediated activation of basophils on T cell skewing.

Results We show the presence of mRNA for TLR1-8 in human basophils, with transcripts of TLR-4 being most abundant. Basophils responded to TLR triggering with cytokine production, but not with degranulation. Remarkably, simultaneous triggering of basophils via TLR-ligands and IgE greatly enhanced cytokine production. Such synergy in cytokine production by basophils led to great enhancement of Th2 skewing.

Conclusions Our data show that human basophils functionally express TLRs and that the activation via these receptors can synergise with IgE-mediated activation. These findings provide a new perspective on the role of basophils and IgE-ACPA in combination with endogenous TLR ligands as a contributor to Th2 responses in RA patients.