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Background: Recently a group of T-cell clones with characteristic T-cell receptor (TCR) motif was identified in peripheral blood and synovial fluid of HLA-B*27+ patients with ankylosing spondylitis (AS) [1-2] - a prototypic disease from a wider group of spondyloarthropathies (SpAs). Extraarticular manifestations of AS could involve skin, intestine or eye. Emerging data indicate linkage between intestinal and joint inflammation, including expression of gut-associated integrins on synovial T-cells [3-4]. However, clonal T-cell composition and presence of identical clones in different inflamed sites in SpAs remains poorly studied.

Objectives: To investigate clonal T-cell repertoire and presence of AS-related TCR motif in different sites of inflammation of patients with SpA.

Methods: Samples of synovial fluid (SF) were obtained from HLA-B*27+ and HLA-B*27- patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA), as well as gut biopsy samples from patients with AS and Crohn's disease (AS/CD) or ulcerative colitis (AS/UC), and conjunctival swabs from patients with uveitis (Uv) and with or without articular manifestations (Table 1). Also SF and gut biopsy samples were obtained from HLA-B*27+ patients with juvenile idiopathic arthritis (JIA). For one patient PsA patient paired samples of SF and gut biopsy were obtained.

Table 1. Detection of the AS-related motif TRBV9_CASS[V/A/L/P][G/A][L/T/V][F/Y]STDTQYF_TRBJ2-3 in bTCR repertoires of samples from different inflamed sites of patients with SpA

Tissue	Diagnosis	B27+	B27-	AS-related TCR motif+ among all samples from B27+ donors
Synovial fluid	AS PsA JIA	20	12	
Intestinal biopsy	AS/CD AS/UC JIA	4	3	3 / 4
Conjunctival swab	Uv	8	0	4 / 8

SF and gut samples were processed to isolate mononuclear cells, while conjunctival swabs were directly lysed in the lysis buffer. CD3+ β 7-intergrin+ cells were isolated from SF by fluorescence-activated cell sorting. Deep TCR repertoire profiling was carried out using UMI-based cDNA library preparation technology [1].

Results: Identical T-cell clonotypes were detected between paired SF and gut samples of the same patient with psoriatic arthritis and intestinal inflammation. The subpopulation of β 7-intergrin+ SF T-cells shared significantly more identical clonotypes with gut biopsy repertoire compared to the bulk SF T-cell repertoire. Clonotypes belonging to the AS-related TCR beta motif TRBV9_CASS[V/A/L/P][G/A][L/T/V][F/Y]STDTQYF_TRBJ2-3 were detected in all inflamed tissues tested: synovial fluid, intestinal biopsies and conjunctival swabs of SpA patients (Table 1). Importantly, we observed these clonotypes exclusively in samples from HLA-B*27+ donors (n=26), but not in HLA-B27- context (n=15) with comparable analysis depth, thus confirming strong HLA-B*27-restriction of the clonotypes. The AS-related clonotypes were detected in the subpopulation of β 7-intergrin+ SF T-cells from HLA-B*27+ patients with PsA.

Conclusion: For the first time we directly report the T-cell clonal sharing between synovial fluid and inflamed gut tissue of SpA patients. In sum our data suggests involvement of identical T-cell clones in inflammation in different anatomical sites in SpA.

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OP0028

CD206+CD163+ PATHOGENIC MACROPHAGES ENRICHED IN RHEUMATOID ARTHRITIS SYNOVIAL TISSUE WITH DISTINCT TRANSCRIPTIONAL SIGNATURES

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Background: Synovial tissue macrophages are an exquisitely plastic pool of innate cells that play a key role in RA disease progression. However, the precise nature, diversity, and function of macrophage subsets within the inflamed joint remains unexplored.

Objectives: Therefore, the aims of this study are to phenotypically, transcriptionally and functionally characterise synovial tissue macrophages residing within the inflamed joint.

Methods: Rheumatoid Arthritis, Psoriatic Arthritis, Osteoarthritis and healthy control synovial-tissue biopsies and synovial-fluid mononuclear cells were analysed using the following panel (CD40,-CD45,-CD64,-CD68,-CD163,-CD206,-CD253,-CCR4,-CCR7,-CXCR1,-CXCR3). CD206+CD163+ and CD206-CD163- macrophages were sorted from RA synovial-tissue by FACSaria sorter; RNAseq and FLIM analysis, autologous T-cell co-culture and healthy fibroblast experiments performed. Cytokine expression was measured by MSD immunoassay.

Results: RA synovial tissue and fluid macrophages display markers typical of both M1 (CD40+CD253+) and M2 (CD206+CD163+) macrophages with a spectrum of macrophage activation states identified. Within this spectrum, significant enrichment of dominant CD206+CD163+ macrophage-subtype is present in synovial tissue versus fluid (p<0.05). CD206+CD163+ synovial tissue macrophages express significantly more CD40 than synovial fluid (p<0.0003), positively correlate with disease activity (r=0.6, p<0.01), with baseline levels predicting response to therapy (p<0.05). Moreover, CD206+CD163+CD40+ macrophages are enriched in RA synovial tissue compared to PsA and OA pathotypes (p<0.05). While the CD206+CD163+ subset is present in healthy synovial tissue, expression of CD40 is completely absent in healthy synovium (p<0.05) with dramatically decreased expression of CX3CR1 on RA macrophages. RNA-seq analysis indicates that CD206+CD163+ population is transcriptionally distinct from synovial tissue CD206-CD163-, synovial fluid CD206+CD163+, and RA monocyte-derived M1/M2 macrophages, with unique tissue-resident gene signatures. Moreover, differing metabolic demands between CD206+CD163+ and CD206-CD163- subsets was demonstrated by RNAseq and FLIM analysis. CD206+CD163+ macrophages enhance autologous T-cell responses, spontaneously secrete high levels of pro-inflammatory cytokines and activate healthy fibroblasts towards pro-inflammatory mechanisms thus further contributing to the local inflammatory response. Finally, inhibition of CD40 activity abrogates the expression of pro-inflammatory mediators (TNF α , IL-1 β , IL-6, IFN γ) and induces IL-10 expression in sorted CD206+CD163+ synovial tissue-macrophages suggesting a key role for CD40 in driving this pathogenic phenotype.

Conclusion: This data identifies for the first-time enrichment of a previously undescribed dysfunctional dominant and transcriptionally distinct macrophage subtype in RA synovial tissue. Taken together, this data provides a greater understanding of the critical role tissue-resident macrophages play in perpetuating inflammation in RA. Further investigation of the molecular patterns and cues that shape specific synovial macrophage subsets may provide opportunities to re-instate RA joint homeostasis.

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OP0029

NEUTROPHIL EXTRACELLULAR TRAPS IN GIANT CELL ARTERITIS INFLAMED TEMPORAL ARTERIES: LOCALIZATION, CO-EXPRESSION OF INFLAMMATORY CYTOKINES AND ASSOCIATION WITH DISEASE EXTENSION

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