OP0117

MICRO-STRUCTURAL CHANGES ASSOCIATED WITH ANTI-CITRULLINATED VIMENTIN AUTOIMMUNITY IN RA-AT-RISK INDIVIDUALS PRECIPITATE THE ONSET OF RHEUMATOID ARTHRITIS

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Background: Development of rheumatoid arthritis (RA) is characterized by a several years lasting phase of autoimmunity, characterized by the presence of anti-modified protein antibodies (AMPA), recognizing citrullinated, carbamylated or acetylated proteins, as well as rheumatoid factor (RF) which precedes the onset of clinical disease (1,2).High resolution peripheral quantitative (HR-pQCT) technique enables the depiction of small cortical changes in peripheral joints (3).
Objectives: To describe microstructural bone lesions in rheumatoid arthritis (RA) at-risk individuals using HR-pQCT technique, their relation to rheumatoid arthritis specific autoimmunity, particularly osteoclast-inducing citrullinated vimentin (cVIM) antibodies and their impact on the later development of RA.
Methods: Cortical micro-channels (CoMiCs) as well as volumetric cortical and trabecular bone densities were analyzed by high-resolution computed tomography in the hand joints of RA at-risk individuals. Anti-modified protein antibody (AMPA) response was profiled including reactivities against citrullinated proteins (vimentin, enolase, fibrinogen) as well as carbamylated and acetylated vimentin. All subjects were followed for the development of RA.
Results: RA at-risk subjects (all N=75) with high-level (>1000U) cVIM antibodies showed a broader AMPA response and significantly more severe microstructural changes (higher CoMiCs, lower cortical and trabecular bone volume) compared to subjects with low/no cVIM reactivity. High cVIM antibodies and microstructural changes (>15 radial CoMiCs/joint) were associated with the presence of arthralgia. Furthermore, progression to RA was high in subjects with high cVIM (53%) vs. those with low (22%) or no (5%) antibodies and those with microstructural changes (46%) vs. those without such changes (16%).
Conclusion: cVIM antibodies are associated to microstructural changes in RA at-risk individuals and predict the onset of RA. These data support the concept of structural priming of joints by autoimmunity before the onset of RA.

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OP0118

DISCRETE PATTERNS OF CITRULLINATED PEPTIDE AUTOANTIBODY REACTIVITIES EMERGE DURING PROGRESSION FROM PRE-DISEASE STATE TO DIAGNOSIS OF RHEUMATOID ARTHRITIS

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Background: Rheumatoid Arthritis (RA) patients with established disease can have autoantibodies reactive to a broad array of citrullinated antigens. Autoantibodies reactive against several citrullinated proteins can develop 10-15 years before the clinical onset of disease.
Objectives: We aimed to identify common patterns of citrullinated peptide reactivities that emerge among subjects during progression from a pre-disease state through diagnosis of RA.
Methods: 500 subjects with RA (based on ICD9-CM code) were identified from the Defense Medical Surveillance System. For each subject, up to four serum samples were obtained from the Department of Defense (DoD) serum repository: 1 from earliest time point before diagnosis (9.2 ± 2.0 years before, mean ± SD); one proximal to (immediately prior to or after) disease diagnosis (127 ± 125 days before diagnosis); plus 2 intermediate time points. A discovery subset of serum samples from 88 RA subjects confirmed to be positive for anti-citrullinated protein antibodies (ACPA) at the diagnosis-proximal time point (>5 U/mL for cyclic citrullinated peptide (CCP)-II test) was assessed for IgG antibodies to 36 antigens (24 citrullinated-peptide antigens among 14 proteins and 12 non-citrullinated antigens among 9 proteins) using a custom Luminex-based assay. Subjects testing above the upper limit of detection for the CCP-II test (300 U/mL) were considered ACPA-high (n=28), with the remainder considered moderate (n=60).
Results: For the group of ACPA-high subjects at the diagnosis-proximal time point, average IgG autoantibody binding to 9 citrullinated peptide antigens (from 7 proteins: clusterin, enolase, fibrinogen A, fibrinogen B, fibronectin, filaggrin, vimentin) showed significant increases from the earliest through diagnosis-proximal time points at the population level (FDR<0.05). In ACPA-moderate subjects, IgG levels to only one antigen (citrullinated-fibronectin) had a nominally significant but small increase (mean +8%) during this time frame. Significant reactivity to the non-citrullinated antigens was not observed. In ACPA -high but not -moderate subjects, group averages for a composite score of the 9 citrullinated peptide antigens increased relative to the earliest time points, with increased average levels observable 6-years before diagnosis that steadily increased as approaching diagnosis. Patterns of increases in IgG to specific citrullinated peptides differed among subjects, for both ACPA -high and -moderate groups. In the ACPA-high group, 46% of subjects had ≥50% increase in a majority (≥5) of the 9 citrullinated-peptide antigen set and the remaining had ≥50% increase for at least 1 of the antigens. In contrast, in the ACPA-moderate group, 58% of subject did not achieve ≥50% increase for any of the 9 antigens and only 8% of subjects had ≥50% increase in a majority of the 9-antigen set. The most commonly increased IgG reactivities were for citrullinated -filaggrin and -fibrinogen A, with ≥50% increase in 64% of ACPA-high and 20% of ACPA-moderate subjects.
Conclusion: Novel patterns of citrullinated peptide autoantibody reactivities that begin to emerge on average about 6 years before diagnosis of RA have been identified in samples from the US DoD serum repository. Evaluation of specific anti-citrullinated peptide autoantibodies could potentially provide sensitive, patient-tailored biomarkers to monitor disease trajectories as at-risk individuals progress to clinically-defined RA.
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OP0119

THE PRE-TREATMENT GUT MICROBIOME PREDICTS EARLY RESPONSE TO RHEUMATOID ARTHRITIS THERAPY

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Background: Early treatment initiation in rheumatoid arthritis (RA) is fundamental to avoid chronic joint destruction and disability. Despite remarkable advances in RA therapeutics, oral methotrexate (MTX) remains the anchor drug and mainstay of treatment worldwide (1,2). However, MTX bioavailability has a wide inter-individual variability and >50% of patients with moderate or severe RA show no or suboptimal improvement in their symptoms in response to MTX (1,3). The reasons for these disparities in treatment response remain unclear. Prior studies have shown that the biotransformation of MTX is altered in germ-free and microbiome-

depleted mice (4), prompting us to hypothesize that inter-individual differences in the human gut microbiome could impact drug bioavailability and thus clinical efficacy.
Objectives: To determine differences in the microbiome of drug-naïve, new onset RA (NORA) patients that could predict response to MTX therapy.
Methods: We performed 16S rRNA gene and shotgun metagenomic sequencing on the baseline gut microbiomes of 27 drug-naïve, NORA patients.
Results: Our analysis revealed significant associations between the abundance of gut bacterial taxa and genes including gene families related with purine and methotrexate metabolism. Machine learning techniques were applied to this metagenomic data, resulting in a robust predictive model based on bacterial gene abundance that accurately predicted response to MTX therapy in an independent group of patients. Finally, MTX available levels remaining after *ex vivo* incubation with distal gut samples from pre-treatment RA patients significantly correlated with the magnitude of future clinical response, suggesting a direct effect of the gut microbiome on MTX bioavailability and response to therapy.
Conclusion: Together, these results provide the first step towards predicting response to oral MTX in NORA patients and support the utility of the gut microbiome as a prognostic tool and perhaps even as a target for manipulation in the treatment of rheumatic and autoimmune disease.

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OP0120

BASELINE CELLULAR AND MOLECULAR CHARACTERISTICS OF SYNOVIAL TISSUE AND RELATION WITH TNFI RESPONSE. RESULTS FROM THE PATHOBIOLOGY OF THE EARLY ARTHRITIS COHORT (PEAC)

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Background: Despite early intervention with disease modifying therapy a high percentage of patients (~30%) fail to respond and require escalation to advanced therapies such as TNFi, with no available biomarkers to predict response. Whether synovial signatures predicting subsequent response to TNFi therapy can be identified at disease onset remains an unanswered question although critical for long term prevention of disease progression and overall health economic impact.
Objectives: The aim of this study was to evaluate in a cohort of treatment naïve early RA patients, whether baseline synovial cellular and molecular signatures predict subsequent response or not to anti-TNF therapy.
Methods: A total of 186 consecutive DMARD naïve inflammatory arthritis patients (disease duration <1 year) recruited as part of the multicentre PEAC study at Barts Health NHS Trust were evaluated. After 12 months 35 patients commenced therapy with a TNFi (DAS28>5.1, failed 2 x cDMARDs as per UK NICE guidelines). EULAR response (DAS28 and DAS improvement from baseline) was calculated 12 months after TNFi was initiated. All patients underwent an US guided baseline synovial biopsy of a clinically active joint along with collection of clinical characteristics. Following H&E staining, sections underwent immunohistochemical staining and semi-quantitative scoring (0-4) to determine the degree of CD20+Bcells, CD3+T cells, CD68+ lining (l) and sublining (sl) macrophage and CD138+ plasma cell infiltration. Sections were categorised into three pathotypes: (i) Fibroid: (CD68 SL<2 and or CD3, CD20, CD138<1), (ii) Myeloid: (CD68SL>2, CD20<1 and or CD3>1) and (iii) Lymphoid: (grade 2-3 CD20+ aggregates, CD20>2). Synovial gene expression was evaluated with Nanostring and RNA sequencing.
Results: 12 months after TNFi was initiated 17/35 (48%) patients responded to therapy (TNFi good EULAR response) and 18/35 (52%) had a moderate or non-response to TNFi. Baseline demographic or US characteristics did not differentiate between the 2 groups. Although we saw no significant differences between groups there was a trend for higher levels of B (CD20+) and T (CD3+) cells, sublining macrophages (CD68+) and plasma cells (CD138+) in the TNFi response group. The cohort was segregated by pathotype and each clinical parameter was compared from baseline to 12months. Interestingly, we observed a significant reduction of levels of CRP, VAS and DAS28 and number of tender and swollen joints in those patients with Lymphoid and Myeloid pathotype ($p<0.05$), but not in those with Fibroid pathotype (Figure 1). We also evaluated gene expression (using Nanostring and RNA-sequencing) and observed increased expression of genes related to macrophages, plasma cells and B/T regulatory cells expression/activation and/or stimulation at baseline in patients who responded to TNFi.
Conclusion: This study demonstrates first evidence of potential novel signatures/biomarkers of TNFi response in treatment naïve early RA. Clinical or US assessment cannot discriminate between responders to TNFi. Lymphoid and Myeloid pathotypes associated with significant falls in clinical outcome. Finally, molecular signatures including differential upregulation of T cells, B cells and macrophage associated genes are associated with good response to TNFi therapy.
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Figure 1. Clinical parameters progression from baseline to 12m post-TNFi according to pathotype