FRI0355

MUCOSAL ASSOCIATED INVARIANT T-CELLS ARE ENRICHED AT THE HUMAN ENTHERESIS AND HAVE A RESIDENT MEMORY PHENOTYPE

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Background: Mucosal associated invariant T-cells (MAITs) are innate-like T lymphocytes that express a semi-invariant TCR repertoire. They are activated by microbial ligands or cytokines including IL-23 and secrete inflammatory cytokines, including IFN γ and IL-17A. MAIT cells are enriched at mucosal surfaces and have been implicated in the pathogenesis of spondyloarthritis (SpA) (1) and inflammatory bowel disease (IBD). Although the human entheresis is not a mucosal surface it is the primary site of inflammation in SpA which has strong association with IBD.

Objectives: To investigate if a population of MAITs is present at the normal human entheresis thereby establishing a potential link between gut and joint inflammation.

Methods: Healthy interspinous ligament and spinous process were harvested from patients undergoing elective surgery for the correction of mechanical spinal defects. Enteseal soft tissue (EST) and peri-enteseal bone (PEB) were separated and cells were harvested by enzymatic and mechanical digestion respectively. The proportion of cells expressing markers consistent with MAITS (CD45+, CD3+, CD161+, TCRV α 7.2+) were measured by flow cytometry in EST, PEB and matched blood. Expression of CD69 and CD45RA were examined for phenotypic analysis. Transcript analysis for IL-23/IL-17 axis and immunomodulatory genes was performed on sorted enteseal MAITs and analysed by TaqMan array.

Results: As a proportion of total T-cells, MAITs were of approximately 3 fold and 2.5 fold greater abundance in EST and PEB respectively in comparison to matched peripheral blood (both $p=0.034$). MAITs in enteseal tissue had an overwhelming resident memory phenotype (CD69+, CD45RA-) median 53.2% (range 42.4 – 78.6%) in EST and 54.9% (45.2 – 82.1%) in PEB compared to those from blood 17.7 (6.8 – 69.4). MAITs robustly expressed RORC, CCR6 and IL-23R transcript. Compared to conventional enteseal T-cells, MAITs expressed significantly less TGF β (6-fold, $p>0.001$) and significantly more IL-23R (29-fold, $p=0.004$).

Conclusion: Healthy human enteseal tissue contains an enriched population of MAITs that strongly express IL-23R transcript at a frequency comparable to that reported in the colon (2). The majority of these cells express a resident memory phenotype suggesting that they are a distinct population residing in enteseal tissue. These observations are potentially relevant to SpA pathogenesis and the observed link between SpA and IBD.

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FRI0356

DIFFERENTIAL EXPRESSION OF HUMAN ENDOGENOUS RETROVIRUSES IN PSORIATIC DISEASE

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Background: Human endogenous retroviruses (HERV) are the stably inherited remnants of ancient retroviruses that infected the ancestral germline. A growing body of research has associated the differential expression and regulation of HERVs with a number of diseases, including

systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). HERVs are thought to contribute to the pathogenesis of autoimmune diseases by modulating the expression of host immune-related genes, molecular mimicry, or cross reactivity of host proteins with HERV encoded products.

Objectives: To compare the expression of 4 HERVs previously associated with autoimmune disorders (HERV-K, HERV-K10, HERV-W, and HERV-H) in whole blood, CD3+ T cells, and CD14+ monocytes of patients with cutaneous psoriasis without arthritis (PsC), psoriatic arthritis (PsA), and healthy controls.

Methods: PsC, PsA patients satisfying the CASPAR criteria, and healthy controls were recruited for the study. RNA was extracted from whole blood collected in Tempus tubes and HERV expression was measured by quantitative real time PCR (qRT-PCR) or droplet digital (dd)PCR with normalization to GAPDH. HERV expression in whole blood RNA from 40 PsA patients was compared to 40 age and sex matched PsC patients and 40 age and sex matched healthy controls. Subsequently, HERV expression in 55 PsC patients who progressed to develop PsA (converters) was compared to 55 age and sex matched PsC patients who did not develop PsA over the same duration of follow-up (non-converters). Finally, HERV expression in RNA isolated from CD3+ T cells and CD14+ monocytes from 19 PsA patients was compared to 13 PsC and 8 healthy controls. Expression differences between groups were determined by one-way ANOVA, Kruskal-Wallis and Mann-Whitney tests where appropriate.

Results: In whole blood, HERV-K was significantly differentially expressed between 40 PsA and 40 PsC patients (fold change [FC]=1.57, $p=0.008$). HERV-K was also significantly differentially expressed in baseline samples from 55 converters compared to 55 non-converters (FC=1.93, $p=0.03$). No other HERV genes were differentially expressed between these groups in whole blood. Significant expression differences were more evident in purified cells (Table 1).

Table 1. Differential expression of HERVs in purified T cells and monocytes.

	PsA vs. PsC		PsA vs. Controls		PsC vs. Controls	
	CD3+ T cells FC, p value	CD14+ Monocytes FC, p value	CD3+ T cells FC, p value	CD14+ Monocytes FC, p value	CD3+ T cells FC, p value	CD14+ Monocytes FC, p value
HERV-K	0.43, $p=0.02$	0.30, $p<0.01$	ns	0.17, $p<0.01$	2.18, $p=0.02$	ns
HERV-K10	2.94, $p=0.02$	ns	6.87, $p<0.01$	2.60, $p=0.04$	ns	ns
HERV-H	ns	ns	3.19, $p<0.01$	0.36, $p=0.02$	2.67, $p=0.01$	0.27, $p<0.01$
HERV-W	1.27, $p=0.04$	ns	4.12, $p<0.01$	ns	3.24, $p=0.01$	0.47, $p=0.04$

Ns, not significant.

Conclusion: In whole blood, expression of HERV-K differentiates PsA and PsC patients, and its expression is significantly elevated in PsC patients prior to the development of PsA. HERV expression differences between the groups are also evident in purified T cells and monocytes. These data suggest a role for HERVs in the pathogenesis of psoriatic disease and their potential use as prognostic markers of arthritis in patients with psoriasis.

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FRI0357

DRUG-INDUCED REMISSION AND SUBCLINICAL ACTIVITY IN PSORIATIC ARTHRITIS: TRANSCRIPTIONAL PROFILING TO CHARACTERIZETHE DISEASE STATE

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Background: Remission is an important goal of therapy in psoriatic arthritis (PsA), but data on molecular players of clinical remission and effective

disease inactivation are scarce. Gene expression profiling analysis could be useful to elucidate the pathogenic mechanisms of diseases, and differential gene expression analysis between diverse disease conditions produces gene signatures characteristic of the state or disease being studied.

Objectives: Our aim was to compare the transcriptional profiles of patients with clinically active versus inactive (remission state) PsA (peripheral joint subset), and healthy controls (HCs).

Methods: From a cohort of around 300 patients affected by PsA according to CASPAR criteria, we first selected 20 patients (peripheral arthritis subset) with active disease state (without biologic treatment ongoing) (A) and 20 patients with >1-year remission induced by TNF α antagonism (R), as assessed by DAPSA > 14, and DAPSA $\leq$ 4 scores respectively, and from 20 HCs matching for age and gender ratio. Both PsA groups were not on corticosteroid treatment. RNA from peripheral blood was extracted and, following quality analysis by Agilent Bioanalyzer, each condition has been profiled using RNAs pools in biological duplicates by distinct Affymetrix Human GeneChip HTA 2.0, for a total of 6 arrays. Data analysis was performed using the commercial software Partek Genomics Suite, V 6.6. To identify a transcript as differentially expressed, a value of fold change 1.5 and *p*-value 0.05 has been set.

Results: The Venn diagram shows all comparative groups (A vs R, A vs HC, R vs HC) with their relative amount of transcripts differentially expressed, generated using abovementioned parameters, and the relationship between sets (fig1, panel A). Using the list of transcripts differentially expressed in at least one of the aforementioned comparison, a hierarchical clustering was carried out to highlight the intra-condition expression profile. We have identified (arbitrarily) 4 clusters of transcripts with analogous transcriptional profile and to each of them a color code has been assigned (Heatmap in Fig1, panel B). For these clusters and for all lists of transcripts differentially expressed founded by our comparative study, we carried out the Gene Set Enrichment Analysis by Gene Ontology (GO), in order to identify how molecular functions, cellular components or biological processes occurs more frequently than expected in a reference list of transcripts.

Conclusion: Observing the amount of differentially expressed transcripts, is evident that while active disease state (A) has a clear-cut different profile, the drug-induced remission (R) is more similar with HCs condition. However, in the hierarchical clustering this trend of similarity does not appear in all clusters of transcripts, as shown particularly in the red, orange and green clusters. Again, the Gene Set Enrichment Analysis Score showed us that mRNA transcripts dysregulated in the R condition vs HCs, are involved in several biological processes related to immune system, development, response to stimulus, localization and others. Our next step will be to validate, by Real Time PCR in a large cohort of patients, the most interesting dysregulated genes covering biological functions eventually sustaining subclinical activity in PsA.

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FRI0358

ROLE OF MIRNA-21-5PAS A POTENTIAL BIOMARKER FOR THE INFLAMMATION PATHWAY IN PSORIATIC DISEASE AND RESPONSE TO METHOTREXATE TREATMENT

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Background: Psoriatic arthritis (PsA) is an inflammatory arthritis occurring in patients with psoriasis. Several studies have shown links between

altered miRNA expression with the pathogenesis of several autoimmune disorders. We previously demonstrated that miR-21-5p was upregulated in PsA compared to psoriasis without arthritis (PsC) and healthy controls (HC) and is thus a potential biomarker for PsA.

Objectives: 1) To determine whether miR-21-5p is differentially expressed in PsC patients who convert to PsA vs non-convertors and validate the previous results in an independent cohort. 2) To determine the role of miR-21-5p in the response to methotrexate treatment (MTX) 3) To determine whether miR-21-5p modulates inflammation in psoriatic disease.

Methods: Serum & whole blood RNA samples were collected from 54 convertors and 54 non-convertors (matched for age, sex, psoriasis duration), 40 patients with early PsA (<2 years' disease duration and not receiving biologic therapy), 40 patients with PsC (>10 years disease duration, not receiving biologic therapy, and matched to PsA patients on age, sex, psoriasis duration, and age of psoriasis onset), and 40 HC (matched to patients based on age, sex). RNA was extracted using the Tempus Spin RNA Isolation Kit. miR-21-5p was validated using droplet digital PCR (ddPCR). Serum IL-17, CXCL10, IL-23, TGF β 1 were measured by commercially available ELISA kits. Mann-Whitney test, Kruskal-Wallis test, Wilcoxon signed rank test and Spearman correlations were performed.

Results: The expression of miR-21-5p was significantly higher in convertors compared to non-convertors (Fold change(FC)=2.16, *p*=0.002). miR-21-5p was upregulated in PsA compared to PsC (FC=2.32, *p*=0.001) and HC (FC=15.7, *p*<0.0001) in the validation cohort. miR-21-5p was significantly down regulated 24 weeks post-MTX treatment in 30 PsA patients (FC=1.9, *p*<0.008), which correlated with swollen (*r*=0.49, *p*=0.003) and tender joint counts (*r*=0.41, *p*=0.02) supporting a possible role in inflammation pathway in PsA patients. IL-17 levels in PsA & PsC were significantly higher from HC (*p*=0.03), but not different between PsA & PsC. IL-17 levels were down-regulated post MTX treatment and correlated with miR-21-5p (*r*=0.56, *p*<0.001), CXCL10 levels (*r*=0.48, *p*=0.01), IL-23 levels (*r*=0.43, *p*=0.02), TGF β 1 (*r*= -0.45, *p*=0.04) and total active joint counts (*r*=0.40, *p*=0.016).

Conclusion: Up regulated expression levels of miR-21-5p in convertors and in PsA patients suggests a role as a potential biomarker for PsA. In the presence of upregulated miR-21-5p, IL-17 and IL-23 are upregulated while TGF β 1 is down regulated. When miR-21-5p is decreased IL-17 and IL-23 downregulate, with up regulation of TGF β 1. We have thus determined the role of miR21-5p as a potential biomarker for inflammation pathway in psoriatic disease and response to MTX possibly through modulation of CXCL10 and IL-17/IL-23 axis.

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FRI0359

KRT77 DELETIONS IN FAMILIAL INFLAMMATORY BOWEL DISEASE MAY OFFER A NOVEL LINK TO FAMILIAL SPONDYLOARTHROPATHY

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Background: Inflammatory bowel disease, either clinical or subclinical is a cardinal pathological process that is central to the spondyloarthropathy (SpA) category of disease that also includes psoriasis, psoriatic arthritis, uveitis and ankylosing spondylitis.

Objectives: To look for novel genes in familial SpA in large multigene families using a whole genome sequencing approach.

Methods: We used Whole Genome Sequencing to screen SpA family members with different disease manifestations. We screened 5 multigene SpA families (up to 8 members) with different disease manifestations.

Results: We found a 1.5MB deletion of the KRT77 gene in 3 of 7 families that segregated with SpA phenotype. Given that KRT77 is a barrier protein and given that tagging SNPs from GWAS studies do not cover the region, and given that both IBD and psoriasis are associated with barrier defects, we looked for an association with KRT77 deletion in