MUCOSAL ASSOCIATED INVARIANT T-CELLS ARE ENRICHED AT THE HUMAN ENTHESIS 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 IFNγ and IL-17A. MAIT cells are enriched at mucosal surfaces and have been implicated in the pathogenesis of spondyloarthritis (SpA1) and inflammatory bowel disease (IBD). Although the human enthesis is not a mucosal surface it is the primary site of infiltration in SpA which has strong association with IBD.

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

Methods: Healthy interstitial ligament and spino-ligamentous tissue were harvested from patients undergoing elective surgery for the correction of mechanical defects. Mucosal soft tissue (EST) and peri-entheseal 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+, TCRVαβ, CD69+, CD161b+) 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 enthesal 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 entheseal tissue had an overwhelming resident memory phenotype (CD69+, CD45RA-) median 53.2% (range 42.4 – 69.4). MAITs in enthesal tissue expressed IL-23R transcript at a frequency comparable to that reported in the colon (2). The majority of these cells expressed a resident memory phenotype suggesting that they are a distinct population residing in entheseal tissue. These observations are potentially relevant to SpA pathogenesis and the observed link between SpA and IBD.

REFERENCES:
[1] Gracey E, Qaiyum Z, Almaghlouth I, Lawson D, Karki S, Avvaru N, et al. HERV-K expression in whole blood RNA from 40 PsA patients was compared to 40 PsC patients (fold change [FC]=1.93, p=0.03). No other HERV genes were differentially expressed between these groups in whole blood.

Conclusion: In whole blood, HERV-K expression differences were more evident in 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.

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DIFFERENTIAL EXPRESSION OF HUMAN ENDODGENOUS RETROVIRUSES IN PSORIATIC DISEASE

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Background: Human endogenous retroviruses (HERVs) are stably inherited remnants of ancient retroviruses that infected the ancestral germine. 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 was compared to matched PsC patients and 40 age and sex matched healthy controls. 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).

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.

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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ENDOGENOUS RETROVIRUSES IN PSORIATIC DISEASE: TRANSCRIPTIONAL PROFILING TO CHARACTERIZE THE 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