versus TNF-tg11

Conclusion

Kathryn J. A. Steel1, Shih-Ying Wu1, Ushani Srenathan1, TISSUE RESIDENT POPULATION ENRICHED IN JOINTS OF inflamed tissue in the TNF-tg11 TRAP staining. Juxta articular and systemic bone losses were assessed using calliper measurements. Histology was assessed in formalin fixed tissues from mice between four and nine weeks of age. Paw swelling was determined using a custom-made device.

Methods

Inflammation in the TNF-tg11 WD1 transgenic mouse model of chronic polyarthritis (TNF-Tg) to generate TNF-tg11 mice. We have identified that localised pre-receptor activation of glucocorticoids (GC) by the enzyme 11beta-hydroxysteroid dehydrogenase type 1 (b-HSD1) is increased within sites of inflammation in the TNF-tg11 KO, 11.08 KO, 530276 3225; p

Results

Significant bone loss was observed in TNF-tg11 KO mice. Clinical scores, including DAS28 CRP score, were significantly worse in the TNF-tg11 KO mouse (synovitis size, TNFtg, 5.2 0.66; p

Conclusions

These novel findings show an enrichment of IL-17+CD8+ T cells in the joints of patients across multiple SpA types, with some cells exhibiting markers of skin homing. Synovial IL-17+CD8+ T-cells have hallmarks of tissue-resident memory cells, the first description of these cells in the synovial fluid. Functionally IL-17+CD8+ T cells exhibit a high pro-inflammatory potential, indicating that these cells may be important contributors to the pathogenesis of SpA.

Disclosures

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O40 IL-17+CD8+ T CELLS ARE A PRO-INFLAMMATORY TISSUE RESIDENT POPULATION ENRICHED IN JOINTS OF PATIENTS WITH SPONDYLOARTHRITIS

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Background: Spondyloarthritis (SpA) describes a group of inflammatory joint diseases affecting ~1% of the population. SpA has strong genetic associations with HLA-B/REX3 implying a role for CD8+ T-cells. Furthermore, genetic associations with IL23R/TRA3P2 and the clinical efficacy of IL-17 blockade in SpA, indicate a role for IL-17 in these diseases. This led us to investigate the presence, phenotype and functional capacity of IL-17+CD8+ T-cells in the joints of patients with SpA.

Methods: Mononuclear cells were isolated from peripheral blood (PB) and synovial fluid (SF) from patients with PsA, other peripheral-SpA types (including ankylosing spondylitis/non-radiographic axial SpA/reactive arthritis/enterophaic arthritis/undifferentiated SpA) and rheumatoid arthritis (RA). Cells were stimulated ex-vivo before analysis of surface marker/cytokine expression by flow cytometry or cytokine secretion assay. Sorting was performed on unstimulated SFMC and gene expression analysis performed by RT-PCR.

Results: Frequencies of IL-17+CD8+ T-cells were increased in the SF of PsA (p = 0.0005) and SpA (p = 0.0009), but not RA patients (p = 0.3) vs. paired PB, with IL-17 secretion confirmed by cytokine secretion assay. This increase was not dependent on carriage of HLA-B27 haplotype. Phenotypically, SF IL-17+CD8+ T-cells were largely composed of TCRβ+ T-cells (~95%), with small proportions of MAIT/NK/γδ-T-cells (all ~5%). Synovial fluid IL-17+CD8+ T-cells displayed general characteristics of IL-17+ cells (CCR6/CD2161 expression) but also of tissue resident memory T cells (FoxP3, CD45RA-CCR7-CD103+). Indeed, when we sorted CD8+CD69+CD103+ Treg cells from the PsA joint, they were enriched for IL-17, whilst expressing RORC transcript. Functionally, a high frequency of SF IL-17+CD8+ T-cells co-expressed pro-inflammatory cytokines IFN-γ, GM-CSF, TNF-α, some IL-21 and IL-22, but very little anti-inflammatory IL-10. Considerable proportions of SF IL-17+CD8+ T-cells expressed skin-related markers CD49a (median-57%) and cutaneous lymphocyte antigen (27%), suggesting homing potential between these tissue sites.

Conclusion: These novel findings show an enrichment of IL-17+CD8+ T cells in the joints of patients across multiple SpA types, with some cells exhibiting markers of skin homing. Synovial IL-17+CD8+ T-cells have hallmarks of tissue-resident memory cells, the first description of these cells in the synovial fluid. Functionally IL-17+CD8+ T cells exhibit a high pro-inflammatory potential, indicating that these cells may be important contributors to the pathogenesis of SpA.