
Proceedings Paper:
Cuthbert, RJ orcid.org/0000-0002-9054-5260, Fragkakis, EM, Millner, P et al. (3 more authors) (2016) Innate Lymphoid Cells are Present at Normal Human Enthesis Providing a Potential Mechanism for Spondyloarthropathy Pathogenesis. In: Annals of the Rheumatic Diseases. Annual European Congress of Rheumatology EULAR 2016, 08-11 Jun 2016, London, UK. BMJ Publishing Group .

https://doi.org/10.1136/annrheumdis-2016-eular.2270

Innate Lymphoid Cells are Present at Normal Human Enthesis Providing a Potential Mechanism for Spondyloarthropathy Pathogenesis

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Background and objectives

The pathogenesis of murine spondyloarthropathy (SpA) has been intimately linked to the presence of IL-23 responsive, innate like lymphocytes at peripheral and spinal enthesis. Human SpAs are associated with SNPs in genes related to the IL-23 pathway and drugs that block IL-12/23 have shown efficacy. We hypothesised that the normal human enthesis has a population of resident innate lymphoid cells (ILCs) that could be key in governing entheseal immune homeostasis partly via interaction with resident mesenchymal stromal cells (MSCs).

Materials and methods

Normal spinal enthesis were harvested from patients undergoing spinal decompression surgery and enzymatically digested prior to sorting or flow cytometry. Immunophenotyping and cell sorting was performed on enthesis samples harvested from 6 patients and unmatched peripheral blood. The expression of RORγt and key immunomodulatory transcripts was tested in sorted populations by RTqPCR. Anterior cruciate ligament and Achilles enthesis were obtained from patients with knee OA and Achilles tendon rupture and analysed by immunohistochemistry (IHC). Adherent cells from entheseal digest were cultured under standard MSC culture conditions and expression of known MSC markers was assessed by flow cytometry.

Results

All sorted samples contained ILC3s, median proportion 0.09% (range 0.015-0.63). Transcript analysis confirmed the expression of RORγt transcript in sorted ILC3 populations. ILC3s expressed 51-fold greater relative expression of RORγt in comparison to unsorted mononuclear cells. 5 of 6 sorted samples contained ILC2s, median proportion 0.20% (range 0-0.49). RORγt expression was detected in knee OA and there was widespread expression of RORγt in inflammatory infiltrates in injured enthesis as shown by IHC. Culture expanded adherent cells grew in characteristic fibroblastoid colonies and expressed phenotypic markers consistent with bone marrow derived MSCs.

Conclusions

Our findings show that both ILCs and MSCs are present in the normal human spinal enthesis. ILCs may also be greatly increased in frequency following injury. The co-localisation of ILC and MSC populations at the enthesis suggests a potential link between cellular dysregulation of the IL-23/17 axis and human SpA pathology.