Spondyloarthritis etiology, pathogenesis and animal models FRI0353 Misregulation of BMP/TGFβ sheds light on the pathogenicity of HLA-B27 in spondyloarthritis

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Spondyloarthritis – etiology, pathogenesis and animal models

FRI0353 MISREGULATION OF BMP/TGFB SHEDS LIGHT ON THE PATHOGENICITY OF HLA-B27 IN SPONDYLOARTHRITIS

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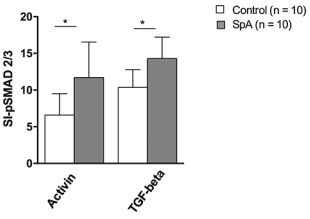
Background: The class I MHC allele, HLA-B27 is the main genetic factor predisposing to ankylosing spondylitis (AS) and related spondyloarthritis (SpA), a group of osteo-articular disorders combining inflammation with ossification. Until now, hypotheses to explain such striking association discovered 45 years have speculated either on the presentation of particular peptides to $CD8^+$ T cells or on aberrant behaviors of the HLA-B27 molecule independent of its antigen presenting function, including slow folding and homodimers formation

Objectives: To unravel aberrant function(s) of HLA-B27 independent of antigen presentation that may explain its pathogenicity.

Methods: *Drosophila* transgenic for SpA-associated HLA-B*27:04 or HLA-B*27:05 or non-SpA -associated HLA-B*07:02, alone or in combination with human β2-microglobulin (hβ2m) were produced. Genetic interaction tests were used to identify altered pathway(s). Protein-protein interactions were evidenced by proximity ligation assay. Phosphorylation of Smad2/3 was tested on CD4+ T cells from HLA-B27+ SpA patients and HLA-B27- neg healthy controls (6-10/group) by PhosFlow.

Results: *Drosophila* transgenic for HLA-B*27:04 or HLA-B*27:05 but not for control HLA-B*07:02 allele, in the presence of hβ2m that allows expression of well-folded HLA-B molecules at the cell surface, developed *crossveinless* phenotype. This was due to a disturbance of BMP signaling by HLA-B27/hβ2m which repressed Saxophone (Sax) BMP type I receptor (BMPR1) function, resulting in widening of phosphorylated Mad, the *Drosophila* receptor-mediated Smad, gradient, and increased expression of its target genes *dpp* and *omb*. Consistently, HLA-B27/hβ2m well-folded conformers co-localized with Sax at the surface of *Drosophila* cells and also with Sax mammal ortholog ALK2, on immune cells from SpA patients. As predicted, given that Sax orthologs ALK1 and ALK2 are known to exert antagonistic function on TGFβ/BMP signaling, we found heighthened p-Smad in response to TGFβ or Activin A in CD4+ T cells from HLA-B27+ SpA patients ($p<0.05$).



Conclusion: The pathogenic role of HLA-B27 in SpA may result from a TGFβ/BMP signaling misregulation due to specific antagonistic interaction with ALK1/ALK2 BMPR1, at the crosstalk between inflammation and ossification. Interestingly, ALK2 mutations are responsible for the rare mendelian disorder, Fibrodysplasia Ossifians Prgogressiva that mimicks AS (Ref).

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FRI0354 ASSESSING THE ROLE OF TENDON-T CELL INTERACTIONS IN THE DEVELOPMENT OF CHRONICITY IN SPONDYLOARTHRITIS

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Background: Enthesitis is a hallmark of spondyloarthropaties[1], with mechanical stress or damage in the tendon being proposed as a trigger for the development of inflammation at the enthesis that propagates to the synovial compartment through what has been termed "synovio-entheseal complex"[2]. Increasing evidence supports the role that stromal cells play in the shift of the inflammatory process towards chronicity promoting T cell migration, retention and survival[3]. Therefore, we hypothesize that after tendon damage the crosstalk between stromal and immune compartments contributes to the development of chronic inflammation.

Objectives: We aimed to assess the effect of tendon stromal cells (tenocytes) on T cell migration and activation and the impact of these activated T cells on the stroma.

Methods: Tenocytes were explanted from tissue obtained from anterior cruciate ligament (ACL) reconstructions. The effect of damage on tenocytes after stimulation with conditioned media from tendon explants or IL-1ß was evaluated by qPCR. A transwell membrane system was used to test the impact of conditioned media from tenocytes on T cell migration. T cells and tenocytes were co-cultured with or without the presence of a transwell membrane to quantify T cell activation (CD69 by FACS and IFN-γ by ELISA). Changes in gene expression on tenocytes after co-culture with activated T cells were analysed by qPCR.

Results: In the presence of damage, tenocytes upregulated inflammatory mediators (IL-6, COX2), chemokines (CCL2, CCL5, CXCL10, CXCL12) and adhesion molecules (ICAM-1). Conditioned media, particularly after stimulation with IL-1ß, from tenocytes induced T cell migration. Co-cultures of tenocytes and T cells resulted in activation of T cells that was contact dependant. In turn, these activated T cells upregulated the production of inflammatory mediators in tenocytes and increased the COL3/COL1 ratio.

Conclusion: Our results support a communication between the stromal and immune compartment within the tendon that could be involved in the progression towards chronicity in the context of spondyloarthritis. Following damage, tendon stromal cells are able to induce the recruitment of T cells, that once enter the tissue interact with the stroma. Stromal cells are then further activated to produce inflammatory cytokines and chemokines that amplify and maintain this inflammatory response.

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