



HAL
open science

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

Benjamin Grandon, Aurore Rincheval, Nadège Jah, Jean-Marc Corsi, Luiza Araujo, Simon Glatigny, Delphine Roche, Gilles Chiocchia, Isabelle Guéna, Sébastien Gaumer, et al.

► To cite this version:

Benjamin Grandon, Aurore Rincheval, Nadège Jah, Jean-Marc Corsi, Luiza Araujo, et al.. Spondyloarthritis etiology, pathogenesis and animal models FRI0353 Misregulation of BMP/TGF β sheds light on the pathogenicity of HLA-B27 in spondyloarthritis. Annual European Congress of Rheumatology, EULAR 2019, Madrid, 12–15 June 2019, Jun 2019, Madrid, Spain. pp.859, 10.1136/annrheumdis-2019-eular.3344 . hal-04416962

HAL Id: hal-04416962

<https://hal.uvsq.fr/hal-04416962>

Submitted on 25 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Spondyloarthritis – etiology, pathogenesis and animal models

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

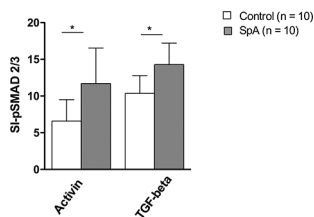
Benjamin Grandon¹, Auroe Rincheval¹, Nadège Jah^{2,3}, Jean-Marc Corsi¹, Luiza M. Araujo^{2,3}, Simon Glatigny^{2,3}, Delphine Roche¹, Gilles Chiochia^{2,3}, Isabelle Guéna¹, Sébastien Gaumer¹, Maxime Breban^{2,3,4}. ¹University of Versailles-saint-Quentin, LGBC, Montigny-le-Bretonneux, France; ²UMR 1173 University of Versailles Saint-Quentin-INSEERM, Team Chronic Inflammation and Immune System, Montigny-le-Bretonneux, France; ³University Paris Diderot, Sorbonne Paris Cité, INFLAMEX, Laboratoire d'Excellence, Paris, France; ⁴Ambroise Paré Hospital, Rheumatology, Boulogne-Billancourt, France

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 β 2-microglobulin ($h\beta$ 2m) 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 $h\beta$ 2m 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/ $h\beta$ 2m 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/ $h\beta$ 2m 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 TGF β /BMP signaling, we found heightened p-Smad in response to TGF β 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 TGF β /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 Ossificans Progressiva that mimics AS (Ref).

REFERENCES:

- [1] Hatsell, S. J. et al. ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin. *Science Translational Medicine* 7, 303ra137-303ra137 (2015).

Disclosure of Interests: Benjamin Grandon: None declared, Auroe Rincheval: None declared, Nadège Jah: None declared, Jean-Marc Corsi:

None declared, Luiza M. Araujo: None declared, Simon Glatigny: None declared, Delphine Roche: None declared, Gilles Chiochia: None declared, Isabelle Guéna: None declared, Sébastien Gaumer: None declared, Maxime Breban Grant/research support from: Pfizer, UCB, Novartis, MSD, Consultant for: UCB

DOI: 10.1136/annrheumdis-2019-eular.3344

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

Emma Garcia-Melchor¹, Giacomo Cafaro¹, Lindsay AN Crowe¹, Michael Mclean^{1,2}, James H. Reilly¹, Iain McInnes¹, Moeed Akbar¹, Neal L. Millar^{1,2}. ¹Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom; ²Department of Orthopaedic Surgery, Queen Elizabeth University Hospital Glasgow, Glasgow, United Kingdom

Background: Enthesitis is a hallmark of spondyloarthropathies[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-1 β 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-1 β , 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.

REFERENCES:

- [1] G. Schett, et al., "Enthesitis: from pathophysiology to treatment," *Nat. Rev. Rheumatol.*, vol. 13, no. 12, pp. 731–741, 2017.
 [2] D. McGonagle, S. Z. Aydin, and A. L. Tan, "The synovio-entheseal complex and its role in tendon and capsular associated inflammation," *J. Rheumatol.*, vol. 39, no. SUPPL. 89, pp. 11–14, 2012.
 [3] C. D. Buckley, "Why does chronic inflammation persist: An unexpected role for fibroblasts," *Immunol. Lett.*, vol. 138, no. 1, pp. 12–14, 2011.

Disclosure of Interests: Emma Garcia-Melchor: None declared, Giacomo Cafaro: None declared, Lindsay AN Crowe: None declared, Michael McLean: None declared, James H Reilly: None declared, Iain McInnes Grant/research support from: AstraZeneca, Celgene, Compugen, Novartis, Roche, UCB Pharma, Consultant for: AbbVie, Celgene, Galvani, Lilly, Novartis, Pfizer, UCB Pharma, Moeed Akbar: None declared, Neal L Millar: None declared

DOI: 10.1136/annrheumdis-2019-eular.6970