AB0158 IMPACT OF JAK INHIBITORS ON MACROPHAGE POLARISATION: PERSPECTIVES FOR SYSTEMIC SCLEROSIS

A. Lescoat¹, A. Ballerie², M. Leblond², C. Morzadec², S. Jouneau³, P. Jégò³, L. Vernhet¹, O. Fardel², V. Lecureur¹, L. Varnhet¹, O. Fardel², V. Lecureur¹. ¹Univ Rennes, CHU Rennes, Inserm, EHESS, IRSET (Institut de recherche en santé, environnement et travail) – UMR_S 1085, F-35000 Rennes, France, Rennes, France; ²Univ Rennes, CHU Rennes, EHESS, IRSET (Institut de recherche en santé, environnement et travail) – UMR S 1085, F-35000 Rennes, France, Rennes, France; ³Univ Rennes, CHU Rennes, EHESS, IRSET (Institut de recherche en santé, environnement et travail)

Background: Macrophage can adopt various phenotypes and activation states according to their surrounding microenvironment. M1 or inflammatory macrophages are generated under IFNγ/LPS signaling and express the M1i and M1Li marker CD86. Different subtypes of M2 macrophages are also described: M2a macrophages (generated under IL-4/IL-13 signaling) and characterized by a high expression of CD206 and pro-fibrotic properties and, M2c macrophages (generated under IL-10 and/or glucocorticoid signaling), considered as anti-inflammatory resolving macrophages. There is growing interest in the role of macrophages in the pathogenesis of Systemic Sclerosis (SSc).

Recent studies highlight that macrophages from fibrotic tissues such as lung or skin from SSc patients have a M2 phenotype whereas, in blood monocytes derived macrophages (MDM), SSc MDM have a mixed signature associating M1 and M2 characteristics. Jak inhibitors are treatments used in rheumatoid arthritis and that can variously target signals that could be involved both in M1 and in M2 polarisation.

Methods: This study evaluates the impact of three Jak inhibitors on the polarisation state of human MDM in vitro.

Results: Concerning phenotypes, all Jak inhibitors reduced the expression of the M1i and M1Li marker CD86, but ruxolitinib had a higher effect. Only ruxolitinib reduced the expression of the M1 marker MHCIi. All Jak inhibitors reduced the expression of CD206 in M2a. They had no impact on the expression of CD163, CD204 in any M2 conditions. Key M1 genes were repressed by all Jak inhibitors, such as CXCL10, IL6 or TNFα with a more significant effect of ruxolitinib. All Jak inhibitors reduced the gene expression of CXCL13 and SOCS3 in M2c. Secretion levels of IL6 and CCL18 were also repressed, with a more significant effect of ruxolitinib.

Conclusion: Jak inhibitors can limit M1 and M2 polarization state in vitro, with a more significant effect of the Jak2/Jak1 inhibitor ruxolitinib. The relevance of these results in MDM from SSc patients and in vivo models of SSc is still to be determined.

Disclosure of Interests: Alain LESCOAT: None declared, Alice Ballerie: None declared, Marie Leblond: None declared, Claudine Morzadec: None declared, Stéphane Jouneau Grant/research support from: AIRB, Boehringer Ingelheim, LVL Medical, Novartis, Roche, Bellorophon Therapeutics, Biogen, Fibrogen, Galecto Biotech, Gilead Sciences, Pharm-Olam, Pliant Therapeutics, Savara Pharmaceuticals/Serendex Pharmaceuticals, Consultant of: Actelion, AIRB, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Chiesi, Genzyme, GlaxoSmithKline, LVL Medical, Mundipharma, Novartis, Pfizer, Roche, Sanofi, Patrick Jego: None declared, Laurent Vernhet: None declared, Olivier Fardel: None declared, Valerie Lecureur: None declared DOI: 10.1136/annrheumdis-2020-eULAR.3125

AB0159 INTERLEUKIN-16 PLAYS A ROLE IN THE PATHOGENESIS OF SYSTEMIC SCLEROSIS

J. Luo¹, A. Kerstein-Staehle¹, S. Comduhr², T. Dreyer², A. Müller², S. Schinke², G. Riemekasten². ¹Department of Rheumatology and Clinical Immunology, University of Lübeck, Luebeck, Germany

Background: Systemic sclerosis (SSc) is an autoimmune disorder with chronic and persistent inflammation. Interleukin-16 was originally described as a factor that could attract activated T cells in humans [1]. Elevated amounts of IL-16 have been demonstrated in SSc [2].

Objectives: This study was undertaken to find out if IL-16 is associated with clinical characteristics of SSc.

Methods: IL-16 was measured by Elisa in serum of patients with SSc (n=119) and healthy controls (n=50). Further, the presence of active IL-16 in mononuclear cells from peripheral blood of SSc patients (n=10) was examined by Western blot. Statistical analyses were done employing Graph Pad prism software (v 6). Patients with SSc were characterized based upon epidemiological and clinical parameters.

Results: The serum concentration of IL-16 was higher in patients with SSc than in healthy controls (272.7±165.4 vs 172.8±64.8 pg/ml, p<0.0001). Further, the difference in the IL-16 serum concentration was more prominent in females (295.6±174.2 vs 160.1±53.37 pg/ml, p<0.0002) than in males (267.1±144.1 vs 187.6±74.64 pg/ml, p=0.0034). In addition, the concentration of IL-16 was elevated in patients with diffuse SSc compared to limited SSc (p=0.0206). The concentration of IL-16 in serum of SSc patients positively correlated with CRP (r=0.49, p<0.0001). There was a weak positive correlation between IL-16 in serum of SSc patients and the mRSS (r=0.22, p=0.0175). Noteworthy, the concentration of IL-16 was heightened in SSc patients with lung fibrosis compared to SSc patients without lung fibrosis (p=0.009). The ROC value of SSc patients with lung fibrosis was 0.64 (95%CI: 0.58-0.83). Moreover, active IL-16 derived from peripheral blood mononuclear cells (PBMC) of SSc patients with lung fibrosis was present in higher amounts compared to PBMC of SSc patients without lung fibrosis (5 vs 5, p=0.0567).

Conclusion: Our results confirm and extend previous data by showing not only an increased concentration of IL-16 in the circulation of SSc patients, but also new findings pointing towards a role of IL-16 for contributing to lung fibrosis in SSc.

References:


Disclosure of Interests: None declared, Anja Kerstein-Staehle: None declared, Sara Comduhr: None declared, TatjanaKathleen Dreyer: None declared, Antje Müller: None declared, Susanne Schinke: None declared, Gabriela Riemekasten Consultant of: Cell Trend GmbH, Janssen, Actelion, Boehringer Ingelheim, Speakers bureau: Actelion, Novartis, Janssen, Roche, GlaxoSmithKline, Boehringer Ingelheim, Pfizer

DOI: 10.1136/annrheumdis-2020-eULAR.3125