AB0158

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

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Background: Macrophage can adopt various phenotypes and activation states according to their surrounding microenvironment. M1 or inflammatory macrophages are generated under IFN γ /LPS signaling and express the membrane marker CD86. Different subtypes of M2 macrophages are also described: M2a macrophages (generated under IL4/IL13 signaling) and characterized by a high expression of CD206 and pro-fibrotic properties and, M2c macrophages (generated under IL10 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.

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

Methods: Blood monocytes from healthy donors (HD) were differentiated with M-CSF (for 7 days) in MDM and pre-treated by ruxolitinib (Jak2-Jak1 inhibitor), tofacitinib (Jak3 inhibitor) or itacitinib (Jak1 inhibitor) (1 μ M for all). They were then polarised into M1i (IFN γ , 20 μ g/mL), M1Li (IFN γ +LPS, 20 μ g/mL), M2a (IL4+IL13; 20 μ g/mL), M2c (IL10, 20 μ g/mL) and M2c(dex) (IL10+dexamethasone, 10nM). The impact of each Jak inhibitor on phenotype (flow cytometry), gene expression (qPCR) and cytokine secretion (ELISA) was evaluated in each polarisation state.

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 M1i 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 TNF α 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 polarisation 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.

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AB0159

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

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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 8). 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 $\pm$ 165.4 vs 172.8 $\pm$ 64.84 pg/ml, p<0.0001). Further, the difference in the IL-16 serum concentration was more prominent in females (265.6 $\pm$ 174.2 vs 160.1 $\pm$ 53.37 pg/ml, p=0.0002) than in males (287.1 $\pm$ 144.1 vs 187.6 $\pm$ 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 (n=115, r=0.49, p<0.0001). There was a weak positive correlation between IL-16 in serum of SSc patients and the mRSS (n=112, 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=0.0557).

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 new findings pointing towards a role of IL-16 for contributing to lung fibrosis in SSc.

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AB0160

CARDIAC AUTONOMIC NEUROPATHY PREVALENCE IN A COHORT OF SYSTEMIC SCLEROSIS (SSC) PATIENTS

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Background: Systemic sclerosis is a rare disease determining a damage to the connective tissue and, consequently, an involvement of several organs. Besides the damage of the connective tissue, preminent is also the small vessels injury, detectable by videocapillaroscopy. Some authors report that the vascular damage may be also responsible of a cardiovascular impairment as cardiac autonomic disease (CAN) and heart rate variability [1].

Objectives: Our study aims to assess the presence and entity of CAN in patients with systemic sclerosis (SSc).

Methods: This is a pilot prospective cohort study. We enrolled 28 patients in a period of six months, from May 2019 to November 2019, afferent to the outpatient clinic of internal medicine and immunology of the Primo Policlinico of Naples, with definite SSc diagnosis in absence of other comorbidities. All patients underwent diagnostic tests for autonomic cardiac neuropathy (NAC) and videocapillaroscopy. In particular, four test were performed to search for the presence of NAC: orthostatic hypotension, deep breathing, lying to standing and Valsalva maneuver. Each test was corrected for age and diagnosis was made in the case at least two tests resulted positive. Primary endpoint of the study was the assessment of the prevalence of autonomic cardiac neuropathy in the study population.

Results: Our cohort was mainly characterized by females (92.9%), with a median age of 58.5 years [IQR: 49-64.8 yrs.] and a median duration of the disease of 4 years [IQR 2-13 yrs.]. The observed prevalence of NAC was equal to the 46.4% (13 cases). In addition, we evaluated the potential association of NAC with age, duration of disease, gastrointestinal dysmotility, sicca syndrome, cutaneous involvement and type of videocapillaroscopy pattern, from which no statistically significant result emerged. Hence, a further analysis, by using a time-dependent Cox regression model (with the duration of disease as time covariate), was performed on the same variables. From this model a