important role in IFN production in B cells through regulation of TLR7/9 activation 2). We also identified that SLE patients with risk allele of SLC15A4 had tendency to show higher plasma His level, indicating His homeostasis could become a novel treatment target for SLE. Moreover, the inverse correlation of His level to SDI as well as OXPPOS signature suggests that His might play a key role for promoting organ damages in SLE.

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THU0226 MESENCHYMAL STEM CELL TRANSPLANTATION AMELIORATES EXPERIMENTAL SJÖGREN'S SYNDROME BY DOWNREGULATING MDSCs VIA COX2/PGE2 PATHWAY

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Background: Although mesenchymal stem cells (MSCs) transplantation have been demonstrated to be an effective therapeutic approach to treat experimental Sjögren's syndrome (ESS)¹, the specific underlying mechanisms remain to be elucidated. Myeloid-derived suppressor cells (MDSCs) were significantly increased with decreased suppressive capacity during disease development in ESS²⁻³. However, the therapeutic effects and mechanisms by which MSCs regulating MDSCs in SS still remain unknown.

Objectives: Here we aim to explore whether regulation of MDSCs was responsible for the beneficial effects of MSC transplantation on SS.

Methods: The MSCs were infused into non-obese diabetic (NOD) mice via the tail vein. The histological features of submandibular glands, lung, saliva flow rate were evaluated. The number and immune-suppressive activity of MDSCs, the subsets of MDSCs, polymorphonuclear MDSCs (PMN-MDSCs) and monocytic-MDSCs (M-MDSCs) in NOD mice were determined. The bone marrow cells under MDSCs differentiation conditions were co-cultured with or without MSCs. The COX2 inhibitor NS-398, anti-TGF- β 1, or anti-IFN- β antibodies were added to coculture medium of MSCs and MDSCs induced from bone marrow cells respectively.

Results: We found that MDSCs in bone marrow and peripheral blood increased in ESS mice. MSC transplantation ameliorated SS-like syndrome and down-regulated the percentages of MDSCs, PMN-MDSCs and M-MDSCs and promoted their suppressive ability in ESS mice significantly (Figure 1). *In vitro*, MSCs could down-regulate the differentiation and up-regulate the suppressive ability of MDSCs. Mechanistically, MSCs inhibited the differentiation of MDSCs and PMN-MDSCs via secreting prostaglandin E2, and inhibited the differentiation of M-MDSCs by secreting interferon- β (Figure 2).

Figure 1. MSCs ameliorated SS symptoms and decreased MDSCs in NOD mice.

Figure 2. MSCs inhibited the differentiation of PMN-MDSCs and M-MDSCs by COX2/PGE2 and IFN- β respectively.

Conclusion: Our findings suggested that MSCs alleviated SS-like symptoms by suppressing the aberrant accumulation and improving the suppressive function of MDSCs in ESS mice via COX2/PGE2 pathway.

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THU0227 CAFFEINE INTAKE MODULATES DISEASE ACTIVITY AND CYTOKINES LEVELS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease mainly affecting women of childbearing age. The interplay between genetic and environmental factors may contribute to disease pathogenesis¹. At today, no robust data are available about the possible contribute of diet in SLE. Caffeine, one of the most widely consumed products in the world, seems to interact with multiple components of the immune system by acting as a non-specific phosphodiesterase inhibitor². *In vitro* dose-dependent treatment with caffeine seems to down-regulate mRNA levels of key inflammation-related genes and similarly reduce levels of different pro-inflammatory cytokines³.

Objectives: We evaluated the impact of caffeine consumption on SLE-related disease phenotype and activity, in terms of clinimetric assessment and cytokines levels.

Methods: We performed a cross-sectional study, enrolling consecutive patients and reporting their clinical and laboratory data. Disease activity was assessed by SLE Disease Activity Index 2000 (SLEDAI-2k)⁴. Caffeine intake was evaluated by a 7-day food frequency questionnaire, including all the main sources of caffeine. As previously reported, patients were divided in four groups according to the daily caffeine intake: <29.1 mg/day (group 1), 29.2-153.7 mg/day (group 2), 153.8-376.5 mg/day (group 3) and >376.6 mg/day (group 4)⁵. At the end of questionnaire filling, blood samples were collected from each patient to assess cytokines levels. These were assessed by using a panel by Bio-Plex assays to measure the levels of IL-6, IL-10, IL-17, IL-27, IFN- γ , IFN- α and Blys.

Results: We enrolled 89 SLE patients (F/M 87/2, median age 46 years, IQR 14; median disease duration 144 months, IQR 150). The median intake of caffeine was 195 mg/day (IQR 160.5). At the time of the enrollment, 8 patients (8.9%) referred a caffeine intake <29.1 mg/day (group 1), 27 patients (30.3%) between 29.2 and 153.7 mg/day (group 2), 45 patients (51%) between 153.8

and 376.5 mg/day (group 3) and 9 patients (10.1%) >376.6 mg/day (group 4). A negative correlation between the levels of caffeine and disease activity, evaluated with SLEDAI-2K, was observed ($p=0.01$, $r=-0.26$). By comparing the four groups, a significant higher prevalence of lupus nephritis, neuropsychiatric involvement, haematological manifestations, hypocomplementemia and anti-dsDNA positivity was observed in patients with less intake of caffeine (figure 1 A-E). Furthermore, patients with less intake of caffeine showed a significant more frequent use of glucocorticoids [group 4: 22.2%, versus group 1 (50.0%, $p=0.0001$), group 2 (55.5%, $p=0.0001$), group 3 (40.0%, $p=0.009$)]. Moving on cytokines analysis, a negative correlation between daily caffeine consumption and serum level of IFN γ was found ($p=0.03$, $r=-0.2$) (figure 2A); furthermore, patients with more caffeine intake showed significant lower levels of IFN α ($p=0.02$, figure 2B), IL-17 ($p=0.01$, figure 2C) and IL-6 ($p=0.003$, figure 2D).

Conclusion: This is the first report demonstrating the impact of caffeine on SLE disease activity status, as demonstrated by the inverse correlation between its intake and both SLEDAI-2K values and cytokines levels. Moreover, in our cohort, patients with less caffeine consumption seems to have a more severe disease phenotype, especially in terms of renal and neuropsychiatric involvement. Our results seem to suggest a possible immunoregulatory dose-dependent effect of caffeine, through the modulation of serum cytokine levels, as already suggested by *in vitro* analysis.

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Figure 1. Prevalence of lupus nephritis (A), neuropsychiatric involvement (B), haematological manifestations (C), hypocomplementemia (D) and anti-dsDNA positivity (E) in the four groups

Figure 2. Correlation between daily caffeine intake and IFN γ serum level (A); IFN α (B), IL-17 (C) and IL-6 (D) serum levels in group 1+2 and group 3+4

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THU0228

PROTECTIVE EFFECT OF LEFLUNOMIDE ON THE SALIVARY SECRETION OF SUBMANDIBULAR GLAND IN THE NOD MOUSE

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Background: A study of 15 PSS patients showed that leflunomide had no significant effect on the decrease of salivary flow rate and the formation of lymphocytic infiltrates in salivary glands [1]. However, due to the small number of samples included in this study and the small size of human salivary gland biopsies, the therapeutic effect of leflunomide may be underestimated. At present, there is no further study on this issue, the effect of leflunomide on Sjogren's syndrome is still not clear.

Objectives: To investigate the therapeutic effect of leflunomide on salivary gland secretion dysfunction in the NOD mice with Sjogren's syndrome.

Methods: The NOD mice were randomly divided into four groups: preventive drug group, preventive control group, therapeutic drug group, and therapeutic control group. Salivary flow rate was measured after pilocarpine stimulation; After hematoxylin and eosin staining, the average number and area of infiltrating lesions were compared; The percentage of CD3⁺ T, CD4⁺ T, CD8⁺ T, CD44⁺ CD62L⁺ CD4⁺ T, CD19⁺ B, and CD138⁺ B cells in submandibular gland and spleen were detected by flow cytometry; The levels of serum inflammatory factors TNF- α , IL-17A and IL-6 were detected by CBA method.

Results: The salivary flow rate ($t = -5.81$, $P < 0.001$; $z = -3.61$, $P < 0.05$), the number of infiltrating foci ($t = 3.95$, $P < 0.01$; $t = 4.94$, $P < 0.001$) and the average area of infiltrating foci ($t = 3.18$, $P < 0.05$; $z = 2.35$, $P < 0.05$) in the treatment groups were significantly ameliorated. CD4⁺ T cells ($t = 2.39$, $P < 0.05$; $t = 3.82$, $P < 0.01$) and CD44⁺CD62L⁺CD4⁺ T cells ($t = 3.53$, $P < 0.05$; $t = 3.36$, $P < 0.05$) in the submandibular gland were significantly decreased. CD3⁺ T ($t = 6.08$, $P < 0.001$; $t = 2.76$, $P < 0.05$), CD4⁺ T ($t = 3.73$, $P < 0.05$; $t = 2.39$, $P < 0.05$), CD19⁺ B ($t = 5.88$, $P < 0.001$; $t = 4.23$, $P < 0.01$) and CD138⁺ B ($t = 4.30$, $P < 0.001$; $t = 4.46$, $P < 0.01$) cells in the spleen were also significantly decreased. In addition, the serum IL-17A of the treatment group reduced to lower level ($t = 4.15$, $p < 0.01$; $t = 3.36$, $p < 0.01$), and the TNF- α level of the preventive drug group decreased ($t = 4.56$; $p < 0.001$).

Figure 1. Leflunomide reduced lymphocyte infiltration and improved salivary gland function in NOD mice. A-D: Histology of the submandibular glands of NOD mice in control and treated groups. E-H: The comparison of the submandibular gland index, salivary flow rate, number of infiltrating foci and average area of the submandibular gland, between the control and treated groups. (mean $\pm$ SD; n=7 per group; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

Figure 2. Changes of lymphocyte subsets in submandibular gland and spleen A-L: Frequencies of CD3⁺ T cells, CD4⁺ T cells, CD8⁺ T cells, CD44⁺ CD62L⁺ CD4⁺ T cells, CD19⁺ T cells