

AB0075

INTRAAARTERIAL INJECTION OF HUMAN ADIPOSE-DERIVED MESENCHYMAL STEM CELLS (HAD-MSCS) ATTENUATES INFLAMMATION IN ACUTE ARTHRITIS MODEL

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Background: MSC are a potential therapeutic approach for the treatment of inflammatory diseases. Their anti-inflammatory role in both local and systemic diseases has been demonstrated in different experimental models and human diseases. Gouty arthritis is a systemic disease characterised by deposition of monosodium urate (MSU) crystals in soft tissues and joints. Frustrated phagocytosis of MSU crystals by resident leukocytes leads to NLRP3 inflammasome activation and subsequent amplification of inflammatory response resulting in severe tissue damage. MSCs are able to attenuate inflammatory response through different mechanisms, including NLRP3 inflammasome inhibition. Thus, MSCs could be a promising therapy for the attenuation of acute flares in gouty arthritis

Objectives: To study the antiinflammatory effect of hAD-MSCs in an acute gouty arthritis model

Methods: Acute gout flare was induced in 15 NZ rabbits by intra-articular injection of MSU crystals in both knees. 7 of these rabbits received a single dose of 2.5×10^6 hAD-MSCs/kg, administered through the right femoral artery 1 hour after MSU injection (MSU+MSC group), while 8 animals were not treated (MSU group) This route of administration allowed the study of the effect of a direct MSC administration in the right knee synovial membrane (SM) in comparison to the contralateral knee, which received the cells after their vascular distribution through the organism. Inflammation was followed up measuring knee swelling and serum CRP. 4 healthy rabbits were simultaneously followed (Ctrl group). Animals were sacrificed 72 hour after MSU injections and SM were collected for further studies

Results: hAD-MSCs were able to attenuate joint swelling in both knees 24 hour after MSU injections, inducing a decrease in knee perimeter. Additionally, a significant decrease in serum CRP after 24 hour was observed in the treated group (Ctrl 73 ± 51 ; MSU $818 \pm 238^*$; MSU+MSC 270 ± 241 mg/ml*#; $p < 0.05$ *vs. Ctrl; # vs. MSU). Histopathological analysis showed that hAD-MSCs were able to significantly diminish SM inflammation after 72 hours of MSU injection (Krenn Score: Ctrl 0.2 ± 0.4 ; MSU, $5.6 \pm 2.3^*$, MSU+MSC $3.4 \pm 1.2^* \#$). SM vascularisation was reduced in treated animal (%CD31 +staining: Ctrl 0.5 ± 0.2 ; MSU $0.8 \pm 0.2^*$; MSU +MSC $0.6 \pm 0.2^* \#$). hAD-MSC treatment also evoked a significant reduction of the inflammasome components in the SM: pro-IL1 β (Ctrl 0.9 ± 0.2 ; MSU $1.5 \pm 0.5^*$; MSU+MSC $1.1 \pm 0.2^* \#$), pro-caspase-1 (Ctrl 1 ± 0.6 ; MSU $3.5 \pm 3.1^*$; MSU+MSC $1.4 \pm 0.5^* \#$), NALP3 (Ctrl 1 ± 0.3 ; MSU $2.9 \pm 2.1^*$; MSU+MSC $1.4 \pm 0.7^* \#$). The synthesis of the pro-inflammatory cytokines COX-2 (Ctrl 0.9 ± 0.1 ; MSU $4.2 \pm 3.3^*$; MSU +MSC $2.1 \pm 1.4^* \#$) and TNF α (Ctrl 0.9 ± 0.3 ; MSU $1.3 \pm 0.3^*$; MSU+MSC $0.9 \pm 0.2^* \#$) were also reduced in the MSU+MSC animals, while TGF β (Ctrl 0.9 ± 0.2 ; MSU $0.7 \pm 0.2^*$; MSU+MSC $1.3 \pm 0.3^* \#$) and IL10 (Ctrl 1.1 ± 0.5 ; MSU $1.1 \pm 0.7^*$; MSU+MSC $1.8 \pm 0.5^* \#$) were increased in comparison to MSU group. There were no differences between the direct and the indirect treatment, since both right and left SMS were equally damaged

Conclusions: Our data showed that a single dose of hAD-MSCs is able to modulate the inflammatory response in an acute gouty arthritis model in rabbit. Therefore, it is a promising therapeutic approach to attenuate gout flares, especially in patients with different comorbidities that complicate a conventional treatment

Disclosure of Interest: None declared

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AB0076

JAK INHIBITOR BARICITINIB MODULATES HUMAN INNATE AND ADAPTIVE IMMUNE SYSTEM

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Background: Janus kinase (JAK), which constitutively binds to cytokine receptors, plays an important role in the cytokine signalling. While JAK is comprised of JAK1, JAK2, JAK3, and tyrosine kinase-2 (Tyk2), more than 40 types of cytokines transmit signals through JAK. After several clinical studies, baricitinib, a highly selective inhibitor of JAK1 and JAK2, has been approved recently for treatment of RA in Europe, Japan, and other countries. Although this drug is available orally due to its small molecular weight, it has comparable efficacy to the biological DMARDs (bDMARDs).

Objectives: The present study was designed to determine the effects of a highly-selective JAK1 and JAK2 inhibitor, baricitinib, on human immunocompetent cells, in order to establish the significance of JAK and the potential for baricitinib in the therapeutic armamentarium against immune-mediated diseases.

Methods: The effects of baricitinib and tofacitinib were evaluated using human monocyte-derived dendritic cells (MoDCs), plasmacytoid dendritic cells (pDCs), B cells and T cells.

Results: The expression of costimulatory molecules CD80/86 on MoDCs were induced 48 hours after LPS stimulation. Baricitinib concentration-dependently suppressed the expression of CD80/CD86. Inhibition of CD80/CD86 expression by tofacitinib was comparable to that induced by baricitinib. pDCs stimulated for 5 hours with CpG produced both TNF- α and IFN- α . Baricitinib reduced the proportion of these IFN- α producing pDCs in a concentration-dependent manner. On the other hand, TNF- α production was not affected by baricitinib. Baricitinib also suppressed the differentiation of B cells into plasmablasts by B cell receptor (BCR) and type-I IFN stimuli, and inhibited the production of IL-6 from B cells. Tofacitinib also suppressed BCR- and IFN- α -induced plasmablast differentiation and IL-6 production. However, neither baricitinib nor tofacitinib altered IgG production by B cells. Human CD4 +T cells proliferated after T cell receptor stimulation with anti-CD3 and anti-CD28 antibody; however, such proliferation was suppressed by baricitinib in a concentration-dependent manner. In addition, baricitinib inhibited Th1 differentiation after IL-12 stimulation and Th17 differentiation by TGF- β 1, IL-6, IL-1 β and IL-23 stimulation. Tofacitinib showed similar effects in these experiments. In naive CD4 +T cells, IFN- α and IFN- γ induced phosphorylation of STAT1, which was inhibited by baricitinib as well as tofacitinib. Furthermore, IL-6-induced phosphorylation of STAT1 and STAT3 was also inhibited by JAK inhibitors.

Conclusions: The present study demonstrated that JAK inhibitors affect innate and adaptive immunity in humans. They can fine-tune various immune networks through a variety of mechanisms and seem suitable potential therapeutic agents for the treatment of diverse autoimmune diseases.

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AB0077

HIGH-MOBILITY GROUP BOX 1 MEDIATED MONOSODIUM URATE CRYSTAL-INDUCED NLRP3 INFLAMMASOME ACTIVATION IN HUMAN MACROPHAGES

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Background: High-mobility group box 1 (HMGB1) was identified originally as a highly conserved non-histone DNA-binding factor and recently noted as a potent inflammatory mediator under inflammatory conditions.

Objectives: This study is to investigate the inflammatory cascade between HMGB1 protein and activation of NLRP3 inflammasome in human macrophage under uric acid-induced inflammation.

Methods: The study used human U937 macrophage cell line under stimulation with monosodium urate (MSU) crystal or HMGB1. Total reactive oxygen species (ROS) were measured by flow cytometry. Interleukin-1b (IL-1b), NLRP3, TXNIP, HMGB1, NF- κ B, I κ Ba, and caspase-1 protein expression was detected using western blotting. IL-1b, IL-18, caspase-1, and HMGB1 gene expression were assessed by quantitative real-time polymerase chain reaction. Intracellular HMGB1 expression was assessed by immunofluorescent staining with Mito-Tracker Red.

Results: MSU crystals induced HMGB1 and ROS production by activation of NF- κ B signal pathway in human macrophages. HMGB1 mRNA expression was markedly attenuated under stimulation using TXNIP siRNA. Enhanced release of IL-1 was noted through increased HMGB1 expression and TXNIP-mediated NLRP3 inflammasome activation under stimulation of MSU. Combination of MSU and HMGB1 augmented NLRP3 inflammasome, compared to either MSU or HMGB1 stimulation.

Conclusions: This study demonstrated that HMGB1 is a crucial molecule for ROS-mediated TXNIP and NLRP3 inflammasome activation in uric acid-induced inflammation.

Disclosure of Interest: None declared

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