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EXPANSION, ACTIVATION AND FUNCTION PROMOTION OF MYELOID-DERIVED SUPPRESSOR CELLS IN ADJUVANT-INDUCED ARTHRITIS

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ABSTRACT

The role of myeloid-derived suppressor cells (MDSCs) in autoimmune diseases is starting to be elucidated. No previous studies demonstrate the role of these cells in adjuvant-induced arthritis (AA) rat model. MDSCs are one of the main cell populations that negatively regulate immune responses. Thus, MDSC targeting represents a promising tool to increase the efficacy of immune-based therapies. The objective of the present study was not only to investigate the role of myeloid-derived suppressor cells in AA rat model, but also to clarify the correlation between these cells and some factors which may promote their expansion, activation and suppressive activity. Body weight gain, white blood cells count, serum antinuclear autoantibodies, flow cytometry for MDSCs percentage in peripheral blood, serum IL-6, macrophage-colony stimulating factor (M-CSF), inducible nitric oxide synthase (iNOS) and arginase-1 were assessed in both control group and AA rat model supported by a histopathological study on joints. Results of the current study established for the first time the elevation of MDSCs percentage in AA rat model suggesting their possible potential role in the disease. Also, there is a positive correlation between increase in MDSCs percentage and elevated serum levels of IL-6, M-CSF, iNOS and arginase-1.

KEYWORDS: Myeloid-Derived Suppressor Cells, Adjuvant-Induced Arthritis, IL-6, macrophage-colony stimulating factor.

INTRODUCTION

The field of myeloid-derived suppressor cell research has more outstanding questions than answers. The first observations of myeloid-derived suppressor cells were described more than 21 years ago in patients with cancer.[1] However, the importance of these cells in the immune system has recently been increased. Myeloid-derived suppressor cells comprise a group of highly heterogeneous cells derived from immature myeloid progenitors.[2] They are expanded in various disease states including autoimmune diseases[3], cancer[4], parasitic and bacterial infections in addition to acute and chronic inflammation.[5] Normally, hematopoietic stem cells differentiate into common myeloid progenitor cells and then into immature myeloid cells (IMCs) which in turn differentiate into dendritic cells, macrophages and/or granulocytes. However, in a pathological condition such as tumor, infection, bone marrow transplantation or some autoimmune disorders, a partial block in the differentiation of IMCs occur resulting in an accumulation, expansion and activation of these immature cells terming MDSCs.[6] MDSC population suppresses the activity of various types of immune cells, including CD4+ T cells, CD8+ T cells[7], and NK cells[8] while enhancing the immunosuppressive functions of regulatory T cells.[9] In addition to their suppressive effects on adaptive immune responses, MDSCs have also been reported to regulate innate immune responses by modulating the cytokine production of macrophages.[10] Although numerous reports have demonstrated the potent immunosuppression effects of MDSCs under abnormal conditions, yet their roles in autoimmune diseases remain unclear.[3] It was demonstrated that MDSCs are involved in a number of different autoimmune disorders, including multiple sclerosis[11], inflammatory bowel disease[12], type 1 diabetes[13], autoimmune hepatitis[14], autoimmune uveoretinitis[15], systemic lupus erythematosus[16], alopecia areata[17] and rheumatoid arthritis (RA).[18] While, the MDSC expansion has been demonstrated in the synovial fluid and peripheral blood of patients with RA[19], their role in arthritis animal models remains undistinguishable. However, Boros et al.,[20] demonstrated that MDSC accumulation in the spleen correlated with the course of the disease in collagen induced arthritis (CIA) mouse model. Also, other studies revealed that adoptive transfer of MDSCs can decrease the severity of CIA.[21] Nevertheless, abnormal expression of MDSCs in inflammatory rheumatic patients is still unclear and their role in rheumatic diseases is less well understood. However, no previous

studies demonstrate the role of MDSCs in adjuvant-induced arthritis rat model. Accordingly, the purpose of the present study was not only to investigate the role of myeloid-derived suppressor cells in adjuvant-induced arthritis rat model, but also to clarify the correlation between these cells and some factors which may promote the expansion, activation and suppressive activity of myeloid-derived suppressor cells.

MATERIALS AND METHODS

Animals: Adult male albino rats were bred and maintained under conventional conditions at the experimental animal research unit of Medical Research Centre and Bilharzia, Faculty of Medicine, Ain Shams University. Their weights ranged between 165-180 gm representing 7-8 weeks of age. Animals were kept under a 12:12 light/dark cycle with a temperature of 23–25 ˚C. Fresh tap water was available all time. Rats were acclimatized to laboratory conditions for a week before the beginning of the study. All animal procedures were performed in accordance with the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and the National Institutes of Health (NIH) protocol approved by Ain Shams University.

Arthritis Induction: Arthritis was induced in rats as described previously by Snekhalatha et al.[22] The rats were injected with 0.1 ml of complete Freund's adjuvant (Sigma Chemical Co. St. Louis,MO) into the right hind paw. To increase the severity of arthritis, a booster injection with 0.1 ml of emulsion was administered in the same manner on day 5.

Animal grouping: Twenty-four rats were divided into two main groups, Control group (C) and Adjuvant-Induced Arthritis group (AA). Individual body weights were monitored and recorded to the nearest 1mg to determine body weight gain. After 10 days from adjuvant injection, all animals were sacrificed by ether inhalation anaesthesia. Blood samples were withdrawn by heart acupuncture. Each sample was divided into two parts. The first half was collected into ethylenediaminetetraacetic acid (EDTA) containing tubes to be used in the determination of total leukocyte count. The second half of blood sample was collected in clean dry tubes and allowed to clot, then centrifuged at 14000g for 10 min for serum extraction to be used in estimation of antinuclear autoantibodies (ANA), IL-6, macrophage-colony stimulating factor (M-CSF), inducible nitric oxide synthase (iNOS) and arginase-1 (Arg-1).

Determination of Total Leucocytic Count: Blood samples were withdrawn by heart acupuncture from all groups in clean sample tubes containing EDTA for the determination of complete blood picture.

Autoantibody Measurement: Antinuclear antibodies level was performed in serum samples by the competitive enzyme immunoassay technique utilizing Rat Nuclear antigen and an ANA-HRP conjugate using ELISA Kit, catalogue number: MBS730007.

Histological Studies: For histological analysis, joints were fixed in neutral buffered formalin and decalcified with formic acid at 4 ˚C before embedding in paraffin. To ensure extensive evaluation of the arthritic joints, at least three serial sections were cut and stained with haematoxylin and eosin.

Flow Cytometric Assessment of CD11bc+/His48+ MDSCs: For flowcytometric analysis peripheral blood mononuclear cells were isolated and stained with a combination of Anti-Rat CD11bc PE (catalog number:12-0110, clone OX42) and Anti-Rat Granulocyte Marker Biotin FITC (catalog number: 13-0570, clone His48). The tubes were then mixed well using vortex and incubated for 20 minutes in the dark at room temperature. After lysing red cells, cells were analyzed by flow cytometer (Coulter EPICS-XL flow cytometer system for 3 color fluorescence detection with catalog number 4327296). A coulter flow center multimedia work station was used as an offline computer system for data analysis.

Measurements of IL-6, M-CSF, iNOS and Arg-1.
Measurements were performed according to the manufacturer's instructions as following:
IL-6 by Rat Interleukin-6 ELISA Kit, catalogue number: KT-19418, Kamiya Biomedical Company.
M-CSF by Rat Macrophage Colony-Stimulating Factor ELISA Kit, catalogue number: CSB-E07424r, CUSABIO Company.
iNOS by Rat Inducible Nitric Oxide Synthase ELISA Kit, catalogue number: CSB-E08325r, CUSABIO Company.
Arg-1 by Rat Arginase-1 ELISA Kit, catalogue number: CSB-E17519r, CUSABIO Company.

Statistical Analysis
Statistical analysis was done using the statistical package for social science (SPSS) version 19 statistical software (T-Test). Data are expressed as the mean ± standard error of mean (SEM). $^{*}P < 0.001$ is considered a significant for treatment compared to control rats.

RESULTS

Body weight gain
Body weight gain in control animals (C) evidenced gradual significant increase in the mean of body weight from 166.5±3.2 gm reaching 189±2.6 gm at the end of the study. On the other hand, adjuvant-induced arthritis rats (AA) suffered severe decrease in body weight gain reaching a mean body weight of 152.5±2.3 gm highlighting the adverse effect of arthritis induction on body weight gain.

Arthritis Induction: AA group was examined for arthritis induction after 10 days of adjuvant injection. A high WBC count of 9.15 was considered a positive sign

of inflammation due to arthritis induction in comparison to normal WBC count of 5.68 (Table 1). Moreover, the autoantibody marker ANA levels were measured in serum samples. AA rats recorded a significant elevation ($p<.001$) in ANA level compared to controls confirming disease induction (Table 1).

Table. (1): White blood cell (WBC) count and antinuclear antibodies (ANA) in control and adjuvant-induced arthritis groups.

Parameter	Control Group	AA Group
WBCs Count (X103)	5.68±0.13	9.15±0.21*
ANA (pg/ml)	0.12±0.02	1.17±0.07*
*P<0.001 for significant results compared to control group.		

Histological observations

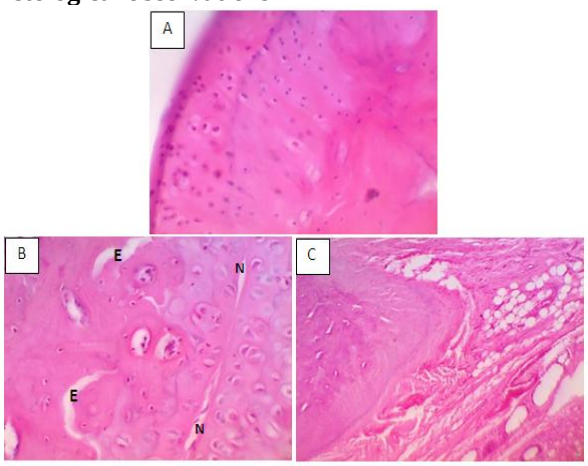

Figure. (1): Photomicrograph of hind paw sections in joint of rat. A: Normal control group; 40X. B : shows narrowing of the joint spaces (N) with bone erosion (E) from adjuvant arthritic rat; 40X. C: shows hyperplastic diffuse synovial membrane with enlargement in synovial cell lining, increased synovial vascularity and mononuclear inflammatory infiltration from adjuvant arthritic rat; 10X.

Flow Cytometric Assessment of CD11bc+/His48+ MDSCs: Flowcytometry studies using CD11bc and His48 antibodies were performed on blood cells from control and AA rats at the end of the experiment. Current results revealed a significant ($P<0.001$) increase in the mean values of MDSCs percentage in AA group (95.33±1.58) compared to control group (72.30±1.73). However, figure 2 shows flow cytogram of animal from the control group with 87.6% of MDSCs and an animal from AA group with 75.7% of MDSCs as an example.

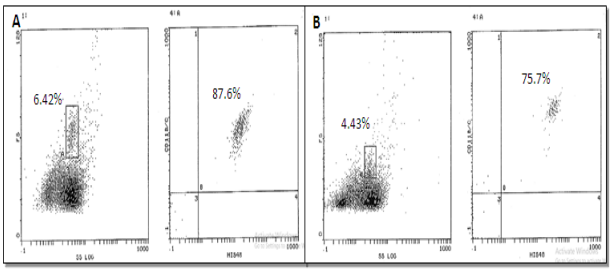

Figure. (2): Flow cytometry analyses of CD11bc+/His48+ cells. (A) Representative flow cytograms of animal from the control group. (B) Representative flow cytograms of animal from AA group.

IL-6, M-CSF, iNOS and Arg-1 Measurements: Adjuvant-induced arthritic rats recorded significant ($P<0.001$) elevated serum levels of IL-6, M-CSF, iNOS and Arg-1 compared to control rats.

Table. (2): IL-6, M-CSF, iNOS and Arg-1 levels in control and adjuvant-induced arthritis groups.

Parameter	Control Group	AA Group
IL-6 (pg/ml)	10.01±0.17	42.72±0.45*
M-CSF (pg/ml)	21.94±0.48	53.82±0.83*
iNOS (IU/ml)	1.56±0.04	4.05±0.06*
ARG-1 (ng/ml)	0.49±0.02	1.37±0.03*
*P<0.001 for significant results compared to control group.		

DISCUSSION

Rheumatoid arthritis (RA) is a destructive polyarthropathy associated with joint swelling and massive pain. Adjuvant-induced arthritis is one of the most widely used rat models greatly similar to RA.[23] Results of the present study revealed that body weights, WBCs count and ANA serum levels were significantly elevated in AA group compared to control group. These results were associated with hyperplastic diffusion of synovial membrane, inflammatory cell infiltration into articular tissue and bone erosion as histologically observed in H&E sections form adjuvant arthritic rats (Figure 1). Collectively, all these results indicate a positive sign of arthritis induction. It was previously reported that decrease in body weight is primarily due to deficient absorption of nutrients through the intestine because of high inflammation in addition to metabolic alterations that result in a decrease in skeletal muscle and white adipose tissue mass.[24,25] Moreover, WBCs count results were in accordance with[26, 27], who proved that white blood cell count increases due to massive production of T lymphocytes, B lymphocytes, monocytes and neutrophils which are normally associated with the systemic inflammatory reaction of arthritis. Furthermore, ANA is an autoantibody directed against nuclear components and is commonly elevated in arthritis.[28]

In the present study, flowcytometric analyses for MDSCs were performed. The percentage of MDSCs in AA group was significantly increased compared to control group. No previous studies demonstrated MDSCs percentage in

adjuvant-induced arthritis rat model. However, a few reports were obtained on RA patients and collagen-induced arthritis (CIA) mouse model. It was verified that the proportion of MDSCs in peripheral blood was higher in patients with RA than in healthy controls which correlated with the disease activity and joint inflammation.[18] More to the point, it was confirmed that synovial fluid of RA patients contained a high number of MDSCs that have the ability to limit the expansion of joint-infiltrating T cells.[29] Also,[30] proved that the frequency of MDSCs significantly was expanded in blood, lymphoid tissues, inflamed paws and synovial fluid of arthritic mice. Additionally, other studies on CIA model demonstrated that MDSCs were increased in the splenic tissues and draining lymph nodes compared to control ones.[31,32]

Moreover, MDSCs are induced and expanded by several factors such as IL-6[33], macrophage colony-stimulating factor (M-CSF)[34] cyclooxygenase-2 (COX-2), prostaglandins, stem cell factor (SCF)[35], vascular endothelial growth factor (VEGF)[36] and granulocyte-macrophage colony-stimulating factor (GM-CSF).[37] However, elevated level of both IL-6 and M-CSF in AA group in the present work may be held as the principle cause in MDSCs expansion and activation (Table 2).

The signaling pathways in MDSCs expansion by these factors converge on Janus kinase (JAK) protein family members and signal transducer and activator of transcription 3 (STAT3) which are signaling molecules that are involved in cell survival, proliferation, differentiation and apoptosis.[38,39]

As a multifunctional cytokine, IL-6 plays an important role in many responses, such as B and T cell differentiation, acute-phase response, fever induction, angiogenesis and lipid and iron metabolism.[40] Also, it was demonstrated that IL-6 plays an important role in STAT3 activation leading to MDSCs survival and expansion.[41, 42]

In the present work, serum levels of IL-6 in adjuvant arthritic rats were significantly elevated compared to control ones. These results are to a greater extent in accordance with previous studies.[43, 44] Similarly, Larson[44] demonstrated that a large level of IL-6 mediates the process of joint inflammation. More to the point, it was confirmed that serum and synovial fluid levels of IL-6 and IL-6R are high in patients with RA compared to normal conditions.[45, 46] Additionally, macrophage colony-stimulating factor (M-CSF) is recognized as a promoter for MDSC expansion.[34] It is a cytokine that acts via its receptor (CSF-1R, c-Fms) to regulate the development and proliferation of the monocyte/macrophage lineage cells and to act locally in tissues to control macrophage numbers and function.[47] In the current results, significant elevated serum levels of M-CSF in adjuvant arthritic rats is in accordance with Kawaji et al.,[48] Also, M-CSF has been reported to participate in the induction of osteoclasts and may be important in the destruction of bone and cartilage in patients with rheumatoid arthritis.[48] Moreover, it was provided that M-CSF can exacerbate collagen induced arthritis.[49]

Additionally, results of the present study revealed that iNOS and Arg-1 serum level were significantly increased in AA group compared to control (Table 2). Most studies have addressed that the ability of MDSCs to be a potential suppressive cell was through production of high levels of both iNOS (inducible nitric oxide synthase) and arginase-1 (Arg-1).[5,6] Briefly, the suppressive activity of MDSCs has been associated with the metabolism of L-arginine. L-arginine serves as a substrate for two enzymes: iNOS and arginase. iNOS generates NO which acts as a potential suppressor for T-cell function through inhibition of JAK/STAT signaling in T cells, inhibition of MHC class II expression[50] and induction of T-cell apoptosis.[51] Moreover, the increased activity of arginase in MDSCs leads to enhanced L-arginine catabolism into urea and L-ornithine which inhibits T-cell proliferation through different mechanisms, including declining their CD3ζ expression[52] and preventing their upregulation of the expression of the cell cycle regulators cyclin D3 and cyclin-dependent kinase 4.[53]

CONCLUSION

In conclusion, the current study established for the first time the elevation of MDSCs percentage in adjuvant-induced arthritis rat model. In addition, the present study findings elucidated the positive correlation between IL-6 and M-CSF serum levels and MDSCs percentage confirming their role in MDSCs expansion and activation in the disease. Moreover, this study confirmed that both iNOS and arginase-1 may promote the suppressive activity of myeloid-derived suppressor cells in the disease. Accordingly, concurrent findings suggest that MDSCs may play an effective role in adjuvant-induced arthritis and more researches are needed to further elucidate the major role MDSCs as a potential future therapeutic target in arthritis.

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