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Research Paper

Serum IL-10 from systemic lupus erythematosus patients suppresses the differentiation and function of monocyte-derived dendritic cells

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Abstract

The role played by cytokines, other than interferon (IFN)-α, in the differentiation and function of dendritic cells (DCs) in systemic lupus erythematosus (SLE), remains unclear. Serum interleukin-10 (IL-10) levels are generally elevated in SLE patients, which might modulate the differentiation of DCs. In this study, DCs were induced from monocytes either by transendothelial trafficking or by culture with granulocyte-macrophage colony-stimulating factor (GM-CSF) + IL-4 + tumor necrosis factor (TNF)-α. Both systems were used to investigate the effects of elevated serum IL-10 level on DC differentiation in SLE patients. The results showed that monocyte-derived DCs induced by either SLE serum or exogenous IL-10 reduced the expression of human leukocyte antigen (HLA)-DR and CD80, decreased IL-12p40 level, and increased IL-10 level, and exhibited an impaired capacity to stimulate allogenic T-cell proliferation. These results indicate that serum IL-10 may be involved in the pathogenesis of SLE by modulating the differentiation and function of DCs.

Keywords: lupus erythematosus systemic (SLE), interleukin-10 (IL-10), dendritic cells (DCs), differentiation

INTRODUCTION

Dendritic cells (DCs) are key regulators in immune responses capable of priming naive T cells and initiating primary T-cell responses when they are pulsed with antigenic peptides or proteins, and they are also capable of inducing anergy in autoreactive T cells. T-cell populations show functional disorders in systemic lupus erythematosus (SLE), such as abnormal activation of autoreactive T cells, and defects in responses

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to microbial antigens. These disorders may result from underlying defects in the function of DCs. It is indicated that both DCs and cytokines are involved in the induction of autoimmune diseases[1]. Phenotypic and functional abnormalities have been described in DCs isolated from patients with SLE[2] and it is believed that abnormal DCs play an important role in the pathogenesis of SLE. It has been shown that interferon (IFN)-α derived from the sera of SLE patients induces normal monocytes to differentiate into DCs, which could capture antigens from apoptotic cells and present them to $CD4^+$ T cells[3]. The central role of DCs and IFN-α in SLE has received much attention[4-6]. Recently, the IFN-induced protein, IFN-induced protein with tetratricopeptide repeats 4 (IFIT4), was found to be associated with SLE, and to promote the differentiation of monocytes into DC-like cells, supporting the key role of IFN-α in the pathogenesis of SLE[7]. However, there is a disorder of multiple cytokines in patients with SLE, in whom abnormal elevation of interleukin (IL)-1β, IL-6, IL-10, IL-17 or IL-23 is detected[8-10]. Our previous study demonstrated that IL-6 in SLE serum significantly affected the differentiation and function of DCs derived from $CD34^+$ haematopoietic precursor cells (HPCs) and promoted the expression of human leukocyte antigen (HLA)-DR, CD80 and CD86, IL-10 production and the ability to stimulate allogenic T-cell proliferation, while decreasing IL-12 secretion by DCs[11]. The role played by cytokines, other than IFN-α and IL-6, in the differentiation and function of DCs in SLE patients remains unclear till now.

IL-10 has both immunosuppressive and immunostimulatory properties, and its potential for dampening inflammatory responses has attracted much interest in research of autoimmune diseases[12]. Increased IL-10 production by SLE peripheral blood B cells and monocytes is observed, which is thought to correlate with disease activity[13]. Inhibition of IL-10 activity by neutralizing antibodies results in decreased expression of disease markers in both SLE patients and murine models of lupus[14,15]. The results of these studies are explained by the intrinsically high levels of IL-10 related to lupus susceptibility and severity through the promotion of B-cell proliferation, and immune stimulation by this cytokine seems to trump immunesuppression in lupus patients. However, the effect of serum IL-10 on the differentiation and function of DCs in pathogenesis of SLE remains unclear. IL-10 has been demonstrated to inhibit the differentiation and function of DCs by reducing the expression of co-stimulators and major histocompatibility complex (MHC)-II molecule and IL-12 production[16-18]. It is, therefore, hypothesized that increased levels of IL-10 in the serum of SLE patients may modulate the differentiation of DCs. The major purpose of this study was to obtain the direct evidence of the effects of IL-10 present in the serum of SLE patients on the differentiation and function of monocyte-derived DCs (MDDCs).

SUBJECTS AND METHODS

Subjects

Totally 50 SLE patients recruited during routine clinic visits to the Department of Rheumatology, the First Affiliated Hospital of Nanjing Medical University, were enrolled in this study. All of the patients met the revised SLE criteria of the American Rheumatism Association[19]. The patients were all female, with a median age of 29 years (range, 24-37 years). Thirteen age-matched healthy female volunteers served as controls. Informed consent was obtained from all subjects.

Serum preparation

The blood samples were collected from all participants and allowed to clot at room temperature for 2 h. The sera were separated by centrifugation at 2000 rpm for 10 min and stored in aliquots at -20°C until required. The IL-10 concentrations in the sera from SLE patients were measured using ELISA reagent kits (Diaclone Research; Besancon Cedex, France) according to the manufacturer's instructions. The sera with different levels of IL-10 were selected, grouped and pooled, and the sera were grouped as follows: Group 1, SLE sera with normal levels of IL-10 (< 10 pg/mL); Group 2, SLE sera with mildly elevated levels of IL-10 (10-20 pg/mL); Group 3, SLE sera with highly elevated levels of IL-10 (20-40 pg/mL).

Separation of peripheral blood mononuclear cells (PBMCs)

Peripheral blood from healthy donors was supplied by Jiangsu Province Blood Centre. Heparinized blood (200 mL) was collected from each donor and PBMCs were isolated by standard Ficoll-Hypaque density-gradient centrifugation for 2 h. PBMCs were then washed twice with phosphate buffered saline (PBS) before use.

Induction of DCs

DCs were induced from monocytes by two methods, transendothelial trafficking and culture with granulocyte-macrophage colony-stimulating factor (GM-CSF) + IL-4 + tumor necrosis factor α (TNF-α). Transendothelial trafficking was performed using a method modified from Randolph et al.[20]. Fresh hu-