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The role of dendritic cells and regulatory T cells in the pathogenesis of morphea

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Abstract

Morphea is one of diseases characterised by fibrosis of the skin and subcutaneous tissue. It is a chronic disease that does not shorten the life of the patient, yet significantly affects its quality. The group of factors responsible for its pathogenesis is thought to include disturbed functioning of endothelial cells as well as immune disturbances leading to chronic inflammatory conditions, accompanied by increased production of collagen and of other extracellular matrix components.

Dendritic cells (DC) are a type of professional antigen-presenting cells and can be found in almost all body tissues. Individual investigations have demonstrated high numbers of plasmacytoid DC (pDC) in morphoeic skin lesions, within deeper dermal layers, around blood vessels, and around collagen fibres in subcutaneous tissue. It appears that DC has a more pronounced role in the development of inflammation and T cell activation in morphea, as compared to systemic sclerosis (SSc).

Regulatory T (Treg) cells represent a subpopulation of T cells with immunosuppressive properties. Recent studies have drawn attention to the important role played by Treg in the process of autoimmunisation. Just a few studies have demonstrated a decrease in the number and activity of Treg in patients with SSc, and only such studies involve morphea.

This article reviews recent studies on the role of DC and regulatory T cells in the pathogenesis of morphea. Moreover, mechanisms of phototherapy and potential therapeutic targets in the treatment of morphea are discussed in this context.

Key words: *scleroderma, phototherapy, mDC, pDC, morphea.*

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Introduction

Morphea (localised scleroderma) is one of diseases characterised by fibrosis of the skin and subcutaneous tissues. The group of factors responsible for the pathogenesis of this disease is thought to include disturbed functioning of endothelial cells as well as immune disturbances leading to chronic inflammatory conditions, accompanied by increased production of collagen and of other extracellular matrix components. The presence of various antibodies indicates that the background of morphea is autoimmunological, as it is in systemic sclerosis. It is noteworthy that antinuclear autoantibodies are found in approximately 60% of cases of various morphea forms [1, 2].

Dendritic cells (DC) are a type of professional antigen-presenting cells (APC) and can be found in almost all body tissues. Depending on the developmental line of their origin, one can distinguish two major groups: plasmacytoid DC (pDC) and myeloid DC (conventional DC, mDC, or cDC). Myeloid DC forms the most numerous group of DC. They inhabit non-lymphoid peripheral tissues, lymph nodes, and blood. Immature mDC constantly sample their environment, ingest antigens, and once activated they maturate and migrate from non-lymphoid peripheral tissues to lymph nodes. There they present their collected antigen to naďve T cells, which leads to their activation. Dendritic cells and T cells both cooperate in the course of the induction of immune reactions as well as during the development of a tolerance. Dendritic cells affects the differentiation, migration, and activity of T cells by both direct contact and released cytokines [3, 4].

In the process of maintaining tolerance to the body's own antigens, substantial significance is ascribed to regulatory T cells (Treg), which differentiate under the effect of a specific subpopulation of DC, cytokines, and types of antigens presented by DC. Disturbances in the process of Treg differentiation lead to allergies, autoimmune disorders, and neoplastic diseases and may effect graft rejection [3]. In light of recent knowledge, DC plays a significant role in autoimmunological phenomena through the activation of autoreactive T cells in lymph nodes and in target tissues [4].

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Dendritic cells

Scientific studies on the possible involvement of individual DC subpopulations in the development of inflammatory infiltrates in morphea have been very scarce. Their results were based on small groups and were not confirmed by other authors. In most cases, DC focused studies involved the pathogenesis of other autoimmune diseases, such as systemic lupus erythematosus, psoriasis, insulin-dependent diabetes mellitus, or multiple sclerosis [5]. Individual investigations demonstrated high numbers of pDC in morphoeic skin lesions, within deeper dermal layers, around blood vessels, and around collagen fibres in subcutaneous tissue [6]. However, the visualisation of these DC was based on immunohistochemistry, which only allows for semiquantitative evaluation of cutaneous cell subpopulations.

Substantial differences in the pathogenesis of systemic sclerosis and morphea have been suggested in literature. In contrast to the former, inflammatory infiltrate in morphea is rich in cells. The inflammatory infiltrate, consisting of CD3+, CD4+, and CD8+ T cells, as well as DC, is primarily detected around collagen fibres in deeper layers of dermis and subcutaneous tissue only in the early stages of the disease. Immunohistochemical studies have demonstrated a more pronounced role of DC in the development of inflammation and T cell activation in morphea, as compared to systemic sclerosis [7]. On the other hand, CD8+ T cells seem to be primarily responsible for the development and maintenance of inflammation in systemic sclerosis [8].

The most numerous population of DC are mDC, which colonise almost all non-lymphoid peripheral tissues. They are thought to play a significant role in both the development of immune tolerance mechanisms and in the activation of autoreactive T cells [5]. It has been suggested that cutaneous DC may regulate collagen production, and that fibrosis, which appears along with the progression of the disease, reflects a decrease in the number of these cells in the dermis [9]. A morphea investigation has demonstrated a decreased population of cutaneous CD34+ DC in inflammatory infiltrates [10]. However, the results of that study should be interpreted with caution due to the fact that CD34 undergoes expression also by other cells, such as endothelial cells and fibroblasts, and thus it is not a specific DC marker. Intensive studies performed on animal models seem to confirm that DC phenotype is the decisive factor for the formation of the appropriate microenvironment that stimulates fibrosis of various organs and tissues [11].

Regulatory lymphocytes

Treg represents a subpopulation of T cells with immunosuppressive properties. Recent studies have drawn attention to the important role played by regulatory T cells (Treg) in the process of autoimmunisation. Treg manifests a beneficial activity by inhibiting autoreactive T cells and warranting tolerance to grafts. On the other hand, they may induce undesirable phenomena, e.g. tolerance to neoplastic antigens.

Strict cooperation takes place between dendritic and T cells during the induction and silencing of immune response, through their direct contact or mediation with cytokines. As a result, induction or inhibition of Foxp3 (forkhead box P3) factor may take place in T cells, leading to acquisition or loss of regulatory functions. The course of cooperation depends both on the maturity of DC and the type of antigen presented. During apoptosis antigen presentation takes place with the involvement of MHC (major histocompatibility complex), but without co-stimulatory molecules, which results in the development of tolerance. The accompanying increase in transforming growth factor β (TGF-β) affects differentiation of Foxp3+ Treg. On the other hand, due to the presence of IL-6 in the microenvironment, regulatory abilities may be lost.

The most commonly studied group of T regulatory cells are nTreg (natural) presenting CD4+, CD25+, and Foxp3+ phenotype. Apart from these, other subpopulations can be distinguished, such as CD8+, CD25+, Foxp3+ cells, Tr1 cells that release interleukin (IL)-10, or Th3 cells that produce TGF-β [3, 4].

Originally, Treg were identified as CD4+ T cells, additionally manifesting a pronounced expression of CD25 (IL2-Rα) molecules both in mice and in humans. In turn, various other surface or intracellular molecules were identified, including glucocorticoid-induced TNF receptor (GITR), cytotoxic T-lymphocyte antigen 4 (CTLA4), and L-selectin (CD62L). However, these molecules undergo expression on all activated T cells. At present, one of the most specific markers of Treg is Foxp3 transcription factor. The significance of this molecule was confirmed in Foxp3-deficient mice, presenting a defect of Treg and severe lymphoproliferative autoimmune syndrome. In a similar manner, Foxp3 humans suffer from IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) [12].

Dendritic cells and regulatory T cells in the pathogenesis of morphea

Systemic sclerosis (SSc) is a connective tissue disease characterised by increased production and deposition of collagen fibres in skin and connective tissue of the inner organs, vascular lesions, and autoimmunisation. Morphea does not involve inner organs, but skin lesions are histologically similar. It is a chronic disease that does not shorten the life of the patient, yet significantly affects its quality. Depending on the form of the disease, orthopaedic, neurological, and ophthalmological complications may develop. Little is known about the pathogenesis of morphea. Its clinically evident element is the excessive

fibrosis caused by disturbed metabolism of extracellular matrix. Nevertheless, vascular lesions and activation of the immune system that trigger autoaggressive processes may appear first [1, 2].

In skin, perivascular infiltrates are dominated by CD4+ T helper (Th) cells. During the preliminary, inflammatory stage of scleroderma, Th1 cells dominate accompanied by Th17 lymphocytes. On the other hand, at the late phase of the disease, Th2 cells appear and their levels correlate with fibrosis [13].

In line with recent hypotheses, autoimmune diseases may involve quantitative changes in individual DC populations, resulting in a decrease in Treg number and autoreactive T cell activation. Increased numbers of pDC were detected in the skin of patients with systemic lupus erythematosus and psoriasis [14]. Autoimmune diseases are accompanied by the production of IFN type I (IFN-α/β) by activated pDC. Myeloid DC seems to play a significant role in trapping autoantigens, leading to the differentiation of Treg lymphocytes, which results in maintenance of tolerance to the host's own tissues and cells (Fig. 1A) [3, 4].

In recent years, intensive studies have been conducted in both animal models and *in vitro* on the possible factors engaged in the activation of specific DC populations in the aforementioned group of diseases. A significant role of cytokines such as INF type I, and specific DC markers such as Toll-like receptors (TLR), or the recently discovered lectin receptors (BDCA2 – blood dendritic cell antigen 2, and DEC205) is suggested [15-18]. These studies demonstrate that DC that maturates under intensive TLR stimulation becomes resistant to the suppressive effect of Treg lymphocytes, which may lead to the breaking of tolerance to autoantigens. It is assumed that autoimmune diseases involve activation of pDC due to binding of endogenous ligands (such as products of extracellular matrix decomposition) or immune complexes to TLR (Fig. 1B) [4]. Moreover, results of these studies indicate that BDCA-2 is a specific marker of pDC and plays a significant role preventing DC activation that would lead to the production of IFN-α/β and the development of antigen-specific T cells (Fig. 1B) [15, 16].

Expression of the CD205 receptor is typical for mDC, the presence of which is detected in non-lymphoic peripheral tissues, e.g. in the skin. The CD205 receptor participates in the recognition and trapping autoantigens released during apoptosis or cell necrosis [18]. According to some authors, ingestion of apoptotic bodies by CD8+, CD205+ DC promotes differentiation of Treg [18, 19]. The CD205 receptor, due to its ability to induce tolerance to autoantigens, currently represents an intensely studied element for potential therapy in autoimmune diseases. Research on animal models of autoimmune diseases has provided proof of CD205 efficacy in the manipulation of antigen-specific tolerance [20]. Although CD11c+, CD8+, CD205+ immunophenotype DC may play a significant role in the maintenance of tolerance to the host's own antigens, no investigations on their possible involvement in the pathogenesis of morphea have been carried out [3].

Recently, there have been reports on the possible role of IFN-α/β in the development and/or maintenance of in-

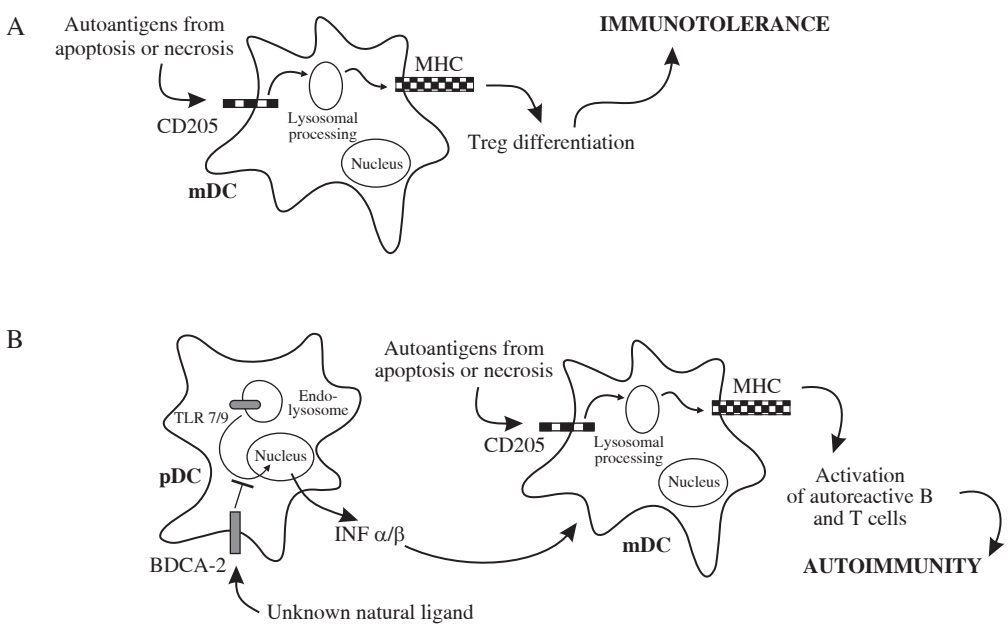

Fig. 1. A) Development of immunotolerance through mDC under normal conditions. **B**) Development of autoimmunity through pDC releasing IFN-α/β and mDC activation

flammation and fibrosis in morphea. The principal source of IFN type I involves pDC, the augmented numbers of which were detected in dermal infiltrates in the course of inflammatory skin diseases [14]. One hypothesis related to the origin of autoimmune diseases assumes that abolishment of peripheral tolerance mechanisms results from mDC activation under the effect of IFN-α/β (Fig. 1B) [21]. In animal studies DC activation and induction of antigen-specific immune response were noted under the effect of IFN type I in response to contact with the antigen [22, 23]. In turn, *in vitro* studies demonstrated that IFN-activated DC in blood of patients with systemic lupus erythematosus stimulated differentiation of autoreactive T cells [5]. Until now, the significance of IFN type I has been proven in the pathogeneses of such autoimmune diseases as psoriasis, lupus erythematosus, lichen planus, alopecia areata, or systemic sclerosis. Immunohistochemical studies have demonstrated positive correlation between the number of pDC in dermal inflammatory infiltrates and the level of IFN-α tissue expression in the course of lupus erythematosus and morphea [6].

Just a few studies have demonstrated a decrease in the number and activity of Treg in patients with systemic sclerosis (SSc), and only such a study involved morphea. Antiga *et al.* demonstrated a significantly decreased number of Treg in the blood and dermis of patients with systemic sclerosis and morphea, as well as decreased levels of IL-10 and TGF-β in serum. Glucocorticoids, widely used in the treatment of the disease, were found to re-establish their normal serum levels [24]. In turn, other studies revealed the effect of calcitriol (the active form of vitamin D_3) on cutaneous mDC and Langerhans cells and their IL-10 and TGF-β expression, resulting in an increased number and activity of Treg. A different group of investigators observed no differences in the number of Treg in peripheral blood, but detected a decrease in Treg within typical cutaneous lesions in SSc. They postulated a role of the so-called skin-specific Treg in the pathophysiology of the disease [25].

The treatment possibilities of morphea and its potential influence on dendritic cells and regulatory T cells

The treatment of morphea poses a serious challenge. First of all, due to its complex and incompletely recognised pathogenesis, but also due to its heterogeneous clinical expression. Treatment options usually focus on controlling particular pathological phases such as inflammatory, immune, or fibrotic processes, and these include corticosteroids, vitamin D analogues, or topical tacrolimus. Recent treatment strategies indicate that combination treatment, i.e. anti-inflammatory and anti-fibrotic agents, is more effective. Amongst the topical forms of treatment, one randomised placebo-controlled trial revealed high effectiveness of tacrolimus, while a prospective pilot study confirmed the effectiveness of calcipotriol in combination with betamethasone. Two prospective studies involving systemic treatments suggest high efficacy of a combination of methotrexate and corticosteroids [1, 2, 26]. Topical tacrolimus – a calcineurin inhibitor – exhibits anti-inflammatory and immunomodulatory effects on T cells by inhibiting their proliferation and cytokine production. Tacrolimus was also found to inhibit DC migration *ex vivo* in a skin DC migration in a mice model of allergic eczema [27]. Vitamin D_3 (Vit. D) analogues such as calcipotriol or calcitriol, which form a standard treatment of another inflammatory skin disorder, psoriasis, have an anti-proliferative effect on fibroblasts in morphea [26]. It was also shown that Vit. D may control murine and human pDCs function and impairs the capacity of pDC to induce T-cell proliferation and secretion of cytokines. Plasmacytoid DCs expresses various proteins of Vit. D receptor pathway [28]. The combination of calcipotriol with betamethasone enriched their anti-inflammatory, immunomodulatory, and anti-fibrotic properties [26]. In more severe forms of morphea, systemic agents are necessary. However, the mechanisms responsible for the immunosuppressive properties on skin of systemic glucocorticosteroids are not fully recognised. Recent studies have revealed an increased number of Foxp3(+) CD25(+) T cells and epidermal Langerhans cells in patients treated with systemic glucocorticosteroids due to allergic eczema [29]. On the other hand, in vitro studies have shown a reduction in Th17 population followed by an increase in Th17 IL-10(+) and Treg after treatment with methotrexate and/or methylprednisolone in PBMCs of rheumatoid arthritis patients [30].

The introduction of UVB, PUVA (psoralen + UVA), and UVA1 phototherapies has significantly enriched the therapeutic panel [31, 32]. Clinically, the efficacy of high, moderate, and low doses of UVA1 has been confirmed, while better results were obtained with the use of high doses. According to modern literature, in disseminated forms of morphea the first-line treatment should include phototherapy (UVA1, narrow band UVB, 311 nm, or broad band UVA), due to a higher safety profile than that of methotrexate or systemic glucocorticoids [1, 2, 26]. While UVB (290-320 nm) affects the epidermis, the longest wavelength UVA1 (340-400 nm) radiation penetrates deeper, into the papillary layer of the dermis. The exact mechanism of UVA1 action has not been fully clarified, in contrast to UVB, which is absorbed by cells' DNA and results in the formation of cyclopyrimidine dimers. The molecule that absorbs UVA1 remains unknown, but the action on the DNA is indirect and mediated by generated oxygen radicals, yet recent studies have also revealed the possibility of direct DNA mutagenesis. Ultraviolet A1 phototherapy is a method that affects various stages of the sclerodermic pathomechanism. It inhibits inflammatory processes and affects fibrosis, which diminishes further

progress of the disease. It is also a potent immunomodulator through the induction of cell apoptosis (including the unique phenomenon of early apoptosis, which is not generated by UVB irradiation). It affects the ability to produce pro-inflammatory cytokines and the ability to induce collagenase production by fibroblasts. Ultraviolet A1 may also act on endothelial cells, promoting growth on new blood vessels [33-35]. Studies have confirmed that UVR suppress cell-mediated immune response in human skin, leading to inhibition of contact hypersensitivity. Skin specific DCs – Langerhans cells (LCs) – together with Tregs play a role in the induction of UVR-induced immunosuppression as well as tolerance. It has been shown in numerous studies that UV of various wavelengths (solar simulated radiation, UVB, broad band UVA, and UVA1) lead to a decreased number of DCs resulting from migration or apoptosis. Not only were these changes described quantitatively, but also morphological alterations of those APCs were reported qualitatively. Moreover, UVR is able to influence DCs function, maturation, migration, and cooperation with Tregs. A study has revealed that the effectiveness of UVA1 phototherapy in the treatment of morphea was associated with an increase in the number of CD34+ DCs in the dermis [36-39]. No one has yet studied the potential effects of UVA1 phototherapy on the number of Treg in skin and blood of morphea patients. Any demonstration of such effects would be consistent with the excellent results of this therapy observed clinically. In a recent study on the application of extracorporeal photopheresis (ECP) in patients with scleroderma, a decrease in peripheral Th17 count was observed, along with a decrease in skin thickness and an increase in Treg level [40]. Notably, Singh *et al.* demonstrated inhibition of the Th17/IL23 pathway and induction of Foxp3 Treg in a psoriatic murine model, following the application of photochemotherapy [41].

It should be stressed that DC, along with the aforementioned markers, provide potential targets for therapeutic approaches that are already available. The chance for selective recruitment of specific DC populations in autoimmune diseases by the regulation of DC activating factors, such as BDCA2, is of special interest. This phenomenon is already targeted in the therapy of systemic lupus erythematosus [16]. Due to the high efficacy in activation of lymphocytes and the induction of immune responses, it has been attempted to use DC as a vaccine in the therapy of tumours. However, preliminary studies on animals indicate that vaccines consisting of DC induce autoimmune reactions [42]. Accurate immunophenotypical characteristics of DC participating in both autoimmunisation and fibrotic processes would lead to the development of more effective therapeutic approaches and better usage of the currently available methods of treatment. That statement is true not only for morphea but also for other fibrotic diseases (systemic sclerosis, graft-versus-host disease, lichen sclerosis). Attempts to block Treg have already been undertaken in neoplastic diseases, while studies on their activation in autoimmune disorders, allergic diseases, and in post-transplantation patients are also on the way. The results of these attempts are, for the time being, far from expected [43].

The authors declare no conflict of interest.

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