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REVIEW ARTICLE

Dendritic cells in the pathogenesis of ankylosing spondylitis and axial spondyloarthritis

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Abstract

The interaction of dendritic cells (DCs) with the human microbiome, with distorted handling of the microbiota or its products via the direct effect of HLA B27, probably represents the initial element in the chain of events leading to the development of clinical axial spondyloarthritis. The mechanism of disease extension onto the skeleton and other tissues involved, such as uvea, may also involve migratory DCs. Finally, the role of DCs in the initiation of the inflammatory tissue response with activation of the IL-17 axis has been demonstrated. Further, some initial data suggests the possible connection of DCs with disease-related new bone formation.

Keywords Ankylosing spondylitis · Axial spondyloarthritis · Dendritic cells

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic inflammatory disease, primarily affecting sacroiliac joints (SIJ) and spine and eventually manifesting with new bone formation and bony ankylosis. The early phase of AS, with radiographic studies still normal, diagnosed on the basis of characteristic clinical presentation and sometimes supported by magnetic resonance imaging (MRI) or HLA B27 testing is referred to as non-radiographic axial spondyloarthritis (nrAxSpA). These two entities, nrAxSpA and AS together, form the recently defined nosologic entity of axial spondyloarthritis (AxSpA) [1].

The pathogenesis of AxSpA is not well understood. Genetic association with HLA B27 has been known since the 1970s, but the mechanisms derived from this association have not been sufficiently elaborated [2, 3]. The central role of gut bacteria in disease initiation was reported long ago in the animal models of the disease, while further studies of the human microbiome have mainly concentrated on a search for a specific bacterial specie as a possible disease initiator [4–6]. Recently, it was shown that gut dysbiosis is accompanied by a change in the metabolic profile of the gut, including alterations in microbial bioactive metabolites, which then modulate host physiology and immune responses [7]. The role of dendritic cells (DCs) in the handling of the microbiome is believed today to be a critical factor in the pathogenesis of many autoimmune and chronic inflammatory diseases, and its role in AxSpA [8] has begun to be evaluated.

The first characteristic musculoskeletal manifestation of AxSpA is typically sacroiliitis. At present, the earliest detectable lesion of sacroiliitis is bone marrow edema—termed osteitis—in the proximity of SIJ, seen on MRI. Further involvement of SIJ manifests with erosions of adjacent bony margins of the joint, local proliferation of mesenchymal tissue, and exaggerated new bone formation. A similar process takes place in other typical disease locations, such as vertebra, sternum, and entheses of calcaneus bones, leading sometimes to pronounced ossification of the skeleton [1]. The cytokines currently known to drive inflammation in AxSpA include tumor necrosis factor (TNF)-α and interleukin (IL)-17, produced by the immune cells. DCs are known to function as a major regulator of the immune response in general, and some fascinating data on the functioning of DCs in AxSpA has become available during the last decade.

Activity of DCs in AxSpA has been shown to be regulated by a variety of intracellular factors and inter-cellular

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interactions [9, 10]. Also, the role for DCs in disease transmission from the gut to SIJ and axial skeleton has been recently suggested [11].

Although substantial data on the functioning of DCs in AxSpA is being constantly accumulated, a comprehensive review on the topic has never been published. The aim of the present manuscript is to collect, sort, and analyze the available published data connecting DCs and AxSpA.

Methods

1. Search strategy. A systematic and unlimited by time period search using the keywords "dendritic cells" and "ankylosing spondylitis" or "spondyloarthritis" was performed in PubMed/Embase/Cochrane libraries.
2. All acquired abstracts were analyzed by the first author, and full texts of relevant original manuscripts were extracted and studied. The data, pertinent to the subject of this review, was critically assessed and summarized.

Results

One hundred ninety-five articles containing chosen keywords were located by the search, while only 23 of reviewed articles contained original data on the behavior and/or significance of DCs in human AxSpA or spondyloarthritis-like disease in relevant animal models and were used as a basis of this review.

HLA B27$^+$ DC activation

Experiments performed on splenic DCs of HLA B27 transgenic rats, developing a spontaneous spondyloarthritis-like disease, have demonstrated significant changes in the activation patterns and functioning of DCs ex vivo. Both CD103$^+$ and CD103$^-$ splenic CDs, isolated by different methods, demonstrated defective function of costimulatory molecules, in particular CD86, with respective diminished ability to stimulate T lymphocytes. Of particular interest was the fact that normal co-stimulation in these experiments was restored by citric acid treatment, which removes mature HLA B27 molecules from the cell surface. Based on the previous knowledge that MHC molecules co-cluster with costimulatory molecules, the authors suggested that direct engagement of the latter by HLA B27 may be a mechanism of the observed phenomenon [12, 13].

Remarkably, both splenic DCs of HLA B27 transgenic rats and, in a separate experiment, monocyte-derived DCs of patients with AS have demonstrated significantly lower baseline expression of class II MHC molecules [14, 15].

The clinical significance of the aforementioned defective capacity of DCs to activate other immune cells was also shown in another series of experiments on HLA B27 transgenic rats [16]. In ex vivo studies, the capacity of splenic DCs to prime CD4$^+$ T cells well correlated with the clinical phenotype of different lines of transgenic animals, with more severe impairment seen in lines from more dramatic phenotypes [16]. Similarly, monocyte-derived CD14$^-$CD40$^+$HLA DR$^+$CD86$^+$ DCs from HLA B27$^+$ patients with AxSpA had a markedly decreased capacity to stimulate T cells, when compared to healthy controls [17].

On the other hand, tolerogenic DCs, which contribute to tolerance rather than immunity, by inducing T cell anergy and generation of regulatory T cells, may also be affected in AxSpA. As such, reduced ex vivo viability of tolerogenic CD103$^+$CD4$^-$ DCs and relative depletion of migratory CD172a^{low} DCs, responsible for triggering IL-10 production by naïve CD4$^+$ T cells, have been found on analysis of subsets of migrating intestinal DCs of transgenic rats, collected via the cannulation of thoracic duct [14, 18]. Reduced numbers of tolerogenic DCs were observed in experiments on ERAP$^{-/-}$ mice [10]. Decreased IL-10 signature was reported in rats' HLA B27+ DCs, as well, in a transcriptome-based study [19].

Remarkably, HLA B27, normally composed of a heavy chain connected to β2-microglobulin, was shown to form abnormal heavy chain homodimers on the surface of activated dendritic cells [20, 21]. These HLA B27 heavy chain homodimers have been shown to bind to different groups of immune receptors when compared with classical HLA B27 molecule, particularly KIR (killer cell immunoglobulin-like receptor) 3DL2 receptor, expressed by natural killer (NK) and NK T cells. Ligation to HLA B27 heavy chain homodimer through KIR3DL2 has led to expansion of the pool of KIR3DL2 bearing cells as well as diminished interferon (IFN)-γ production [22]. Notably, splenic DCs of transgenic rats and monocyte-derived macrophages of AxSpA patients as well demonstrated diminished interferon signature by themselves in another study [19].

DC migration

Migration of DCs from tissues to lymph nodes is essential for initiation of specific immune responses. In ex vivo conditions, splenic DCs of HLA B27 transgenic rats were found to have a downregulated expression of some cytoskeletal proteins and demonstrated diminished fibronectin-induced motility associated with formation of longer, more branched and less mobile pseudopodia [14]. In another study, mentioned above, HLA B27$^+$ DCs of transgenic rats, collected from the mesenteric lymph nodes and lymph duct and, presumably, representing migratory DCs traveling after encounter with the pathogen within the gut, were depleted of the CD103$^+$CD172a^{low} tolerogenic subset, consisted mainly of CD172a$^{high/intermediate}$

phenotype, most effective in stimulation of the immune cells [18]. The process of DCs trafficking from the gut to axial skeleton in AxSpA has not been elaborated yet. And yet, Berthelot and Claudepierre, in their recent critical analysis of the available indirect evidence of such, formulated a very plausible hypothesis of the connection between the immune response in the gut and axial skeleton and proposed a central role of DCs in this process [11]. In brief, the authors suggested that in AxSpA, dead or dormant bacteria may migrate within DCs, similar to that in reactive arthritis, from the gut via the mesenteric lymphatic system and lymph nodes and further through thoracic duct to the axial skeleton. The activated DCs may then induce and maintain a specific chronic inflammatory response in the affected tissues. This hypothesis has been built mostly on knowledge translated from studies in the fields of infectious diseases, gastroenterology, and general anatomy and has not been directly tested/supported by experiments in the animal models nor patients with AxSpA, as yet.

DCs' triggered immune response

DCs can exhibit their immune regulatory function in AxSpA in the gut, circulation, and tissues involved in inflammation, such as axial skeleton, entheses, or uvea. Circulating DC numbers, as well as frequencies, of majority of DC subsets, including $CD141^+$ DC—the human analog of rats' $CD103^+CD172a^{low}$ subset—have been found to be similar between patients with AS and healthy controls [23]. In one study of interest, reduction in the frequency of circulating $CD1c^+$ DCs in AS patients was demonstrated [23]. Anti-TNF-α treatment was associated with increased numbers of circulating myeloid DCs in another report [24]. Of importance, DCs have been detected in affected tissues of AxSpA patients, implicating the immune-regulating role of DCs at the foci of disease-related inflammatory reaction. As such, $CD1c^+$ as well as $CD141^+$ DCs has been found in the synovial fluid, and the metagene signature of DCs was overexpressed in the synovial biopsies of patients with AxSpA [23, 25]. IL-23^+CD1a^+ DCs have been demonstrated along with IL-23^+ macrophages and IL-23^+MPO^+ myeloid precursors in the bone marrow of facet joints of AS patients [26].

While the role of IL-17 in the pathogenesis of AxSpA is well established, DCs of both animal models and patients with AxSpA have been shown to trigger immune response polarized towards excessive production of IL-17. Splenic and bone marrow–derived DCs of HLA B27 transgenic rats induced higher concentrations of IL-17 in in vitro conditions, compared to DCs of non-transgenic animals in several studies [18, 27]. Intriguingly, the mechanism of this preferential priming of T lymphocytes to Th17 phenotype by rats' DCs was not dependent on the cytokine microenvironment, but rather on the direct cell-to-cell contact involving particularly CD86. The inhibition of CD86 via monoclonal antibody resulted in decreased Th17 cell proliferation [27].

"Reverse" IFN signature with upregulated genes underexpressed and downregulated genes overexpressed was shown in $CD103^+CD4^+$ DCs of HLA B27 transgenic rats in a whole-transcriptome study [19]. Confirming these results was a report of similar "reverse" IFN signature in the macrophages of AS patients, supported also by data showing that messenger RNA encoded by the IFN-γ gene was approximately twofold lower at baseline and was poorly responsive to LPS in these patients, as compared with that in healthy controls [28]. Autocrine and/or systemic significance of disordered regulation of IFN in antigen-presenting cells in AxSpA has not been clarified as yet.

The presence of active DCs in the inflamed tissues in AS patients may not only maintain the inflammation but also influence bone formation, typical for the disease. While proof-of-concept studies in this field are still missing, at least two

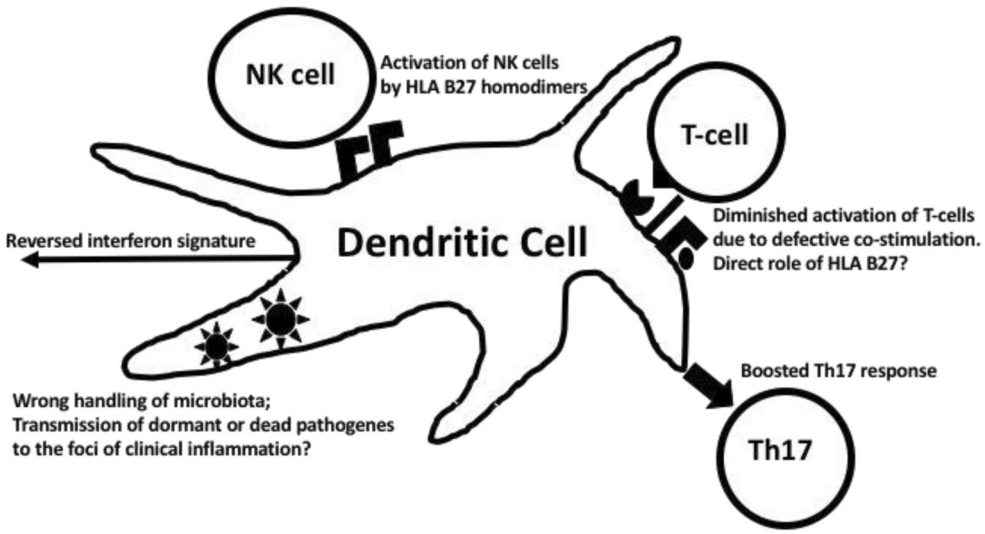

Fig. 1 Possible role of dendritic cells in the pathogenesis of axial spondyloarthritis

recent reports challenge the likelihood of this. In one study, transcriptomic analysis revealed that monocyte-derived DCs of patients with AxSpA had downregulated expression of *CITED2* and increased expression of *ADAMTS15*, genes encoding a metallopeptidase and a transcription factor and co-regulated with other genes of the *wnt* signaling pathway of bone formation [17]. Another association study of genes related to bone formation in AS patients revealed significant association of rs8092336 SNP within *RANK*, which regulates both osteoclast activation and DC-T cell interaction [29]. Possible interaction of DCs and mesenchymal stem cells in spondyloarthritis was recently suggested as well [9].

Summary

There are several DC subsets, such as plasmacytoid DCs and two subsets of myeloid DCs with their distinct markers, features, and functions [30]. In humans, the total pool of circulating DCs represents less than 1% of cells, which makes it challenging to study. Human monocyte-derived DCs, easily grown with IL-4 and GM-CSF and frequently used for in vitro experiments as myeloid DC substitute, while producing a spectrum of regulatory cytokines and able to activate T cells, represent in vivo a subset distinct from myeloid DCs, for example in its inability to migrate [30]. Of importance, and similar to other immune cells, DCs change their phenotype depending on the state of activation and during migration as well [31, 32]. Moreover, DCs possess plasticity features and, depending on conditions, can undergo transformation and acquire, for example, a tolerogenic profile [33]. Our main body of knowledge on DC function in AxSpA has been learned from the experiments on HLA B27 transgenic rats. However, while HLA B27 transgenic rats represent an exceptionally valuable animal model for the study of AxSpA, there may be some important disparities in both the pathogenesis of the disease and physiology of DCs in rats and humans. It is also questionable to what extent rats' splenic DCs, used for experiments, reflect the features of circulating and tissue-settled DCs.

Nevertheless, after acknowledging the potential limitations of the published research on the role of DCs in AxSpA, the progress in the field has to be appreciated (Fig. 1). The interaction of DCs with the gut microbiome with distorted handling of the microbiota or its metabolic products, due to the direct effect of HLA B27, represents probably the initial element in the chain of events leading to clinical disease. The mechanism of disease expansion onto the skeleton and other tissues involved, such as uvea, plausibly also involves migratory DCs, which have not been studied yet in the setting of AxSpA. Hypothetically, migratory DCs can be attracted as well to the sites of active hematopoietic marrow, the foci of which almost perfectly overlap with the anatomical locations of musculoskeletal inflammation in AxSpA https://en.wikipedia.org/wiki/Haematopoiesis#/media/File:Hematopoesis_EN.svg. The role of DCs in the initiation of inflammatory tissue response with activation of IL-17 axis has already been shown at the centers of inflammatory activity. Moreover, some initial data imply the connection of DCs with disease-related new bone formation. Further research is needed to show the real impact of the DCs on the development of AxSpA, but the preliminary knowledge in the field, reviewed herein, opens new horizons to this research.

Compliance with ethical standards

Disclosures None.

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References

1. Taurog JD, Chhabra A, Colbert RA (2016) Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med Jun 374(26):2563–2574
2. Robinson PC, Brown MA (2014) Genetics of ankylosing spondylitis. Mol Immunol Jan 57(1):2–11
3. Powis SJ, Colbert RA (2016) Editorial: HLA-B27: the story continues to unfold. Arthritis Rheumatol. 68(5):1057–1059
4. Breban M, Tap J, Leboime A, Said-Nahal R, Langella P, Chiocchia G, Furet JP, Sokol H (2017) Faecal microbiota study reveals specific dysbiosis in spondyloarthritis. Ann Rheum Dis 76(9):1614–1622
5. Wen C, Zheng Z, Shao T, Liu L, Xie Z, Le Chatelier E, He Z, Zhong W, Fan Y, Zhang L, Li H, Wu C, Hu C, Xu Q, Zhou J, Cai S, Wang D, Huang Y, Breban M, Qin N, Ehrlich SD (2017) Quantitative metagenomics reveals unique gut microbiome biomarkers in ankylosing spondylitis. Genome Biol 18(1):142
6. Gill T, Asquith M, Rosenbaum JT, Colbert RA (2015) The intestinal microbiome in spondyloarthritis. Curr Opin Rheumatol 27(4):319–325
7. Asquith M, Davin S, Stauffer P, Michell C, Janowitz C, Lin P, Ensign-Lewis J, Kinchen JM, Koop DR, Rosenbaum JT (2017) Intestinal metabolites are profoundly altered in the context of HLA-B27 expression and functionally modulate disease in a rat model of spondyloarthritis. Arthritis Rheumatol 69(10):1984–1995
8. Smolinska S, Groeger D, O'Mahony L (2017) Biology of the microbiome 1: interactions with the host immune response. Gastroenterol Clin N Am 46(1):19–35
9. Krajewska-Wlodarczyk M, Owczarczyk-Saczonek A, Placek W, Osowski A, Engelgardt P, Wojtkiewicz J (2017) Role of stem cells in pathophysiology and therapy of spondyloarthropathies-new therapeutic possibilities? Int J Mol Sci 28(19):1
10. Pepelyayeva Y, Rastall DPW, Aldhamen YA, O'Connell P, Raehtz S, Alyaqoub Blake MK, Raedy AM, Angarita AM, Abbas AM, Pereira-Hicks CN, Roosa SG, McCabe L, Amalfitano A (2018) ERAP1 deficient mice have reduced type 1 regulatory T cells and develop skeletal and intestinal features of ankylosing spondylitis. Sci Rep 8(1):12464
11. Berthelot JM, Claudepierre P (2016) Trafficking of antigens from gut to sacroiliac joints and spine in reactive arthritis and spondyloarthropathies: mainly through lymphatics? Joint Bone Spine 83(5):485–490

12. Hacquard-Bouder C, Falgarone G, Bosquet A, Smaoui F, Monnet D, Ittah M, Breban M (2004) Defective costimulatory function is a striking feature of antigen-presenting cells in an HLA-B27-transgenic rat model of spondyloarthropathy. Arthritis Rheum 50(5):1624–1635
13. Hacquard-Bouder C, Chimenti MS, Giquel B, Donnadieu E, Fert I, Schmitt A, André C, Breban M (2007) Alteration of antigen-independent immunologic synapse formation between dendritic cells from HLA-B27-transgenic rats and CD4+ T cells: selective impairment of costimulatory molecule engagement by mature HLA- B27. Arthritis Rheum 56(5):1478–1489
14. Dhaenens M, Fert I, Glatigny S, Haerinck S, Poulain C, Donnadieu E, Hacquard-Bouder C, Andre C, Elewaut D, Deforce D, Breban M (2009) Dendritic cells from spondyloarthritis-prone HLA-B27-transgenic rats display altered cytoskeletal dynamics, class II major histocompatibility complex expression, and viability. Arthritis Rheum 60(9):2622–2632
15. Slobodin G, Kessel A, Kofman N, Toubi E, Rosner I, Odeh M (2012) Phenotype of resting and activated monocyte-derived dendritic cells grown from peripheral blood of patients with ankylosing spondylitis. Inflammation 35(2):772–775
16. Fert I, Glatigny S, Poulain C, Satumtira N, Dorris ML, Taurog JD, Breban M (2008) Correlation between dendritic cell functional defect and spondyloarthritis phenotypes in HLA-B27/HUMAN beta2-microglobulin-transgenic rat lines. Arthritis Rheum 58(11): 3425–3429
17. Talpin A, Costantino F, Bonilla N, Leboime A, Letourneur F, Jacques S, Dumont F, Amraoui S, Dutertre CA, Garchon HJ, Breban M, Chiocchia G (2014) Monocyte- derived dendritic cells from HLA-B27+ axial spondyloarthritis (SpA) patients display altered functional capacity and deregulated gene expression. Arthritis Res Ther. 16(4):417
18. Utriainen L, Firmin D, Wright P, Cerovic V, Breban M, McInnes I, Milling S (2012) Expression of HLA-B27 causes loss of migratory dendritic cells in a rat model of spondyloarthritis. Arthritis Rheum 64(10):3199–3209
19. Fert I, Cagnard N, Glatigny S, Letourneur F, Jacques S, Smith JA, Colbert RA, Taurog JD, Chiocchia G, Araujo LM, Breban M (2014) Reverse interferon signature is characteristic of antigen-presenting cells in human and rat spondyloarthritis. Arthritis Rheumatol. 66(4):841–851
20. Santos SG, Lynch S, Campbell EC, Antoniou AN, Powis SJ (2008) Induction of HLA- B27 heavy chain homodimer formation after activation in dendritic cells. Arthritis Res Ther 10(4):R100
21. Raine T, Brown D, Bowness P, Hill Gaston JS, Moffett A, Trowsdale J, Allen RL (2006) Consistent patterns of expression of HLA class I free heavy chains in healthy individuals and raised expression in spondyloarthropathy patients point to physiological and pathological roles. Rheumatology (Oxford) 45(11):1338–1344
22. Wong-Baeza I, Ridley A, Shaw J, Hatano H, Rysnik O, McHugh K, Piper C, Brackenbridge S, Fernandes R, Chan A, Bowness P, Kollnberger S (2013) KIR3DL2 binds to HLA-B27 dimers and free H chains more strongly than other HLA class I and promotes the expansion of T cells in ankylosing spondylitis. J Immunol 190(7): 3216–3224
23. Wright PB, McEntegart A, McCarey D, McInnes IB, Siebert S, Milling SW (2016) Ankylosing spondylitis patients display altered dendritic cell and T cell populations that implicate pathogenic roles for the IL-23 cytokine axis and intestinal inflammation. Rheumatology (Oxford) 55(1):120–132
24. Pang L, Wang L, Suo T, Hao H, Fang X, Jia J, Huang F, Tang J (2008) Tumor necrosis factor-alpha blockade leads to decreased peripheral T cell reactivity and increased dendritic cell number in peripheral blood of patients with ankylosing spondylitis. J Rheumatol 35(11):2220–2228
25. Hallett RM, Chew T (2014) Immune cell transcript modules reveal leukocyte heterogeneity in synovial biopsies of seronegative spondyloarthropathy patients. BMC Musculoskelet Disord 15:446
26. Appel H, Maier R, Bleil J, Hempfing A, Loddenkemper C, Schlichting U, Syrbe U, Sieper J (2013) In situ analysis of interleukin-23- and interleukin-12-positive cells in the spine of patients with ankylosing spondylitis. Arthritis Rheum 65(6):1522–1529
27. Glatigny S, Fert I, Blaton MA, Lories RJ, Araujo LM, Chiocchia G, Breban M (2012) Proinflammatory Th17 cells are expanded and induced by dendritic cells in spondyloarthritis-prone HLA-B27-transgenic rats. Arthritis Rheum 64(1):110–120
28. Smith JA, Barnes MD, Hong D, DeLay ML, Inman RD, Colbert RA (2008) Gene expression analysis of macrophages derived from ankylosing spondylitis patients reveals interferon-gamma dysregulation. Arthritis Rheum 58(6):1640–1649
29. Cortes A, Maksymowych WP, Wordsworth BP, Inman RD, Danoy P, Rahman P, Stone MA, Corr M, Gensler LS, Gladman D, Morgan A, Marzo-Ortega H, Ward MM, SPARCC (Spondyloarthritis Research Consortium of Canada); TASC (Australo-Anglo-American Spondyloarthritis Consortium), Learch TJ, Reveille JD, Brown MA, Weisman MH (2015) Association study of genes related to bone formation and resorption and the extent of radiographic change in ankylosing spondylitis. Ann Rheum Dis 74(7):1387–1393
30. Collin M, Bigley V (2018) Human dendritic cell subsets: an update. Immunology 154(1):3–20
31. Tiberio L, Del Prete A, Schioppa T, Sozio F, Bosisio D, Sozzani S (2018) Chemokine and chemotactic signals in dendritic cell migration. Cell Mol Immunol 15:346–352. https://doi.org/10.1038/s41423-018-0005-3
32. Clark GJ, Silveira PA, Hogarth PM, Hart DNJ (2018) The cell surface phenotype of human dendritic cells. Semin Cell Dev Biol pii S1084-9521(17):30494–30499
33. Domogalla MP, Rostan PV, Raker VK, Steinbrink K (2017) Tolerance through education: how tolerogenic dendritic cells shape immunity. Front Immunol 8:1764