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Review

Monocyte-derived interferon-alpha primed dendritic cells in the pathogenesis of psoriasis: New pieces in the puzzle

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ABSTRACT

Psoriasis is a common chronic inflammatory skin disorder with serious clinical, psychosocial, and economic consequences. There is much evidence that different dendritic cell (DC) subsets, various proinflammatory cytokines and Toll-like receptors (TLRs) have a central role in the pathogenesis of the disease. One of the early events in psoriatic inflammation is the secretion of interferon (IFN)-α by activated plasmacytoid DCs, a special DC subset present in symptomless psoriatic skin. Secreted IFN-α along with other proinflammatory cytokines can lead to monocyte-derived DC (moDC) development, which might contribute to T-helper (Th)1 and Th17 lymphocyte differentiation/activation and to keratinocyte proliferation. Recently it was proven that interleukin (IL)-12 and IL-23 play a critical role in this process. Additionally in psoriatic lesions, Th1 and Th17 lympocytes can interact with monocytes and instruct these cells to differentiate into Th1- and Th17-promoting moDCs, further governing the formation and function of specialized moDC subsets. The concept we present here focuses on the initial and central role of IFN-α, on the importance of other proinflammatory cytokines, on TLR stimulation and on the effect of T lymphocytes in priming moDCs, which may play an important role in initiating and maintaining psoriasis.

Contents

1. Introduction

Psoriasis vulgaris is a chronic, systemic, inflammatory, multigenic disease, which is characterized by red, scaly skin plaques. A quarter of patients also develop psoriatic arthritis. Aberrant keratinocyte proliferation and differentiation; development of new blood vessels; infiltration of T lymphocytes; dendritic cells (DCs); neutrophils; and elements of innate immunity all contribute to the pathogenesis of the disease [1,2]. Activated plasmacytoid DCs (pDCs) producing interferon (IFN)-α [3,4] and inflammatory myeloid DCs (mDCs) producing tumor necrosis factor (TNF)-α, interleukin (IL)-12 and IL-23 with the activation of both T-helper (Th)1 and Th17 cells are thought to be central players in psoriasis pathogenesis [5].

It is known from a wide range of studies, that type I IFNs alone or in combination with other cytokines and growth factors such as granulocyte/monocyte colony-stimulating factor (GM-CSF) promote the in vitro differentiation and activation of DCs derived from monocytes [6]. IFN-α-primed monocyte-derived DCs (moDCs) express major

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histocompatibility complex molecules, costimulatory markers, adhesion molecules and markers that are involved in antigen processing and uptake. These DCs have the combined phenotype of pDCs and mDCs associated with natural killer (NK) cell characteristics and mostly sense conserved structures, or pathogen-associated molecular patterns through Toll-like receptors (TLRs). IFN-α-primed moDCs are capable of producing numerous Th1 cytokines such as IL-1β, IL-6, IL-8, IL-12, IL-15, IL-18, IL-23, IL-27, IFN-α, IFN-γ and TNF-α and are capable of promoting Th1 type immune responses through the expansion of CD4+ and CD8+ T cells producing large quantities of IFN-γ. A fairly detailed description is given of the most important phenotypical and functional properties of in vitro generated IFN-α-primed moDCs in a recent review [7].

The aim of our paper is to highlight the impact of type I IFNs, other proinflammatory cytokines, natural TLR agonists and T lymphocytes in shaping the development of the in vivo counterparts of IFN-α-primed moDCs in psoriasis.

2. Role of IFN-α and other proinflammatory cytokines in moDC differentiation in psoriasis

Circulating blood-derived monocytes can migrate into the skin due to chemotactic factors and can be activated by the local environment to develop into inflammatory DCs [8]. GM-CSF necessary for DC development is produced by a variety of cell types such as lymphocytes, mast cells, fibroblasts, macrophages, neutrophils and keratinocytes [9,10]. One of the proximal events in psoriatic inflammation is the secretion of IFN-α by activated pDCs [3,11]. Therefore IFN-α together with GM-CSF may initially predict moDC development in psoriatic skin lesions. On the other hand the inflammatory psoriatic cytokine milieu consists of other cytokines such as IL-1β, IL-6, TNF-α and IFN-γ produced by lymphocytes, NK T cells, macrophages, fibroblasts and keratinocytes which very likely additionally influence the final phenotypes and functional properties of IFN-α-primed moDCs [1,2]. Furthermore mature IFN-α-primed moDCs produce IL-1β, IL-6, TNF-α, IL-12, IL-23, IL-27 [12,13] IFN-α [14] and IFN-γ [15,16] themselves further contributing to their phenotypical and functional maturation.

3. Role of TLR stimulation in moDC differentiation in psoriasis

Newly identified factors, which activate pDCs to produce IFN-α, include self-DNA-LL37 and self-RNA-LL37 complexes [13,17]. Normally DC responses to extracellular self-DNA and self-RNA are prevented by the endosomal seclusion of nucleic acid-recognizing TLRs. In psoriasis, however self-DNA and self-RNA form complexes with the antimicrobial peptide LL37; these complexes, which are protected from extracellular degradation are transported into endosomal compartments of pDCs, where they trigger the production of IFN-α through the activation of TLR9 and TLR7 respectively [13,17]. Additionally self-RNA–LL37 complexes and viral single-stranded RNA (ssRNA) trigger the activation of mDCs [12,13]. This occurs through TLR8 (in the case of ssRNA viruses to a lesser extent also through TLR7 [18,19]) and leads to the production of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, IL-12, IL-23 and IL-27, which can additionally enhance the phenotypical and functional maturation of IFN-α-primed moDCs [12,13].

4. Interaction of T lymphocytes and moDCs in psoriasis

A recent paper in PloS ONE by Santini et al. [20] underscores the importance of IFN-α-primed moDCs in shaping the T cell response. Based on their data it can be presumed that mature IFN-α-primed moDCs are capable to migrate to the skin-draining lymph nodes, where they promote naive T cell differentiation into Th1 and/or Th17 cells through IL-12 and IL-23; these T cells migrate via lymphatic and blood vessels into psoriatic dermis and induce the formation of a psoriatic plaque. Th1 cells produce TNF-α and IFN-γ, which enhance keratinocyte proliferation. Th17 cells secrete IL-17A, IL-17F and IL-22, which also stimulate keratinocyte proliferation and the release of proinflammatory cytokines (IL-1β, IL-6 and TNF-α), antimicrobial peptides and chemokines. Furthermore the current paper of Alonso et al. in Blood [21] indicates that in psoriatic skin Th cells and monocytes are found in close apposition and that Th cells can convert monocytes into DCs. This process requires soluble factors such as GM-CSF, TNF-α, IFN-γ and direct cell-cell contact. They found that in psoriasis Th1 cells instruct monocytes to form DCs that secrete IL-12 and express increased CD86 and CD274, whereas Th17 cells elicit the formation of DCs that secrete IL-1β, IL-6 and IL-23, but not IL-12. These cytokines are among the key cytokines, which induce the differentiation of Th1 and Th17 cells [22,23] and may initiate a positive feedback loop where the interaction of monocytes, DCs and lymphocytes govern an intensified and polarized immune response. The phenotypes of T cell induced DC subsets were maintained following subsequent stimulation with a panel of TLR agonists, suggesting that Th-derived signals outweigh downstream TLR signals in their influence on DC function. Fig. 1 shows a proposed psoriasis model highlighting the role of IFN-α-primed moDCs in skin lesions and underlining the role of IFN-α, TLR stimulation and T lymphocytes.

5. Conclusions

Type I IFNs are involved in the pathogenesis of viral/bacterial infections and of several autoimmune diseases like systemic lupus erythematosus (SLE), type I diabetes, rheumatoid arthritis, myositis, Sjogren's syndrome and psoriasis [4,24]. A couple of studies already indicated that monocyte-derived IFN-α-primed moDCs may participate in cutaneous antiviral responses [25,26], may be important in the pathology of autoimmune disorders such as SLE [27,28], and are likely to model DCs in inflammatory skin diseases such as in psoriasis. It seems that one of the key and initial steps in psoriasis pathogenesis is the production of IFN-α by pDCs. Once activated pDCs spark the differentiation from monocytes into DCs, but in vivo under inflammatory conditions it is very likely that the resulting cytokine milieu consisting of GM-CSF, IFN-α and other cytokines such as IL-1β, IL-6, TNF-α and IFN-γ together predict the final phenotypes and functional properties of IFN-α-primed moDCs as monocytes may also receive differentiation signals from other cell types such as lymphocytes NK cells, NK T cells, macrophages, fibroblasts and keratinocytes [29–31]. The situation is further complicated by the fact that IFN-α-primed moDCs promote naive T cell differentiation into Th1 and/or Th17 cells and that Th cells are capable of influencing the differentiation of monocytes into DCs in a cell-cell contact, GM-CSF and TNF-α dependent manner possibly creating an uncontrolled amplification loop during inflammatory diseases. Furthermore the importance of TLR engagement in the maturation and activation of IFN-α-primed moDCs seems to be important at the initial phase of the disease during pDC activation and less important at later stages when T lymphocytes interact with monocytes as it was shown that the phenotypes of T cell induced DC subsets were maintained following subsequent stimulation with TLR agonists.

The presence of type I IFN-producing pDCs, overexpression of mRNAs of type I IFNs and type I IFN-inducible genes and proteins in lesional skin of psoriatic patients already provided a strong rationale for investigating type I IFNs as new therapeutic targets [4]. The possible reduction of high amounts of type I IFNs can inhibit the switch of monocytes to IFN-α-primed moDCs, but well-timed TLR blocking offers an additional approach to disease intervention. However it is still necessary to better identify the in vivo phenotypical and functional properties of different moDC subsets, to understand their exact role in human diseases such as in psoriasis.

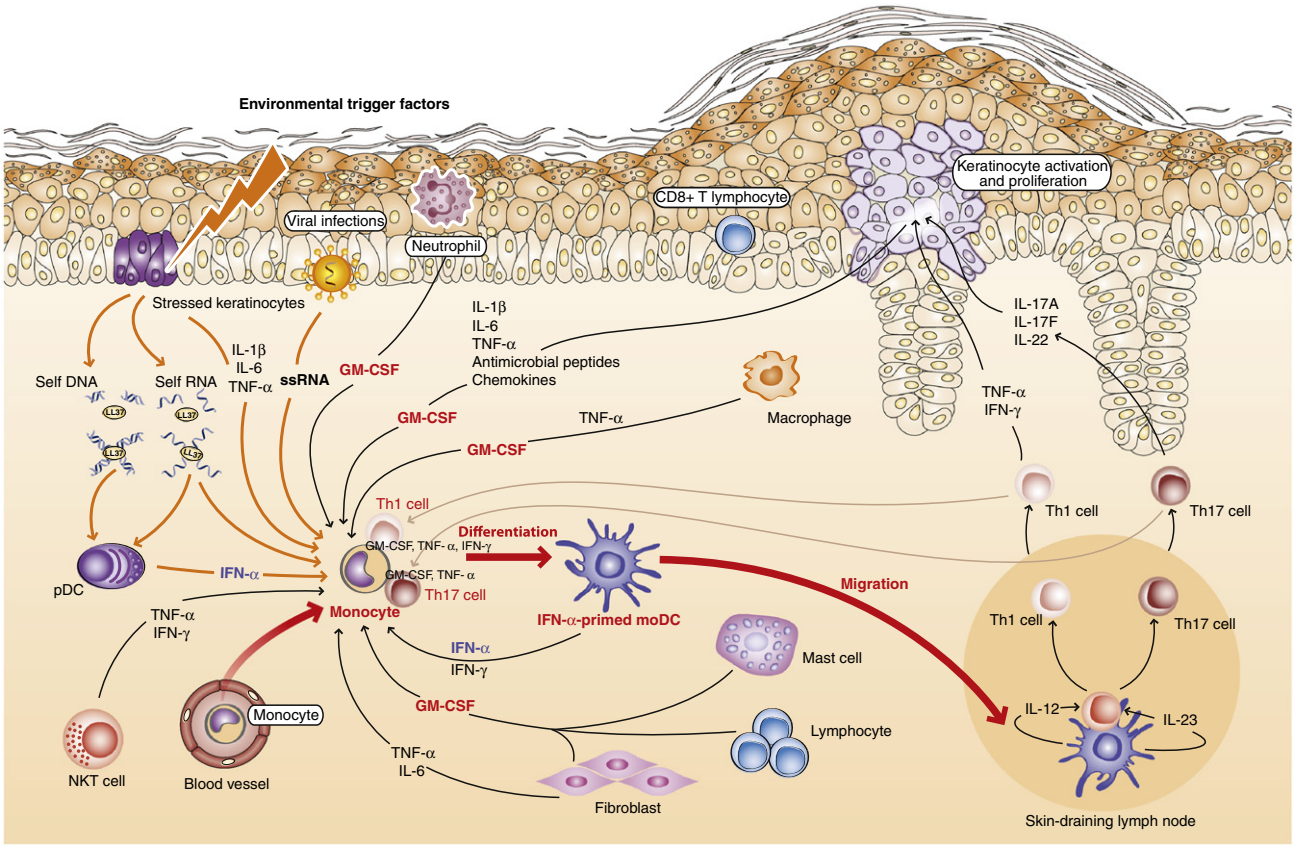

Fig. 1. Proposed model of psoriasis pathogenesis highlighting the role of IFN-α-primed moDCs, TLR stimulation and T lymphocytes.Under inflammatory conditions, blood-derived monocytes are potential precursors of skin DCs. GM-CSF necessary for DC development is produced by a variety of cell types in skin (neutrophils, keratinocytes, macrophages, mast cells, lymphocytes and fibroblasts). IFN-α (a physiological factor for DC development) is mainly produced by pDCs. Stressed keratinocytes (through environmental factors including viral infections) release self-DNA and self-RNA that form complexes with the cathelicidin antimicrobial peptide LL37. Self-DNA-LL37 and self-RNA-LL37 complexes activate pDCs to produce IFN-α. Self-RNA-LL37 complexes and viral ssRNA directly promote the phenotypical and functional maturation of IFN-α-primed moDCs. Other factors released by stressed keratinocytes include IL-1β, IL-6 and TNF-α, which very likely influence IFN-α-primed moDC development. Furthermore IFN-α-primed moDCs produce IFN-α and IFN-γ themselves further contributing to their own maturation. In vivo under inflammatory conditions other cytokines such as IL-1β, IL-6 and TNF-α and IFN-γ are also present in the psoriatic inflammatory infiltrate produced by lymphocytes, macrophages, fibroblasts, NK T cells and keratinocytes therefore IFN-α-primed moDCs are influenced by a variety of proinflammatory cytokines. Mature IFN-α-primed moDCs then possibly migrate to the skin-draining lymph nodes where they promote naive T cell differentiation into Th1 and/or Th17 cells through IL-12 and IL-23. These T cells migrate via lymphatic and blood vessels into psoriatic dermis and contribute to the formation of a psoriatic plaque. Th1 cells produce TNF-α and IFN-γ, which also stimulate keratinocyte proliferation. Th17 cells secrete IL-17A, IL-17F and IL-22, which stimulate keratinocyte proliferation and the release of proinflammatory cytokines, antimicrobial peptides and chemokines. Th1 and Th17 cells can directly interact with monocytes by producing GM-CSF, TNF-α and IFN-γ and instruct these cells to differentiate into specialized moDC subsets. Figure is modified from Ref. 7. Reproduced with permission from John Wiley & Sons, Inc. All rights reserved.
Abbreviations: moDC, monocyte-derived dendritic cell; GM-CSF, granulocyte/macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LL37, cathelicidin antimicrobial peptide; NK, natural killer; pDC, plasmacytoid dendritic cell; ssRNA, singlestranded RNA; Th, T-helper; TNF, tumour necrosis factor.

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References

[1] Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361:496–509.
[2] Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. Nat Rev Immunol 2009;9:679–91.
[3] Nestle FO, Conrad C, Tun-Kyi A, Homey B, Gombert M, Boyman O, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med 2005;202:135–43.
[4] Yao Y, Richman L, Morehouse C, de los RM, Higgs BW, Boutrin A, et al. Type I interferon: potential therapeutic target for psoriasis? PLoS One 2008;3:e2737.
[5] Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, Pierson KC, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. J Invest Dermatol 2009;129:79–88.
[6] Santini SM, Lapenta C, Santodonato L, D'Agostino G, Belardelli F, Ferrantini M. IFN-alpha in the generation of dendritic cells for cancer immunotherapy. Handb Exp Pharmacol 2009:295–317.
[7] Farkas A, Kemeny L. Interferon-alpha in the generation of monocyte-derived dendritic cells: recent advances and implications for dermatology. Br J Dermatol 2011;165:247–54.
[8] Ginhoux F, Tacke F, Angeli V, Bogunovic M, Loubeau M, Dai XM, et al. Langerhans cells arise from monocytes in vivo. Nat Immunol 2006;7:265–73.
[9] Mann A, Breuhahn K, Schirmacher P, Blessing M. Keratinocyte-derived granulocyte-macrophage colony stimulating factor accelerates wound healing: Stimulation of keratinocyte proliferation, granulation tissue formation, and vascularization. J Invest Dermatol 2001;117:1382–90.
[10] Conti L, Gessani S. GM-CSF in the generation of dendritic cells from human blood monocyte precursors: recent advances. Immunobiology 2008;213:859–70.
[11] Szabo G, Dolganiuc A. The role of plasmacytoid dendritic cell-derived IFN alpha in antiviral immunity. Crit Rev Immunol 2008;28:61–94.
[12] Farkas A, Tonel G, Nestle FO. Interferon-alpha and viral triggers promote functional maturation of human monocyte-derived dendritic cells. Br J Dermatol 2008;158:921–9.
[13] Ganguly D, Chamilos G, Lande R, Gregorio J, Meller S, Facchinetti V, et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. J Exp Med 2009;206:1983–94.
[14] Mohty M, Vialle-Castellano A, Nunes JA, Isnardon D, Olive D, Gaugler B. IFN-alpha skews monocyte differentiation into Toll-like receptor 7-expressing dendritic cells with potent functional activities. J Immunol 2003;171:3385–93.
[15] Korthals M, Safaian N, Kronenwett R, Maihofer D, Schott M, Papewalis C, et al. Monocyte derived dendritic cells generated by IFN-alpha acquire mature dendritic and

natural killer cell properties as shown by gene expression analysis. J Transl Med 2007;5:46.
[16] Papewalis C, Jacobs B, Wuttke M, Ullrich E, Baehring T, Fenk R, et al. IFN-alpha skews monocytes into CD56+-expressing dendritic cells with potent functional activities in vitro and in vivo. J Immunol 2008;180:1462–70.
[17] Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature 2007;449:564–9.
[18] Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. Nat Immunol 2002;3:196–200.
[19] Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, et al. Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science 2004;303:1526–9.
[20] Santini SM, Lapenta C, Donati S, Spadaro F, Belardelli F, Ferrantini M. Interferon-alpha-conditioned human monocytes combine a Th1-orienting attitude with the induction of autologous Th17 responses: role of IL-23 and IL-12. PLoS One 2011;6:e17364.
[21] Alonso MN, Wong MT, Zhang AL, Winer D, Suhoski MM, Tolentino LL, et al. TH1, TH2, and TH17 cells instruct monocytes to differentiate into specialized dendritic cell subsets. Blood 2011;118:3311–20.
[22] Kattah MG, Wong MT, Yocum MD, Utz PJ. Cytokines secreted in response to Toll-like receptor ligand stimulation modulate differentiation of human Th17 cells. Arthritis Rheum 2008;58:1619–29.
[23] Volpe E, Servant N, Zollinger R, Bogiatzi SI, Hupe P, Barillot E, et al. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat Immunol 2008;9:650–7.
[24] Trinchieri G. Type I interferon: friend or foe? J Exp Med 2010;207:2053–63.
[25] Gerlini G, Mariotti G, Chiarugi A, Di Gennaro P, Caporale R, Parenti A, et al. Induction of CD83+CD14+ nondendritic antigen-presenting cells by exposure of monocytes to IFN-alpha. J Immunol 2008;181:2999–3008.
[26] Vermi W, Fisogni S, Salogni L, Scharer L, Kutzner H, Sozzani S, et al. Spontaneous regression of highly immunogenic *Molluscum contagiosum* virus (MCV)-induced skin lesions is associated with plasmacytoid dendritic cells and IFN-DC infiltration. J Invest Dermatol 2011;131:426–34.
[27] Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J. Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. Science 2001;294:1540–3.
[28] Zhang Z, Maurer K, Perin JC, Song L, Sullivan KE. Cytokine-induced monocyte characteristics in SLE. J Biomed Biotechnol 2010;2010:507475.
[29] Zhang AL, Colmenero P, Purath U, Teixeira de Matos C, Hueber W, Klareskog L, et al. Natural killer cells trigger differentiation of monocytes into dendritic cells. Blood 2007;110:2484–93.
[30] Wirths S, Reichert J, Grunebach F, Brossart P. Activated CD8+ T lymphocytes induce differentiation of monocytes to dendritic cells and restore the stimulatory capacity of interleukin 10-treated antigen-presenting cells. Cancer Res 2002;62:5065–8.
[31] Hegde S, Chen X, Keaton JM, Reddington F, Besra GS, Gumperz JE. NKT cells direct monocytes into a DC differentiation pathway. J Leukoc Biol 2007;81:1224–35.