Allergology International 66 (2017) 392–397

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Roles of alternatively activated M2 macrophages in allergic contact dermatitis

Kotaro Suzuki [a, *], Kazuyuki Meguro [a], Daiki Nakagomi [b], Hiroshi Nakajima [a]

[a] Department of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan
[b] Department of Third Internal Medicine, University of Yamanashi, Yamanashi, Japan

ARTICLE INFO

Article history:
Received 25 January 2017
Received in revised form
11 February 2017
Accepted 14 February 2017
Available online 18 March 2017

Keywords:
Contact hypersensitivity
mannose receptor
MMP12
M2 macrophages
SOCS3

Abbreviations:
BM, bone marrow; CHS, contact hypersensitivity; DNFB, 2,4-dinitrofluorobenzene; GO, Gene Ontology; LPS, lipopolysaccharide; MerTK, Mer receptor tyrosine kinase; MMP12, matrix metalloproteinase 12; MR, mannose receptor; SOCS3, suppressor of cytokine signaling-3; TLR, toll-like receptor; VEGF, vascular endothelial growth factor

ABSTRACT

Alternatively activated macrophages (M2 macrophages) play key roles in the suppression of Th1 cell responses and the orchestration of tissue repair. However, recent studies have shown that M2 macrophages have potentials to produce high levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, suggesting that M2 macrophages may exacerbate inflammation in some settings. In this regard, we have recently shown that large numbers of M2 macrophages accumulate in the sites of hapten-induced contact hypersensitivity (CHS), an animal model of allergic contact dermatitis, and that M2 macrophages exacerbate hapten-induced CHS by producing matrix metalloproteinase 12 (MMP12). We have also shown that suppressor of cytokine signaling-3 (SOCS3), a member of SOCS family proteins that are cytokine-inducible negative regulators of the JAK/STAT signaling pathways, is highly and preferentially expressed in M2 macrophages in hapten-induced CHS and that SOCS3 expressed in M2 macrophages is involved in the attenuation of CHS by suppressing MMP12 production. These findings underscore the importance of M2 macrophage-derived MMP12 in the development of CHS, and suggest that inhibition of M2 macrophages or MMP12 could be a potential therapeutic strategy for the treatment of allergic contact dermatitis.

Introduction

Allergic contact dermatitis, one of the most prevalent skin diseases, is caused by delayed-type hypersensitivity reactions to foreign substances or hapten-modified proteins.[1] The agents are frequently included in latex materials, protective equipment, soap and cleansers, and resins. A large number of studies using contact hypersensitivity (CHS), which is induced by epicutaneous exposure of haptens in sensitized mice, revealed detailed immunological mechanisms underlying allergic contact dermatitis.[2–4] In addition, recent studies on CHS have revealed that new subsets of $CD4^+$ T cells, such as $Foxp3^+$ regulatory T cells and Th17 cells, are also involved in the regulation of allergic contact dermatitis.[2–4] Moreover, the identification of langerin-positive dermal dendritic cells has questioned the relevance of epidermal Langerhans cells as key antigen-presenting cells in allergic contact dermatitis.[2–4] Furthermore, we have recently shown that M2 macrophages, which are believed to be involved in tissue repair, are involved in the induction of CHS. In this review, we will summarize recent advance which changes some key dogmas of allergic contact dermatitis and also introduce our findings regarding a novel role of M2 macrophages in CHS.

Immunological mechanisms underlying contact hypersensitivity

CHS is composed of two phases; sensitization phase and elicitation phase. During the sensitization phase of CHS, keratinocytes are activated upon hapten application and produce various

* Corresponding author. Department of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuou-Ku, Chiba City, Chiba 260-8670, Japan.
E-mail address: suzuki_k@faculty.chiba-u.jp (K. Suzuki).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2017.02.015

chemical mediators such as IL-1β, TNF-α, and prostaglandin E2, leading to the induction of migration and maturation/activation of skin dendritic cells and Langerhans cells, both of which are believed to play crucial roles in antigen presentation in the sensitization phase of CHS.[5] As a general concept of the process of antigen presentation in the sensitization phase of CHS, when hapten-modified proteins are loaded onto Langerhans cells and dendritic cells, they migrate from the epidermis to the regional draining lymph nodes, where priming of antigen-specific $CD4^+$ T cells and $CD8^+$ T cells occurs.[3,6] Although it is apparent that antigen-presenting cells are necessary for sensitization, however, the process of the antigen presentation has not been fully understood. For example, it remains unclear whether Langerhans cells have a regulatory role or a stimulatory role in the sensitization, and which subtype of dendritic cells plays a dominant role in the sensitization in CHS.[4]

During the elicitation phase of CHS, hapten skin painting reactivates skin-resident cells such as keratinocytes, Langerhans cells, and skin dendritic cells. Keratinocytes are thought to be the important source of chemokines as the activated keratinocytes produce multiple chemokines, such as CXCL1, CXCL2, CXCL9, CXCL10, CCL8, CCL17, and CCL27. Among these chemokines, CXCL10, a ligand for CXCR3 that is highly expressed on Th1 cells, has been shown to play an important role in the infiltration of antigen-specific T cells into the skin.[4,7,8] Infiltrated T cells are activated by skin antigen-presenting cells and produce cytokines including IFN-γ and IL-17 at the site. The cytokines produced by activated T cells stimulate skin-resident cells and lead to further infiltration of T cells, resulting in the amplification of the inflammatory responses.

Many studies have shown that both $CD4^+$ T cells and $CD8^+$ T cells play multiple roles in inflammatory responses in the elicitation phase of CHS. It is well recognized that $CD4^+$ T helper cells are subdivided into at least three subsets; Th1 cells characterized by the secretion of IFN-γ, Th2 cells characterized by the secretion of IL-4, IL-5, and IL-13, and Th17 cells characterized by the secretion of IL-17A, IL-17F, and IL-22. $CD8^+$ T cells are also subdivided into at least three subsets; Tc1 cells characterized by the secretion of IFN-γ, Tc2 cells characterized by the secretion of IL-4, and Tc17 cells characterized by the secretion of IL-17A.[9] In the elicitation phase of CHS, $CD8^+$ T cells mainly play proinflammatory roles, whereas $CD4^+$ T cells play both proinflammatory and anti-inflammatory roles, depending on their producing cytokines.[4] When Th1 cells and Tc1 cells infiltrate into the skin lesion during the elicitation phase of CHS, they release proinflammatory cytokines including IFN-γ. Consistent with the accumulation of Th1 cells and Tc1 cells and the high levels of IFN-γ expression at the inflammatory sites of CHS,[4,10] studies using IFN-γ-deficient mice or IFN-γ receptor-deficient mice have revealed that IFN-γ plays an important role in the induction of CHS. In this regard, IFN-γ has been shown to trigger resident myeloid and non-myeloid cells to secrete chemokines such as CXCL2 and CCL2 that further induce the recruitment of various mononuclear cells including monocytes.[11] While the importance of Th1 cells and Tc1 cells for the induction of CHS is apparent, contributions of other Th/Tc subset in the elicitation phase of CHS may differ depending on experimental models, because each hapten has its own properties regarding the activation of Th/Tc cell subsets.[4]

Macrophage polarization and plasticity

During the last decade, phenotypic heterogeneity and plasticity of macrophages has been intensively investigated. Macrophages are essential components of innate immunity and play a critical role in primary responses to pathogens, inflammation, and tissue repair.[12,13] Circulating monocytes differentiate into macrophages after their migration to tissues and then macrophages acquire distinct characteristics in response to environmental factors including cytokines in the tissues. The phenotypic diversity of macrophages can be assessed by the expression of several surface markers and by their secretome. The concept of classically activated macrophages (M1 macrophages) was established in the 1980's,[14] and some time later, alternatively activated macrophages (M2 macrophages) were discovered.[15] To date, roles of M1 macrophages and M2 macrophages have been extensively investigated in both physiological and pathological conditions in several experimental systems.[14]

Th1 cytokines such as IFN-γ, proinflammatory cytokines such as TNF-α, and microbial products such as lipopolysaccharide (LPS), alone or in combination, promote M1 macrophage differentiation (Table 1). M1 macrophages play important roles in the exacerbation of the inflammation caused by proinflammatory cytokines such as IL-1β, IL-6, IL-12, IL-17A, IL-23, and TNF-α. M1 macrophages also produce toxic agents such as reactive nitrogen and oxygen intermediates which eradicate bacterial, fungal, and viral infections.[12] In addition, M1 macrophages secrete chemokines such as CXCL5, CXCL9, and CXCL10 which promote the recruitment of Th1 cells and NK cells, facilitating the killing of intracellular pathogens. While these activities of M1 macrophages are beneficial for preventing infection, a chronic activation of M1 macrophages can cause tissue damage and impair wound healing.

As the opposite side of the macrophage spectrum, M2 macrophages counteract the inflammatory responses sustained by M1 macrophages. The differentiation of M2 macrophages is promoted by Th2 cytokines such as IL-4 and IL-13 (Table 1). It is generally believed that M2 macrophages play key roles in the suppression of Th1 cell responses and tissue repair, and exhibit phagocytic, pro-angiogenic, and pro-fibrotic capacities.[13,16,17] Several in vitro studies have led to an extended classification with subdivision into four sub-groups: M2a, M2b, M2c, and M2d. The differentiation of M2a macrophages is promoted by IL-4 and IL-13. M2a macrophages express high levels of the mannose receptor (MR) and produce pro-fibrotic factors such as fibronectin, insulin growth factor, and TGF-β, which lead to the tissue repair.[18] The differentiation of M2b macrophages is induced by combined exposure to immune complexes and Toll-like receptor ligands or IL-1 receptor agonists. M2b

Table 1
Characteristics of activated macrophages.

Subtype	Markers	Inducer	Product	Function
M1	CCR7, CD86, CD127, MHCII, iNOS, TLR4	IFN-γ, LPS, bacteria, GM-CSF, HMGB1	TNF-α, IL-1β, NO, IL-6, IL-12, IL-23, CCL1, CCL5, CXCL10	Proinflammatory function, tissue damage, pathogen clearance
M2a	CD206 (MR), CD209, Fizz1, Ym1/2, RELMα, arginase-1, ST2, dectin-1	IL-4, IL-13, M-CSF, helminth	CCL2, CCL17, CCL18, IGF-1	Allergic inflammation, tissue repair
M2c	CD163, CD206 (MR), Fizz1, Ym1/2, arginase-1, SRA-1, MerTK	IL-10, TGF-β, glucocorticoid	IL-10, TGF-β, CCL8, CCL17, MMP9, VEGF	Anti-inflammatory function, tissue remodeling, fibrosis

Because the information on Mb and Md is limited, they do not appear in this Table.
MR, mannose receptor; RELMα, resistin-like molecule α; HMGB1, high-mobility group box 1; SRA-1, scavenger receptor 1; IGF-1, insulin-like growth factor-1; MerTK, Mer receptor tyrosine kinase.