Dendritic cell migration in inflammation and immunity

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INTRODUCTION

Dendritic cells (DCs) play crucial roles not only in initiating protective immunity against invading pathogens but also in inducing immune tolerance toward harmless antigens. The well-coordinated functions of DCs in inflammation and immunity depend on their proper migration to specific destinations. To achieve this, DCs have evolved a complex and dynamic regulatory network involving multiple levels of cellular and molecular interactions for the precise control of DC migration under various immunological or inflammatory conditions [1]. Distinct DC subsets have different mobilization capacities and consequently exert different immunological functions [2]. In particular, CCR7-dependent DC migration from peripheral tissues to lymphoid tissues is essential for host defense against pathogens and immune tolerance of harmless self- or nonself-antigens [3]. CCR7 ligation in DCs induces complicated intracellular signaling pathways involving PI3K/AKT, MAPK/NF-κB, HIF-1α, and IRFs, which feedback to regulate the migratory ability and inflammatory response of DCs. Moreover, multiple intracellular mechanisms, such as protein modification, epigenetic reprogramming, metabolic remodeling, and cytoskeletal rearrangement, play potent roles in determining the stability and activity of migratory signaling in DCs. These regulatory networks cooperatively ensure the efficient and effective migration of DCs under homeostatic or inflammatory conditions, leading to a balance between DC-dependent immunity and tolerance. In this review, we discuss the routes and consequences of DC subset migration across different tissues. In addition, we highlight the key migratory signaling of DCs with a summary of underlying regulatory mechanisms. Furthermore, we provide an overview of the pathogenetic effects of dysregulated DC migration in inflammation-related diseases.

DC MIGRATION ROUTES AND IMMUNOLOGICAL FUNCTIONS

DCs represent a complicated heterogeneous population of antigen-presenting cells with significant phenotypic heterogeneity and functional plasticity [4]. The precursors of conventional dendritic cells (pre-cDCs), plasmacytoid DCs (pDCs) and monocytes originate from the bone marrow and migrate to lymphoid tissues such as lymph nodes and spleen and nonlymphoid tissues such as skin, lung, and intestines via blood circulation [5]. In peripheral tissues such as the skin, pre-cDCs and monocytes differentiate into immature cDCs and monocyte-derived DCs (moDCs), respectively, and localize in the dermis. Langerhans cells (LCs) are a specialized macrophage-DC hybrid population originating from embryonic progenitors and are localized in the epidermis [6]. These distinct DC subsets follow distinct migratory routes and display different migratory properties and consequently exert variable immunological and inflammatory functions (Fig. 1).

Conventional DCs

As the major DC types, conventional DCs (cDCs) are characterized by classical dendritic morphology and high expression of MHC class II molecules and are widespread in tissues and lymph nodes. Immature cDCs act as sentinels of the immune system and are responsible for recognition of a wide range of danger signals
Dendritic cells can be divided into various subpopulations with significant phenotypic heterogeneity and functional plasticity. The major DC subsets, including conventional DCs (cDCs), monocyte-derived DCs (moDCs), plasmacytoid DCs (pDCs) and Langerhans cells (LCs), follow distinct migratory routes and exhibit different migratory properties and consequently exert various immunological and inflammatory functions. (1) Preconventional dendritic cells (pre-cDCs) give rise to immature cDCs (cDC1s and cDC2s), which undergo maturation and express high levels of CCR7 upon stimulation by pathogenic or inflammatory signals. CCR7 interacts with its ligands CCL19 and CCL21 to guide mature cDC trafficking toward lymph nodes via afferent lymphatics to regulate T-cell immunity. Semimature cDCs also express CCR7 under steady-state conditions and migrate to lymph nodes to induce the activation of regulatory T cells and maintenance of immune tolerance against self-antigens or inhaled and food antigens. cDC1s potently cross-prime CD8+ T cells for viral clearance and activation of the Th1/Th17 response to protect against bacteria. CCR7 and CCR8 mediate cDC2 trafficking to the lymph node parenchyma to initiate a Th2 cell-dependent allergic immune response. (2) Blood Ly6Chi monocytes are recruited to inflamed skin or lymphoid tissues via CCR2 and become monocyte-derived DCs (moDCs), which stimulate Th1 or Th2 responses, contributing to local inflammation. CX3CR1hiLy6Clo moDCs at the lamina propria migrate toward lymph nodes via CCR7 ligation during colon inflammation. (3) Plasmacytoid DC (pDC) recruitment from the blood to the lymph nodes or the small intestine is regulated by CCR7 and CCR9, respectively. CCR2 and CXCR3 are also important for the trafficking and distribution of pDCs. After CCR7-mediated extravasation into lymphoid tissues, pDCs are instructed to express CCR6 and CCR10, which mediate their migration to nonabdominal lymph nodes. (4) LCs are localized in the epidermis and efficiently migrate to skin-draining lymph nodes following inflammatory stimulation in a manner dependent on CCR7 and CXCR4. LCs not only induce T-cell activation during skin inflammation but also mediate the inhibition of T-cell function and the induction of regulatory T cells.

**Fig. 1** DC migration in the regulation of immune defense and homeostasis. Dendritic cells can be divided into various subpopulations with significant phenotypic heterogeneity and functional plasticity. The major DC subsets, including conventional DCs (cDCs), monocyte-derived DCs (moDCs), plasmacytoid DCs (pDCs) and Langerhans cells (LCs), follow distinct migratory routes and exhibit different migratory properties and consequently exert various immunological and inflammatory functions. (1) Preconventional dendritic cells (pre-cDCs) give rise to immature cDCs (cDC1s and cDC2s), which undergo maturation and express high levels of CCR7 upon stimulation by pathogenic or inflammatory signals. CCR7 interacts with its ligands CCL19 and CCL21 to guide mature cDC trafficking toward lymph nodes via afferent lymphatics to regulate T-cell immunity. Semimature cDCs also express CCR7 under steady-state conditions and migrate to lymph nodes to induce the activation of regulatory T cells and maintenance of immune tolerance against self-antigens or inhaled and food antigens. cDC1s potently cross-prime CD8+ T cells for viral clearance and activation of the Th1/Th17 response to protect against bacteria. CCR7 and CCR8 mediate cDC2 trafficking to the lymph node parenchyma to initiate a Th2 cell-dependent allergic immune response. (2) Blood Ly6Chi monocytes are recruited to inflamed skin or lymphoid tissues via CCR2 and become monocyte-derived DCs (moDCs), which stimulate Th1 or Th2 responses, contributing to local inflammation. CX3CR1hiLy6Clo moDCs at the lamina propria migrate toward lymph nodes via CCR7 ligation during colon inflammation. (3) Plasmacytoid DC (pDC) recruitment from the blood to the lymph nodes or the small intestine is regulated by CCR7 and CCR9, respectively. CCR2 and CXCR3 are also important for the trafficking and distribution of pDCs. After CCR7-mediated extravasation into lymphoid tissues, pDCs are instructed to express CCR6 and CCR10, which mediate their migration to inflamed skin for IFN-α production and facilitate pathogen clearance and local inflammation. (4) LCs are localized in the epidermis and efficiently migrate to skin-draining lymph nodes following inflammatory stimulation in a manner dependent on CCR7 and CXCR4. LCs not only induce T-cell activation during skin inflammation but also mediate the inhibition of T-cell function and the induction of regulatory T cells.
and developmentally depend on the transcription factors IRF8 and Batf3. cDC2s are a heterogeneous group expressing the surface marker CD11b (but not XCR1) and are developmentally dependent on the transcription factor IRF4. While cDC1s are capable of inducing CD8 T-cell activation and Th1 and Th17 skewing, cDC2s potently induce Th2 and Th17 skewing (Fig. 1) [1]. The Th2-skewing cDC2 subset is further dependent on the transcription factor KLF4, while the Th17-skewing cDC2 subset (which can also express CD103) does not require KLF4 [21]. Although both cDC1s and cDC2s are capable of capturing antigens and migrating to draining lymph nodes for the initiation of adaptive immune responses, they differ in their responsiveness to migratory and inflammatory signals in the microenvironment and their capacity to induce T-cell activation or regulation.

Lung CD103+ cDCs transport influenza viral antigens to the lymph nodes for efficient cross-presentation of CD8 T cells, which is critical for viral clearance [22, 23], as well as induction of Th1/Th17 responses and protection against pulmonary *Chlamydia muridarum* infection [24]. CD8α DC expression of the lectin family member Siglec-G can functionally inhibit DC cross-presentation to antigen-specific CTLs by impairing formation of the MHC class I-peptide complex [25]. During influenza infection, cDC1s can promote S1PR expression on cytotoxic T lymphocytes (CTLs) to facilitate CTL migration toward lymph nodes and express high levels of IL-15 to support CTL survival and activity at the site of infection [26]. Skin CD103+ cDCs are important for the cross-presentation of self- and nonself-antigens to CD8 T cells and efficiently promote CTL responses against keratinocyte-derived antigens or viruses [27, 28]. Interestingly, uterine CD103+ DC subsets have been shown to induce a tolerogenic response of Foxp3+ CD25+ Treg cells upon *Chlamydia trachomatis* infection [29].

cDC2s express lower levels of CCR7 after allergen exposure and are capable of equally upregulating CCR7 in response to PAMP exposure. Various additional signals have been found to initiate or support cDC2 migration toward lymph nodes. Chemokine signals mediated by CCR8 and its ligand CCL8 from macrophages can mediate CD301b− DC trafficking to the lymph node parenchyma to initiate a Th2 cell-dependent allergic immune response [30]. Colony-stimulating factor 1 (CSF1) secreted from airway epithelial cells selectively upregulates CCR7 expression in CSF1R+ cDC2s, contributing to Th2 cell-mediated allergic lung inflammation [31]. Inhibition of the CSF1-CSF1R signaling pathway has been shown to effectively block cDC2 migration and allergen sensitization and consequently abolish chronic allergic lung inflammation in a murine model of chronic asthma, suggesting CSF1/CSF1R as a promising new target for the treatment of allergic asthma [32]. In addition, substance P, a type of neuropeptide produced by allergen-activated sensory neurons, induces CD301b− cDC2 migration to the lymph nodes to prime Th2 cell differentiation, indicating an interesting link between allergen-induced acute activation of the sensory nervous system and chronic allergic inflammation [33].

**Monocyte-derived DCs**

Monocyte-derived DCs (moDCs) represent an inflammatory DC subpopulation induced by various inflammatory stimuli and exist in various lymph nodes and tissues. Blood Ly6C+ monocytes are recruited to the inflamed skin via CCR2 to become monocyte-derived DCs (moDCs), which are capable of activating protective Th1 responses at the site of infection [34]. Although skin moDCs are able to migrate to the auricular lymph nodes in a CCR7-dependent manner upon DNF8-induced skin inflammation, their migratory capacity is very poor compared to that of dermal CD11b+ cDCs [35]. Similarly, despite producing proinflammatory chemokines and mediating Th2 cell immunity to house dust mite allergens in the lung, CD11b+ moDCs are the least prevalent DC population among migratory DCs within the mediastinal lymph nodes, indicating that lung moDCs are also poorly migratory [36]. In the inflamed colon, Ly6C+ monocytes are recruited to the lamina propria via CCR2 and gradually differentiate into CX3C1R+Ly6C+ moDCs with the capacity for antigen capture, presentation and T-cell priming, which express CCR7 for egression from the colonic lamina propria toward the mesenteric lymph nodes, contributing to colonic inflammation [37]. Therefore, inflammatory blood-derived moDCs play important roles in mediating various types of tissue inflammation by producing inflammatory cytokines and stimulating T-cell activation, but their capacity for subsequent emigration toward lymph nodes is regulated differently.

Notably, inflammatory monocytes can be recruited into lymph nodes directly from the blood via CCR2 to become CD11c+CD11b+Gr-1+ inflammatory DCs, which potently activate Th1 responses by producing IL-12p70 [38]. CXCL10-producing inflammatory monocytes infiltrate the interfolllicular regions (IFRs) of lymph nodes from blood following incomplete Freund’s adjuvant (IFA)-containing immunization and promote Th1-skewed niche development in the lymph nodes [39]. In addition, gram-negative bacterial stimulation or LPS can stimulate moDC migration from blood and accumulation in lymph nodes, and these moDCs show antigen cross-presentation activity and migrate to T-cell areas via L-selection and CCR7 [40]. Thus, it will be intriguing to delineate the specific functions and activities of tissue-derived moDCs and blood-derived moDCs in shaping immune responses in the lymph nodes. One recent study suggests that cDC2s may acquire the IRF8 features of cDC1s and the Fc receptor CD64 feature of MoDCs and contribute to the antigen processing function of MoDCs during inflammation. It will be necessary to carefully clarify the potential overlap in markers and functions among cDC1s, cDC2s, and MoDCs under homeostatic and inflammatory conditions [41].

**Plasmacytoid DCs**

Plasmacytoid DCs (pDCs) are potent producers of type I interferons and are important for the host antiviral immune response. pDCs are commonly distributed in peripheral blood and lymphoid organs and have unique migratory properties. The recruitment of pDCs from the blood to the lymph nodes via high endothelial venules is regulated by CCR7 [42], ChemR23 [43], CXCR3 [44, 45], L-selectin, and E-selectin [46]. pDCs also constitutively migrate into the splenic white pulp in a manner dependent on the chemokine receptors CCR7 and CXCR4 [47]. Notably, after CCR7-mediated extravasation into lymphoid tissues, pDCs are induced to express CCR6 and CCR10, which further mediate their migration to inflamed skin in response to CCL20 and CCL27/CCL28, respectively. CCR6-dependent pDC homing to the epithelium contributes to the production of IFN-α and facilitates pathogen clearance and local inflammation [48]. CpG-triggered migration of pDCs from the skin to the draining lymph node via the lymphatics has been observed in pigs and sheep, yet the corresponding chemokine receptors involved in this process and their immunological consequences remain to be identified [49].

CCR9 is required for pDC homing from blood to the small intestine under homeostatic and inflammatory conditions. CCR9-dependent accumulation of intestinal pDCs consequently promotes lamina propria DC mobilization [50, 51]. In addition, pDCs express mucosal addressin cell-adhesion molecule-1 (MADCAM-1) and β7 integrin, which ensures the efficient migration of pDCs into the intestinal intraepithelial compartment [52]. Interestingly, the microbiota enhances homoeostatic trafficking and peripheral distribution of CCR2+ pDCs by inducing homeostatic levels of the chemokine CCL2 produced by mononuclear phagocytes [53]. Therefore, a complex network of chemokines, adhesive molecules, microbiota, immune and nonimmune cells cooperatively regulates pDC trafficking and distribution to orchestrate intestinal homeostasis and inflammation.
Langerhans cells
Langerhans cells (LCs) exhibit mixtures of characteristics from macrophages (self-replenishment) and DCs (migration and T-cell stimulation). LCs are mainly localized in the epidermis and quickly migrate to skin-draining lymph nodes following inflammatory stimulation in a manner dependent on CCR7 [54]. After arriving at the draining lymph nodes, LCs not only induce immune activation but also mediate the inhibition of T-cell function and the induction of regulatory T cells in a context-dependent manner. A recent study on natural CXCR4 mutants harboring a gain of function that causes warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome, a rare immunodeficiency associated with high susceptibility to the pathogenesis of human papillomavirus (HPV), indicated that proper CXCR4 signaling directs efficient migration of both LCs and DCs from skin to lymph nodes and determines their activation state. Therefore, targeting CXCR4-dependent LC and DC migration could be considered a potential therapeutic strategy for CXCR4-associated diseases such as WHIM syndrome [55].

TRANSDUCTION OF DC MIGRATION
While the innate immune signal triggered by PRRs such as Toll-like receptors (TLRs) and Nod-like receptors (NLRs), which recognize a wide variety of pathogenic components, or nuclear acid sensors such as RIG-I-like receptors (RLRs) and cyclic GMP-AMP (cGAMP) synthetase (cGAS), which detect self- or non-self-nucleic acids, has been intensively investigated for its downstream pathways and functional roles in inflammatory activation [56], chemokine receptor-induced intracellular signaling is less well understood. The most important chemotactic response for DC migration is mediated by CCR7, a G protein-coupled receptor that recognizes the chemokine ligands CCL19 and CCL21. CCL21 is constitutively expressed by lymphoid endothelial cells and is essential for guiding DCs to the lymph nodes. Two mouse genes encode functional CCL21 variants, CCL21-Ser and CCL21-Leu. CCL21-Ser is expressed in both secondary lymphoid organs and lymphatics, whereas CCL21-Leu is expressed only in the lymphatic vessels of nonlymphoid organs. Thus, CCL21 isoforms are present in peripheral tissues to promote DC entry into draining lymphatics. CCL19 is expressed by stromal cells within the secondary lymphoid organs but not by lymphatics [57, 58]. Although CCL19 and CCL21 have similar binding affinities for CCR7, CCL19 is more potent in recruiting β-arrestin and inducing clathrin-dependent desensitization and endocytosis of CCR7 into endosomes [59]. Preferential DC migration toward CCL21 over CCL19 was observed in a 3D environment, probably due to a stronger binding affinity to extracellular matrix proteoglycans by the positively charged C terminus of CCL21 [60, 61]. It remains unclear how CCR7 differentially recognizes chemotactic signals from CCL19 or CCL21 and how these different molecular events regulate downstream signal transduction and DC-driven immune responses.

Complex signaling pathways involving PI3K/AKT, MAPK/NF-κB, HIF-1α, and IRFs have been shown to be activated by CCR7 and play regulatory feedback roles in DC migration in a context-dependent manner. As DC migration is closely related to other aspects of DC biology, such as maturation and activation, both spatially and temporally, the crosstalk among distinct signaling pathways initiated by PRRs or chemokine receptors is essential for a coordinated inflammatory and migratory response during the development of immunity and tolerance.

Phosphoinositide 3-kinase/AKT kinase pathway
Phosphoinositide 3-kinase (PI3K) exerts widespread functions in modulating variable aspects of immune cell development and chemotaxis, which is critical for the orchestration of cellular responses and immune homeostasis. CCR7 stimulation induces significant activation of PI3K and its downstream effector Akt [62–64]. CCR7 also induces antiapoptotic signaling in mature DCs via the PI3K/AKT and NF-κB pathways [62]. Interestingly, Fas ligation induces the production of CXC and CC chemokines by DCs via the ERK pathway, resulting in enhanced chemoattraction of neutrophils and T cells, implying the nonapoptotic function of Fas in immune cell chemotaxis [65]. The PI3K family consists of three main groups of enzymes (classes I, II, and III) that are characterized on the basis of their substrate phosphoinositides [66]. Mice deficient in the γ isoform (class Iγ) of PI3K display severely impaired DC migration in response to the chemokines CCL3, CCL5, and CCL19 and an attenuated response during contact hypersensitivity and delayed-type hypersensitivity reactions to both FITC and DNBC [67]. In lymphocytes, class IA PI3Ks are important in regulating basal lymphocyte motility, and p85 regulatory subunit expression is required for B cell morphological control of PI3K catalytic function [68]. Thus, the contributions of distinct PI3K members to cell chemotaxis and migration are regulated in a cell-type-selective manner.

The actin-bundling protein palladin was shown to be an Akt1-specific substrate that modulates breast cancer cell invasive migration [69]. However, the molecular targets of PI3K/AKT in the regulation of immune cell migration remain elusive. In addition, PI3K/AKT signaling influences intracellular metabolic events via multiple pathways, for example, by activating sterol-regulatory element-binding proteins (SREBPs), essential transcriptional regulators of lipid metabolism [70], and by activating AS160, the key enzyme regulating glucose uptake [71]. Whether the interaction between PI3K/AKT signaling and metabolism conversion affects DC migration and the consequent immune responses remains to be unveiled.

Mitogen-activated protein kinase/nuclear factor-κB pathway
The mitogen-activated protein kinase (MAPK)/nuclear factor-κB (NF-κB) pathway is critical for TLR-induced DC maturation and activation via the induction of a series of inflammatory cytokines, such as IL-1, IL-6, and TNF. The activation of MAPK/NF-κB signaling is tightly controlled by multiple intrinsic negative regulators, such as the ubiquitin-editing enzyme A20, the E3 ligase ARIH2, and the Romboid protease RHBD3, to avoid aberrant systemic inflammation [72, 73]. CCR7 stimulation leads to β-arrestin recruitment and MAPK activation, which are important for DC chemotaxis and activation [74, 75]. CCL19 and CCL21 not only drive the migratory capacity of DCs but also enhance the T-cell-stimulating function of mature DCs via upregulation of the costimulatory molecules CD86 and CD40 and promotion of the production of proinflammatory cytokines such as IL-1β, TNF, and IL-12 [76]. CCR7 ligands have also been shown to increase the antigen uptake of mature DCs by activating the Rho guanosine triphosphatases Rho, Rac, and Cdc42 [77]. However, canonical NF-κB target genes, such as Il1b, Il1a, Il6, Il12b, and Trnfsl1a, are suppressed in migratory cDCs, indicating context-specific networks of NF-κB-regulated genes during DC maturation and migration [78]. Therefore, MAPK/NF-κB pathway activation during DC migration is strictly dependent on complex molecular networks involving upstream signaling regulators and downstream-specific gene networks, as well as their interacting transcriptional coactivators or corepressors.

NF-κB-dependent inflammatory signaling feedback regulates CCR7-mediated DC migration via several mechanisms. DCs upregulate the expression of MHC-II, costimulatory molecules, and CCR7 on the cell surface and enhance their migratory ability during LPS/MAPK/NF-κB pathway-induced maturation [79]. Full induction of CCR7 is dependent on immediate activation of the IKK/NF-κB cascade and a secondary AP-1 response [80]. Mice deficient in IKKβ, an upstream regulator of NF-κB, display impairment in homeostatic DC migration and spontaneous development of autoimmune diseases, indicating a role of the noncanonical IKKβ-dependent pathway of NF-κB signaling in the regulation of homeostatic DC migration and the maintenance of...
immune tolerance [78]. This effect has been thought to depend on the putative NF-κB-regulated gene Fscn1, which positively regulates the migration of mature DCs into lymph nodes by enhancing membrane protrusive activity and podosome disassembly [81]. In addition, complete or DC-specific deletion of MyD88, an essential adaptor protein of TLR- and TNF-triggered signaling, results in a reduction in the steady-state migration of CD103+ DCs into draining mesenteric lymph nodes. MyD88-dependent steady-state DC migration is independent of inflammatory cytokines such as IL-18 and TNF but is required for optimal CCR9 induction and CD62L downregulation in T cells [82]. Thus, MyD88/NF-κB activation is unexpectedly involved in steady-state DC migration and the maintenance of immune tolerance, and the underlying mechanisms remain to be investigated.

We previously demonstrated that TLR4 ligation by LPS promotes CT-26 colon cancer cells to produce the chemokine CCL20 and increases the chemotraction of immature DCs via autocrine CCL20 [83]. Cyclosporin A, a powerful immunosuppressive drug, impairs DC migration from the skin to secondary lymphoid organs by regulating chemokine receptor expression and inhibiting cyclooxygenase-2 (COX-2) expression via inhibition of MAPK/NF-κB signaling pathways [84]. Similarly, triptolide, an active component of the Chinese herb Tripterygium wilfordii, impairs CCL19-mediated DC migration toward secondary lymphoid organs by inhibiting CCR7 and COX-2 expression by targeting the PI3K/Akt and NF-κB pathways, providing a potential mechanistic explanation for the anti-inflammatory activities of triptolide [85]. Triptolide also impairs DC-mediated chemotraction of neutrophils and T cells by suppressing DC production of CC and CXC chemokines, including MIP-1α, MIP-1β, MCP-1, and RANTES, in response to LPS through inhibition of Stat3 phosphorylation and NF-κB activation [86]. These findings highlight the importance of modulating the NF-κB pathway to affect DC migration in antitumor immune therapy. The more detailed function of NF-κB and its context-specific target genes in the regulation of CCR7-dependent DC migration under inflammatory conditions or within tumor microenvironments remain to be investigated.

**Hypoxia inducible factor 1-alpha**

Hypoxia inducible factor 1-alpha (HIF-1α) is a central transcription factor controlling cell responses to hypoxic stress and plays essential roles in various aspects of innate and adaptive immune responses [87, 88]. Hypoxia plays important roles in innate immunity both under steady-state (physiologic hypoxia) and during active inflammation (inflammatory hypoxia) and contributes fundamentally to inflammatory and immune responses [89]. HIF-1α has been increasingly shown to support DC migration and function via various mechanisms [90, 91]. Hypoxia-generated DCs show increased migratory ability, which is dependent on HIF-1α, as evidenced by the reduced migration to CCL19 of HIF-1α-deficient DCs compared with wild-type DCs under hypoxic conditions [92]. DCs generated under hypoxia display a distinguishable migratory phenotype, including enhanced mRNA expression of the chemokine receptors CCR3, CX3CR1 and CCR2 and decreased mRNA expression of chemokines such as CCL18, CCL23, CCL26, CCL24, and CCL14, and functionally demonstrate a stronger chemotactic response to CCR2 and CXCR4 agonists [93]. Deletion of HIF-1α in myeloid cells results in impaired inflammatory responses during induced arthritis, in association with defective macrophage aggregation, invasion and motility, as well as severely impaired glycolysis and energy generation [94]. Our recent study determined that CCR7 stimulation enhances the expression of the HIF-1α-dependent glycolytic gene LDHA and the production of glycolytic NAD+, the feedback of which supports DC migration by maintaining F-actin polarization and polymerization [95]. Therefore, HIF-1α serves as a key regulator of DC migration and inflammation by coordinating intracellular glycolytic reprogramming and cytoskeletal rearrangement.

**IFN regulatory factors**

Several IFN regulatory factor (IRF) proteins have been shown to regulate DC migration, such as IRF4 and IRF8. IRF4 and IRF8 are expressed in CD11b+ and CD11b− DC subsets separately and are required for the generation of the respective DC subsets [96–98]. IRF4-deficient mice show reduced CCR7 expression and defective migration of dermal CD11b+ DCs to cutaneous lymph nodes both under homeostasis and during skin inflammation, suggesting a crucial role of IRF4 in supporting the migration of dermal CD11b+ DCs [99]. IRF4 is also required for the survival of intestinal CD103+CD11b+ DCs, which drive Th17 cell differentiation by secreting IL-6 [100, 101]. Interestingly, higher levels of IL-12 production, increased IFN-γ-producing Th1 cells and enhanced effective clearance of parasites after infection with L. major were observed in DC-specific IRF4-deficient mice, suggesting an inhibitory role of IRF4 in regulating IL-12 production of DCs and Th1-induced immune responses against parasites [102]. IRF4 and IRF8 have been found to directly target and activate the genes encoding CD80, CD86 and CCR7 in migratory DCs, and IRF4 preferentially activates genes that encode proteins related to MHC class II antigen presentation [103]. Notably, given the role of IRFs as lineage-defining transcription factors, it is difficult to separate their roles in DC migration versus development. It is intriguing to further explore the molecular mechanisms underlying the distinctive activity of different IRFs in the regulation of DC migration and development.

**MOLECULAR REGULATION OF DC MIGRATION**

To ensure the most beneficial outcome of DC migration in immunity and tolerance, multiple levels of intracellular regulators are employed to modulate the signaling pathways induced by chemokine/chemokine receptor interactions. These regulatory networks occur at the transcriptional or translational level to regulate the adhesive or chemotactic ability of DCs, contributing to the fine-tuned control of DC-dependent inflammation and immunity (Fig. 2).

**Protein modification**

Conventional posttranslational modifications (PTMs), such as phosphorylation and ubiquitination, are essential for CCR7-dependent signal transduction. CCL19 and CCL21 stimulation induces the phosphorylation of CCR7 [75], β-arrestin [104], MAPK/ERK, p38 and JNK [105] successively, which is crucial for DC chemotaxis and migration. Oligomerization of CCR7 induced by the inflammatory mediator prostaglandin E2 (PGE2) and phosphorylation of oligomeric CCR7 by Src are necessary for the migration of DCs and T cells [106]. Internalized CCR7 recycles back to the plasma membrane to replenish the cell surface with fresh CCR7 for chemokine sensing [107, 108]. The β-arrestin-mediated internalization of CCR7 into endosomes triggers an endomembrane signaling complex involving Vav1 and Rac1, leading to lamellipodia formation and sustained DC migration [109]. In addition, polyadenylation of CCR7 is essential for recognition of CCL21 and therefore controls CCR7-mediated DC migration. Mice deficient in the polyadenyltransferase 5'8SIA4 show disrupted immune homeostasis due to an abrogated DC migration ability. Mechanistically, recognition of polysialic acid by the C terminus of CCL21 releases CCL21 from self-inhibition, thus facilitating CCR7 coupling with CCL21 [110]. It will be intriguing to investigate whether other types of PTMs, such as methylation, acetylation, SUMOylation and succinylation, which potently regulate PRR-dependent innate immune signaling [111], also participate in the regulation of migratory signaling triggered by CCR7 or other chemokine receptors.

**Epigenetic reprogramming**

Epigenetic factors such as DNA methylation changes, histone modifications and noncoding RNAs play potent roles in the
Development and activation of innate immune cells via transcriptional regulation of gene expression [112, 113]. Significant differences in the repressive H3K27me3 (trimethylation of histone 3 lysine 27) levels at the CCR7 gene locus were observed between migratory cDCs and nonmigratory moDCs, indicating the involvement of epigenetic modifications in determining the migratory capacity of distinct DC subsets [114]. The lysine methyltransferase SET domain bifurcated 2 (Setdb2), which is upregulated upon viral infection, induces H3K9me3 (a repressive marker) at the Cxcl1 gene promoter, leading to reduced neutrophil infiltration and inhibited host defense against bacterial superinfection. SIRT6 promotes CXC4+ DC migration to the afferent lymph nodes via its effects on monitoring H3K9 acetylation. Ezh2 directly mediates methylation of the cytoplasmic integrin adaptor talin, disrupting the binding of talin to F-actin, thereby promoting the extravasation and motility of DCs under inflammatory conditions. The long-noncoding RNA Inc-Dpl3 directly binds to the transcription factor HIF-1α and suppresses HIF-1α-dependent transcription of the glycolytic gene Ldha, thus inhibiting DC glycolytic metabolism and migratory capacity. (3) Metabolic remodeling (shown in green boxes and arrows). Glycolytic metabolism is essential for CCR7 oligomerization and DC migration, and glycolytic NAD+ supports DC migration by maintaining F-actin polarization and polymerization. Resolvin E1 inhibits DC motility and migration and attenuates the contact hypersensitivity response by disrupting actin polymerization. (4) Cytoskeleton rearrangement (shown in dark red boxes and arrows). Actin polymerization and retrograde flow at the front and actinomyosin contraction at the rear determine cell polarity and provide the driving forces of DC migration. The phosphoinositide transferase protein TIE2 plays dual roles in signaling regulation by inhibiting Rac-dependent actin polymerization at the rear but enhancing PI3K-dependent actin polymerization at the front, thus facilitating cytoskeleton remodeling and leading-edge formation. The ion channel TRPML1 (transient receptor potential cation channel, mucolipin subfamily, member 1) is activated for lysosomal calcium release, leading to rearrangement of the actin-based motor protein myosin II at the cell rear, promoting fast and directional migration.

**Fig. 2 Molecular regulation of DC migration.** Multiple levels of intracellular regulators are employed to modulate the signaling pathways induced by chemokines to ensure the most beneficial outcome of DC migration in the regulation of immunity and tolerance. (1) Protein modification (shown in yellow boxes and arrows). CCL19 and CCL21 stimulation induces the phosphorylation of CCR7, β-arrestin, MAPK/ERK, p38 and JNK successively, which is crucial for DC chemotaxis and migration. Polysialylation of CCR7 is essential for recognition of its ligand CCL21 and therefore controls CCR7-mediated DC migration. (2) Epigenetic reprogramming (shown in blue boxes and arrows). Migratory cDCs and nonmigratory moDCs show different levels of H3K27me3 modifications at the CCR7 gene locus. Setdb2 induces the generation of H3K9me3 (a repressive marker) at the Cxcl1 gene promoter, leading to reduced neutrophil infiltration and inhibited host defense against bacterial superinfection. SIRT6 promotes CXCR4+ DC migration to the afferent lymph nodes via its effects on monitoring H3K9 acetylation. Ezh2 directly mediates methylation of the cytoplasmic integrin adaptor talin, disrupting the binding of talin to F-actin, thereby promoting the extravasation and motility of DCs under inflammatory conditions. The long-noncoding RNA Inc-Dpl3 directly binds to the transcription factor HIF-1α and suppresses HIF-1α-dependent transcription of the glycolytic gene Ldha, thus inhibiting DC glycolytic metabolism and migratory capacity. (3) Metabolic remodeling (shown in green boxes and arrows). Glycolytic metabolism is essential for CCR7 oligomerization and DC migration, and glycolytic NAD+ supports DC migration by maintaining F-actin polarization and polymerization. Resolvin E1 inhibits DC motility and migration and attenuates the contact hypersensitivity response by disrupting actin polymerization. (4) Cytoskeleton rearrangement (shown in dark red boxes and arrows). Actin polymerization and retrograde flow at the front and actinomyosin contraction at the rear determine cell polarity and provide the driving forces of DC migration. The phosphoinositide transferase protein TIE2 plays dual roles in signaling regulation by inhibiting Rac-dependent actin polymerization at the rear but enhancing PI3K-dependent actin polymerization at the front, thus facilitating cytoskeleton remodeling and leading-edge formation. The ion channel TRPML1 (transient receptor potential cation channel, mucolipin subfamily, member 1) is activated for lysosomal calcium release, leading to rearrangement of the actin-based motor protein myosin II at the cell rear, promoting fast and directional migration.
immunity, timely termination of DC trafficking is equally important for the prevention of unwanted inflammatory damage. Our recent study identified a new IncRNA, Inc-Dpf3, as a feedback inhibitor of DC migration and the inflammatory response. Mechanistically, Inc-Dpf3 directly binds to the transcription factor HIF-1α and suppresses HIF-1α-dependent transcription of the glycolytic gene Ldha, thus inhibiting DC glycolytic metabolism and migratory capacity [95]. Inc-Dpf3 bears N6-methyladenosine (m6A) modification for its degradation at steady-state, and CCR7 stimulation upregulates Inc-Dpf3 by relieving m6A-dependent RNA degradation. We also found that RNA methyltransferase Mett3-mediated m6A methylation promotes activation and cytokine production of DCs by enhancing CD40, CD80 and the TLR4 signaling adaptor Tirap and strengthening TLR4/NF-κB signaling [123]. These findings shed new light on the epigenetic regulation of DC migration and activation by noncoding RNAs and RNA modifications. Taken together, these findings show that epigenetic enzymes or regulators participate in the regulation of innate immune cell migration by targeting either histone or nonhistone substrates, leading to transcriptional or translational regulation of signal transduction and metabolic or cytoskeletal reprogramming.

Metabolic remodeling

A variety of metabolic enzymes, sensors or intermediates play potent roles in coordinating cellular immunological responses during inflammation and infection, leading to variable biological and pathological consequences [124]. DCs with different statuses or varied DC subsets demonstrate distinct metabolic characteristics that influence their inflammatory and immunological functions [125]. Mice deficient in ATP-binding cassette transporters A1 and G1 (Abca1/g1), the key enzyme mediating cholesterol efflux from immune cells, develop a systemic autoimmune phenotype including enlarged lymph nodes and glomerulonephritis. Abca1/g1 deletion resulted in increased splenic CD11b+ DCs (which displayed cholesterol accumulation, inflammasome activation and higher expression of the GM-CSF receptor, and enhanced inflammatory cytokine secretion) and consequently enhanced T-cell activation and polarization [126]. This study indicated the importance of DC cholesterol stability in maintaining DC-dependent immune homeostasis. In addition, mice deficient in apolipoprotein A-I (which are characterized by diminished circulating high-density lipoprotein) exhibited increased severity of antigen-induced arthritis in association with enhanced DC-dependent Th1 and Th17 autoimmune responses [127]. Profound changes in lipid composition and membrane fluidity occur during DC maturation, which likely influence the DC migration process and DC-T-cell interaction [128]. A lipid mediator derived from ω3 polyunsaturated fatty acids, resolvin E1, was shown to abrogate leukotriene B4-dependent activation of actin filament reorganization and Cdc42/Rac1-dependent DC motility, thus attenuating cutaneous acquired immune responses [129]. It will be intriguing to investigate whether other components of the lipid and cholesterol pathways affect the migratory ability of DCs.

TLR stimulation induces rapid glycolysis, which is required for anabolic demands of DC activation [130, 131]. Recent evidence indicates that glycolytic metabolism is essential for DC migration to draining lymph nodes because it maintains DC motility and CCR7 oligomerization [132]. While AKT, TBK, and mTOR are involved in the early induction of glycolysis, HIF-1α is required for the late phase of glycolysis. Glycolytic NAD⁺ supports DC migration by maintaining F-actin polarization and polymerization [95]. The respective contributions of the early and late phases of glycolysis to DC migration and function remain to be further identified.

Cytoskeleton rearrangement

The cytoskeleton is important for numerous cellular processes because it regulates cell morphology, structure, movement and function. Actin polymerization and retrograde flow at the front of the cell, as well as actinomyosin contraction at the rear of the cell jointly determine cell polarity and provide the driving forces of cell migration [133]. The small GTPase Cdc42 was shown to be required for DC migration by coordinating leading-edge formation [134]. The guanine nucleotide exchange factor Dock8 (dedicator of cytokinesis 8) is required for the ameboid migration of DCs because it activates small GTPase Cdc42 activators [135, 136]. Dock8-deficient mice exhibit reduced DC migration to skin-draining lymph nodes and impaired germinal center antibody production [137], outlining the importance of the cytoskeleton network in mediating DC migration and DC-dependent immune response. Moreover, the histone lysine N-methyltransferase enhancer of zeste homolog 2 (Ezh2) has been shown to directly mediate methylation of the cytoplasmic integrin adaptor talin, disrupting the binding of talin to F-actin and thereby promoting the extravasation and motility of DCs under inflammatory conditions [138]. In addition, TIPE2 (tumor necrosis factor-alpha-induced protein 8-like 2), a phosphoinositide transferase protein, contributes to leukocyte polarization and infiltration during experimental autoimmune encephalomyelitis (EAE) development. TIPE2 inhibits Rac-dependent actin polymerization at the rear but enhances PI3K-dependent actin polymerization at the front, thus facilitating cytoskeleton remodeling and leading-edge formation [139].

Rearrangement of cytoskeletal networks not only generates the locomotion force of DC chemotaxis and movement but also plays a regulatory role in DC functions, including antigen processing, inflammatory cytokine production and chemotactic migration [140]. Immature DC migration depends on two actin pools, a RhoA-mDia1-dependent actin pool located at the rear, which is important for forward locomotion, and a Cdc42-Arp2/3-dependent actin pool present at the front, which limits cell migration but promotes antigen capture. Upon LPS-induced DC maturation, Arp2/3-dependent actin enrichment at the cell front is markedly reduced, enabling faster and more persistent mDia1-dependent forward locomotion that facilitates chemotactic migration to lymph nodes [141]. In addition, upon bacterial sensing, the antigen micropinocytosis of DCs is decreased, and subsequently, the ion channel TRPM1 (transient receptor potential cation channel, mucolipin subfamily, member 1) is activated for lysosomal calcium release, leading to rearrangement of the actin-based motor protein myosin II at the cell rear, which promotes fast and directional migration [142]. Therefore, cytoskeletal networks are dynamically reorganized by various intracellular pathways to ensure the proper migration of DCs, in accordance with their maturation stages and functional properties.

DYSREGULATION OF DC MIGRATION IN IMMUNE DISEASES

Consistent with the essential role of DC migration in both initiating protective immunity and maintaining immune tolerance, dysregulated trafficking of DCs results in disturbance of immune homeostasis, manifested by delayed and inefficient priming of protective T-cell immune responses on the one hand but aberrant inflammatory activation due to impaired immune tolerance on the other hand, both of which lead to the immunopathogenesis of various inflammatory and autoimmune diseases. Here, we discuss the dysregulation of DC migration in immunological disorders and the pathogenesis of autoimmune diseases and infectious diseases, focusing on rheumatoid arthritis (RA) and coronavirus disease 2019 (COVID-19).

DC migration in rheumatoid arthritis

Various chemokines/receptors are closely related to the development of autoimmune diseases, such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel diseases (IBDs). Increased expression levels of DC-related chemokines and their receptors are detected in blood, synovial fluid, and synovial tissue in patients with RA, and some of
them serve as promising biomarkers of RA disease activity/severity [143]. Early-phase preclinical trials targeting the chemokine system for the treatment of RA have yielded promising results [144]. In particular, CCR7-mediated DC migration is essential for the development of collagen-induced arthritis (CIA), a mouse model of rheumatoid arthritis. Treatment with the immune modulator FTY720 significantly inhibited the incidence and severity of CIA by reducing CCL19 secretion and CCR7-based function in DCs [145]. Treatment of humanized CCR7 mice with an anti-human CCR7 mAb prevented the induction of CIA and inhibited CIA progression, suggesting a potential strategy for the clinical treatment of RA [146]. In addition, blocking matrix metalloproteinase-9 (MMP9) with a specific antibody significantly suppressed the development of CIA in mice by inhibiting CCR7-triggered DC trafficking [147]. These studies highlight CCR7 as a potential therapeutic target for autoimmune diseases such as RA.

DC migration in COVID-19

The COVID-19 pandemic caused by SARS-CoV-2 has led to >3 million deaths worldwide. Infection with SARS-CoV-2 induces the release of large amounts of DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns), which leads to profound production of inflammatory mediators, including IL-6 and IL-1β, plus chemokines, such as MCP-1 and MIP-1α, derived from monocytes and macrophages [148]. These inflammatory and chemotactic cytokines cooperatively recruit innate and adaptive cells from blood into the site of infection, resulting in amplified lung inflammation [149].

Despite strongly activated innate immunity and inflammatory responses, acute SARS-CoV-2 infection impairs DC function and antigen-specific T-cell responses [150] and dampens antiviral type I and type III interferon responses [151]. pDCs, cDC1s, and cDC2s all display decreased expression of CD80, CD86, CCR7 and HLA-DR after stimulation with TLR ligands in acute patients compared to healthy controls, indicating potentially reduced maturation and migration of DC subsets following acute SARS-CoV-2 infection [150]. The bronchoalveolar lavage fluid (BALF) of patients with severe/critical COVID-19 infection contains higher proportions of macrophages and neutrophils but lower proportions of mDCs, pDCs and T cells than the BALF of those with moderate infection [152]. Overall, impaired migration or antigen-presenting function of DCs likely results in a blunted T-cell response to eliminate invading SARS-CoV-2. It will be important to investigate the mechanisms by which SARS-CoV-2 infection impairs DC function to escape immune attack.

CONCLUSIONS AND PERSPECTIVES

Despite our increasing understanding of the immunological roles and molecular mechanisms of DC migration during inflammation and immunity, several intriguing and important aspects of this field remain elusive and are worthy of further investigation. DCs serve distinct immunological functions, including antigen sensing, antigen capture, inflammatory cytokine production, chemotactic migration, and T-cell priming and regulation. The overlap between the migratory processes of DCs and other aspects of DC function is critical to ensuring the most efficient and beneficial immunological outcome, but the underlying mechanisms are poorly understood. Furthermore, DC migration is influenced by multiple extracellular signals derived from the immune microenvironment, such as extracellular matrix and epithelial cells, as well as a complicated intracellular and intercellular network involving metabolic and epigenetic pathways. However, how DCs coordinate these signals to achieve proper and effective polarization and migration remains elusive. In addition, an increasing number of reports have shown that bidirectional interactions between DCs and neuronal cells play important roles in mediating neuroinflammatory responses in the context of infection and injury. However, how neuropeptides and neurotransmitters participate in the regulation of DC migration and, conversely, how the chemokine system in DCs modulates the pathogenesis of neurodegenerative diseases are worthy of further investigation. In summary, with the rapid development of single-cell technologies, single-molecule technologies, high-resolution in vivo imaging technologies and multimomics-based technologies, it will be possible to better elucidate the molecular events and pathways that regulate DC migration under various inflammatory and immunological processes and reveal novel therapeutic strategies targeting DC migration for related immune diseases.

REFERENCES

1. Worbs T, Hammerschmidt SI, Forster R. Dendritic cell migration in health and disease. Nat Rev Immunol. 2017;17:30–48.
2. Qian C, Cao X. Dendritic cells in the regulation of immunity and inflammation. Semin Immunol. 2018;35:3–11.
3. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat Immunol. 2015;16:643–53.
4. Steinman RM. Decisions about dendritic cells: past, present, and future. Annu Rev Immunol. 2012;30:1–22.
5. Randolph GJ, Ochando J, Partida-Sanchez J. Migration of dendritic cell subsets and their precursors. Annu Rev Immunol. 2008;26:293–316.
6. Kashem SW, Haniffa M, Kaplan DH. Antigen-Presenting Cells in the Skin. Annu Rev Immunol. 2017;35:469–99.
7. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010;140:805–20.
8. Förster R, Schubel A, Breitfeld D, Kremmer E, Renner-Müller I, Wolf E, et al. CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. Cell. 1999;99:23–33.
9. Jang MH, Sougawa N, Tanaka T, Hirata T, Hiroi T, Tohyama K, et al. CCR7 is critically important for migration of dendritic cells in intestinal lamina propria to mesenteric lymph nodes. J Immunol. 2006;176:803–10.
10. Gunn MD, Kyuwa S, Tam C, Kakiuchi T, Matsuzawa A, Williams LT, et al. Mice lacking expression of secondary lymphoid organ chemokine have defects in lymphocyte homing and dendritic cell localization. J Exp Med. 1999;189:451–60.
11. Ulvmar MH, Werth K, Braun A, Kelay P, Hub E, Eller K, et al. The atypical chemokine receptor CCLR1 shapes functional CCL21 gradients in lymph node. Nat Immunol. 2014;15:623–30.
12. Braun A, Worbs T, Moschovakis GL, Halle S, Hoffmann K, Bölter J, et al. Affercnt lymph-derived T cells and DCs use different chemokine receptor CCR7-dependent routes for entry into the lymph node and intranodal migration. Nat Immunol. 2011;12:879–87.
13. Ohl M, Mohaupt M, Czeloth N, Hintzen G, Kaward Z, Zwirner J, et al. CCR7 governs skin dendritic cell migration under inflammatory and steady-state conditions. Immunity. 2004;21:279–88.
14. Hintzen G, Ohl L, del Rio ML, Rodriguez-Barbosa JL, Pabst O, Kocks JR, et al. Induction of tolerance to innocuous inhaled antigen relies on a CCR7-dependent dendritic cell-mediated antigen transport to the bronchial lymph node. J Immunol. 2006;177:346–54.
15. Worbs T, Bode U, Yan S, Hoffmann MW, Hintzen G, Bernhardt G, et al. Oral tolerance originates in the intestinal immune system and relies on antigen carriage by dendritic cells. J Exp Med. 2006;203:519–27.
16. Davalos-Misliszt AC, Rieckenberg J, Willenzon S, Worbs T, Kremmer E, Bernhardt G, et al. Generalized multi-organ autoimmunity in CCR7-deficient mice. Eur J Immunol. 2007;37:613–22.
17. Kurobe H, Liu C, Ueno T, Saito F, Ohigashi I, Seach N, et al. CCR7-dependent cortex-to-medulla migration of positively selected thymocytes is essential for establishing central tolerance. Immunity. 2006;24:165–77.
18. Cao X, Zhang W, Wan T, He L, Chen T, Yuan Z, et al. Molecular cloning and characterization of a novel CXC chemokine macrophage inflammatory protein-2 gamma chemotaxactrant for human neutrophils and dendritic cells. J Immunol. 2000;165:2588–95.
19. Shellenberger TD, Wang M, Gajjati M, Jayakumar A, Strieeter RM, Burdick MD, et al. BRAK/CXCL14 is a potent inhibitor of angiogenesis and a chemotactic factor for immature dendritic cells. Cancer Res. 2004;64:8262–70.
20. Schaefer P, Willmann K, Ebert LM, Walz A, Moser B. Cutaneous CXCL14 targets blood precursors to epidermal niches for Langerhans cell differentiation. Immunity. 2005;23:331–42.
21. Lee J, Zhang J, Chung YJ, Kim JH, Kook CM, González-Navajas JM, et al. Inhibition of IRF4 in dendritic cells by PRR-independent and -dependent signals inhibit Th2 and promote Th17 responses. Elife 2020;9:e49416 (1–30).
37. Zigmond E, Varol C, Farache J, Elmaliah E, Satpathy AT, Friedlander G, et al. Ly6C
34. Leon B, Lopez-Bravo M, Ardavin C. Monocyte-derived dendritic cells formed at
36. Plantinga M, Guilliams M, Vanheerswynghels M, Deswarte K, Branco-Madeira F,
35. Tamoutounour S, Guilliams M, Montanana Sanchis F, Liu H, Terhorst D, Malosse
33. Perner C, Flayer CH, Zhu X, Aderhold PA, Dewan Z, Voisin T, et al. Substance P
45. Krug A, Uppaluri R, Facchetti F, Dorner BG, Sheehan KC, Schreiber RD, et al. IFN-
30. Sokol CL, Camire RB, Jones MC, Luster AD. The chemokine receptor CCR8 pro-
29. Stary G, Olive A, Radovic-Moreno AF, Gondek D, Alvarez D, Basto PA, et al.
44. Vanbervliet B, Bendriss-Vermare N, Massacrier C, Homey B, de Bouteiller O,
28. Bedoui S, Whitney PG, Waithman J, Eidsmo L, Wakim L, Caminschi I, et al. Cross-
43. Vermi W, Riboldi E, Wittamer V, Gentili F, Luini W, Marrelli S, et al. Role of
27. Henri S, Poulin LF, Tamoutounour S, Ardouin L, Guilliams M, de Bovis B, et al.
42. Diacovo TG, Blasius AL, Mak TW, Cella M, Colonna M. Adhesive mechanisms
26. Ho AW, Prabhu N, Betts RJ, Ge MQ, Dai X, Hutchinson PE, et al. Lung CD103–
25. Ho AW, Prabhu N, Betts RJ, Ge MQ, Dai X, Hutchinson PE, et al. Lung CD103–
24. Lian J, Ozga AJ, Sokol CL, Luster AD. Targeting lymph node niches enhances
23. Bedoui S, Whitney PG, Waithman J, Eidsmo L, Wakim L, Caminschi I, et al. Cross-
22. Ho AW, Prabhu N, Betts RJ, Ge MQ, Dai X, Hutchinson PE, et al. Lung CD103+
21. Cao X. Self-regulation and cross-regulation of pattern-recognition receptor
20. Sokol CL, Camire RB, Jones MC, Luster AD. The chemokine receptor CCR8 pro-
19. Plantinga M, Guilliams M, Vanheerswynghels M, Deswarte K, Branco-Madeira F,
18. Sokol CL, Camire RB, Jones MC, Luster AD. The chemokine receptor CCR8 pro-
17. Henri S, Poulin LF, Tamoutounour S, Ardouin L, Guilliams M, de Bovis B, et al.
16. Plantinga M, Guilliams M, Vanheerswynghels M, Deswarte K, Branco-Madeira F,
15. Leon B, Lopez-Blanco M, Ardavin C. Monocyte-derived dendritic cells formed at
14. Moon HG, Kim SJ, Jeong JJ, Han SS, Jarjour NN, Lee H, et al. Airway epithelial
13. Perner C, Flayer CH, Zhu X, Aderhold PA, Dewan Z, Voisin T, et al. Substance P
12. Sokol CL, Camire RB, Jones MC, Luster AD. The chemokine receptor CCR8 pro-
11. Leon B, Lopez-Blanco M, Ardavin C. Monocyte-derived dendritic cells formed at
10. Moon HG, Kim SJ, Lee MK, Kang H, Choi HS, Harjith A, et al. Colony-stimulating
9. Moon HG, Kim SJ, Lee MK, Kang H, Choi HS, Harjith A, et al. Colony-stimulating
8. Sokol CL, Camire RB, Jones MC, Luster AD. The chemokine receptor CCR8 pro-
7. Henri S, Poulin LF, Tamoutounour S, Ardouin L, Guilliams M, de Bovis B, et al.
6. Plantinga M, Guilliams M, Vanheerswynghels M, Deswarte K, Branco-Madeira F,
5. Tamoutounour S, Guilliams M, Montanaña Sanchís F, Liu H, Terhorst D, Malosse
4. Leon B, Lopez-Blanco M, Ardavin C. Monocyte-derived dendritic cells formed at
3. Moon HG, Kim SJ, Jeong JJ, Han SS, Jarjour NN, Lee H, et al. Airway epithelial
cell-derived colony stimulating factor-1 promotes allergen sensitization. Immunity.
2. Sokol CL, Camire RB, Jones MC, Luster AD. The chemokine receptor CCR8 pro-
1. Moon HG, Kim SJ, Jeong JJ, Han SS, Jarjour NN, Lee H, et al. Airway epithelial
CCL21 in the presence of CXCL12 and
3. Mature dendritic cells respond to CXCR3 ligands in the presence of CXCL12 and
2. Immature dendritic cells efficiently transport influenza virus to the lymph node and
delivered colon cancer cells to lymphoid organs and in
2. Immature dendritic cells efficiently transport influenza virus to the lymph node and
1. Immature dendritic cells efficiently transport influenza virus to the lymph node and

J. Liu et al. et al. secrete inflammatory chemokines upon activation. J. Immunol. 2002;169:6079–83.
6. Diacovo TG, Blasius AL, Mak TW, Cella M, Colonna M. Adhesive mechanisms
governing interferon-producing cell recruitment into lymph nodes. J Exp Med.
5. 2002;202:687–96.
4. Umemoto E, Otani K, Ikeno T, Verjan Garcia N, Hayasaka H, Bai Z, et al. Con-
sultative presentation of microbial antigens triggers dendritic cell migration to the splenic white pulp which
1. Immature dendritic cells efficiently transport influenza virus to the lymph node and

Cellular & Molecular Immunology (2021) 18:2461 – 2471
SPRINGER NATURE
translocation and glucose-uptake in rat muscle cells. Cell Signal. 2008;20:2237–46.

72. Liu, J. Cao. Regulatory dendritic cells in autoimmunity: A comprehensive review. J Autoimmun. 2015;63:1–12.

73. Liu, J., Han C, Xie B, Wu Y, Liu S, Chen K, et al. Rbhdd3 controls autoimmunity by suppressing the production of IL-6 by dendritic cells via K27-linked ubiquiti- nation of the repressor NEMO. Nat Immunol. 2014;15:612–22.

74. Zidar DA, Violin JD, Whalen EJ, Leftkowitz RJ. Selective engagement of G protein coupled receptor kinases (GRKs) encodes distinct functions of biased ligands. Proc Natl Acad Sci USA. 2009;106:9649–54.

75. Kohout TA, Nicholas SL, Perry SJ, Reinhart G, Junger S, Strutters RS. Differential desensitization, receptor phosphorylation, beta-arrrestin recruitment, and ERK1/2 activation by the two endogenous ligands for the CC chemokine receptor 7. J Biol Chem. 2007;279:23124–22.

76. Marsland BJ, Bättig P, Bauer M, Ruedi C, Lässing U, Beerli RR, et al. CCL19 and CCL21 induce a potent proinflammatory differentiation program in licensed dendritic cells. Immunity. 2005;22:493–505.

77. Yanagawa Y, Ono K. CCR7 ligands induce rapid endocytosis in mature dendritic cells with concomitant up-regulation of Cdc42 and Rac activities. Blood. 2003;101:923–9.

78. Baratin M, Foray C, Demaria O, Habbeddine M, Pollet E, Maurizio J, et al. HIF1alpha is essential for myeloid cell-mediated glycolysis. Immunity. 2019;50:600–11.

79. Zidar DA, Violin JD, Whalen EJ, Leftkowitz RJ. Selective engagement of G protein coupled receptor kinases (GRKs) encodes distinct functions of biased ligands. Proc Natl Acad Sci USA. 2009;106:9649–54.

80. Suzuki S, Honma K, Matsuyama T, Suzuki K, Toriyama K, Akitoyo I, et al. Critical roles of interferon regulatory factor 4 in CD11bhighCD8alpha- dendritic cell function. Proc Natl Acad Sci USA. 2004;101:8981–6.

81. Tamura T, Tailor P, Yamaoka K, Hong JH, Tsuchimura H, O'Shea JI, et al. IFN regulatory factor-4 and -8 govern dendritic cell subset development and their functional diversity. J Immunol. 2005;174:2573–81.

82. Edelson BT, KC W, Juang R, Kohyama M, Benoît LA, Kleotkota PA, et al. Peripheral CD103+ dendritic cells form a unified subset developmentally related to CD103+ conventional dendritic cells. J Exp Med. 2010;207:823–36.

83. Bäuerle P, Roach K, Turner S, Paul J, Kovacs S, et al. IFN promotes cutaneous dendritic cell migration to lymph nodes during homeostasis and inflammation. J Immunol. 2012;189:3368–77.

84. Persson EK, Uronen-Hansson H, Semmrich M, Rivoller A, Hägerbrand K, Marsal J, et al. IRF4 transcription-factor-dependent CD103+ (CD11b+CD8α-) dendritic cells drive mucosal T helper 17 cell differentiation. Immunity. 2013;38:958–69.

85. Suzuki S, Honma K, Matsuyama T, Suzuki K, Toriyama K, Akitoyo I, et al. IRF4 transcription-factor-dependent CD11b+ dendritic cells in human and mouse control mucosal IL-17 cytokine responses. Immunity. 2013;38:970–83.

86. Akbarsi M, Homma K, Kimura D, Miyakoda M, Kimura K, Matsuyama T, et al. IRF4 in dendritic cells inhibits IL-12 production and controls Th1 immune responses against Leishmania major. J Immunol. 2014;192:2271–9.

87. Vander Lugt B, Khan AA, Hackney JA, Agrawal S, Lesch J, Zhou M, et al. Transcriptional programming of dendritic cells for enhanced MHC class II antigen presentation. Nat Commun. 2014;15:161–7.

88. Xiao K, Sun J, Kim J, Rajaogopal S, Zhai B, Villen J, et al. Global phosphorylation analysis of beta-arrestin-mediated signaling downstream of a seven transmembrane receptor (7TMR). Proc Natl Acad Sci USA. 2010;107:15299–304.

89. Eichel J, Jullie D, von Zastrov M. Beta-arrestin drives MAP kinase signaling via clathrin-coated structures after GPCR dissociation. Nat Cell Biol. 2016;18:3303–10.

90. Hauser MA, Schauebel K, Kindinger I, Impellizzieri D, Krueger WA, Hauck CR, et al. Inflammation-induced CCR7 oligomers form scaffolds to integrate distinct signaling pathways for efficient cell migration. Immunity. 2016;44:59–72.

91. Otero C, Groettrup M, Legler DF. Opposite fate of endocytosed CCR7 and its ligands: recycling versus degradation. J Immunol. 2006;177:2314–23.

92. Schauebel K, Hauser MA, Rippal AV, Bruderer R, Otero C, Groettrup M, et al. Ubiquitylation of the chemokine receptor CCR7 enables efficient receptor recycling and cell migration. J Cell Sci. 2012;125:4463–74.

93. Lauffer JM, Hauser MA, Kindinger I, Puruvanov V, Pauli A, Legler DF. Chemokine receptor CCR7 triggers an endomembrane signaling complex for spatial Rac activation. Cell Rep. 2019;29:1009–10.

94. Kiernar E, Moussin C, Veldkamp CT, Gerardy-Schahn R, de Vries I, Williams LG, et al. Polysialylation controls dendritic cell trafficking by regulating chemokine recognition. Science. 2016;351:186–90.

95. Liu J, Qian C, Cao X. Post-translational modification control of innate immunity. Immunity. 2016;45:15–30.

96. Alvarez-Enrico D, Vento-Tormo R, Sieweke M, Ballestar E. Epigenetic control of myeloid cell differentiation, identity and function. Nat Rev Immunol. 2015;15:7–17.

97. Zhang Q, Cao X. Epigenetic Remodeling in Innate Immunity and Inflammation. Annu Rev Immunol. 2021;39:279–311.

98. Moran TP, Nakano H, Kondili-Mangum HD, Wade PA, Cook DN. Epigenetic control of Cxcr7 expression in distinct lineages of lung dendritic cells. J Immunol. 2014;193:4904–10.

99. Schliehe C, Flynn EV, Vilagos B, Richson U, Swaminanthan S, Bosnjak B, et al. The myelotransferase Setdb2 mediates virus-induced susceptibility to bacterial superinfection. Nat Immunol. 2015;16:67–74.

100. Ferraga G, Benzi A, Sturla L, Marubbi D, Frumento D, Spinelli S, et al. Sirt6 inhibition delays the onset of experimental autoimmune encephalomyelitis by reducing dendritic cell migration. J Neuroinflammation. 2020;17:228.

101. Fang H, Wu Y, Huang X, Wang W, Ang B, Cao X, et al. Toll-like receptor 4 (TLR4) is essential for Hsp70-like protein 1 (HSP70L1) to activate dendritic cells and induce Th1 responses. J Biol Chem. 2011;286:30393–400.

102. Liu S, Li Y, Ling M, Jiang J, Song L, Liu J, et al. HSP70L1-mediated intracellular priming of dendritic cell vaccination induces more potent CTL response against cancer. Cell Mol Immunol. 2015;12:135–45.

103. Yi L, Li Z, Hu T, Liu J, Li N, Cao X, et al. Intracellular HSP70L1 inhibits human dendritic cell maturation by promoting suppressive H3K27me3 and H2AK119Ub1 histone modifications. Cell Mol Immunol. 2020;17:85–94.

104. Turner M, Galloway A, Vigorito E. Noncoding RNA and its associated proteins as regulating components of the HSC niche. Science. 2015;349:134–40.

105. Colgan SP, Furuta GT, Taylor CT. Hypoxia and Innate Immunity: keeping Up with the HIFisters. Annu Rev Immunol. 2020;38:341–63.

106. McCutcheon AF, O'Neill LAJ. The role of HIF in Immunity and Inflammation. Cell Metab. 2020;32:524–36.

107. Nizet V, Johnson RS. Interdependence of hypoxic and innate immune responses. Nat Rev Immunol. 2009;9:609–17.

108. Kohler T, Reizis B, Johnson RS, Wegh Haardt H, Forster I. Influence of hypoxia-inducible factor 1alpha on dendritic cell differentiation and migration. Eur J Immunol. 2012;42:1226–37.

109. Ricciardi A, Elia AR, Cappello P, Puppo M, Vanni C, Fardin P, et al. Transcriptome of hypoxic immature dendritic cells: modulation of chemokine/receptor expression. Mol Cancer Res. 2008;6:175–85.

110. Cramer T, Yamashii Y, Clausen BE, Förster I, Pawlinski R, Mackmann N, et al. HIF-1alpha is essential for myeloid cell-mediated inflammation. Cell. 2011;144:653–65.

111. Liu J, Zhang X, Chen K, Cheng Y, Liu S, Xia M, et al. CCR7 chemokine receptor-induced Inc-Dp3 restricts dendritic cell migration by inhibiting HIF-1alpha-mediated glycolysis. Immunity. 2019;50:600–15.

112. Suzuki S, Homma K, Matsuyama T, Suzuki K, Toriyama K, Akitoyo I, et al. Critical roles of interferon regulatory factor 4 in CD11bhighCD8α- dendritic cell development. Proc Natl Acad Sci USA. 2004;101:8981–6.
