

1 **Inflammatory dendritic cells in mouse and human**

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1

2 **Abstract**

3 Dendritic cells (DCs) are a heterogeneous population of professional antigen-presenting cells.  
4 Several murine DC subsets have been identified that differ in their phenotype and functional  
5 properties. In the steady state, DC precursors originating from the bone marrow give rise to  
6 lymphoid organ-resident DCs and to migratory tissue DCs. During inflammation, an  
7 additional DC subset has been described, the « inflammatory DCs » (infDCs), which  
8 differentiate from monocytes recruited to the site of inflammation. Here, we review recent  
9 work on the development and functions of murine infDCs. We also examine the criteria that  
10 define infDCs. Finally, we discuss the characterization of human infDCs and their potential  
11 role in inflammatory diseases.

1

2 Dendritic cells (DCs) are a heterogeneous population comprising several subsets that can be  
3 separated based on phenotypic markers. Murine steady-state DC subsets can be classified in  
4 two main categories: plasmacytoid DCs (pDCs) and conventional DCs (cDCs), which can be  
5 further divided into lymphoid organ-resident DCs (that remain in lymphoid organs during  
6 their entire life cycle) and migratory DCs (that are present in peripheral tissues and non-  
7 lymphoid organs and migrate to the draining lymph nodes). cDCs derive from a common pre-  
8 committed precursor, the pre-cDC, that is dependent on Fms-like tyrosine kinase 3-Ligand  
9 (Flt3L) [1] and share key functional properties, such as constitutive expression of MHC class  
10 II molecules, ability to process antigens and to stimulate naive T cells, as well as molecular  
11 signatures [2, 3].

12

### 13 **Definition of inflammatory DCs**

14 In mice, inflammatory DCs (infDCs) were initially identified as MHC II<sup>+</sup> CD11b<sup>+</sup> CD11c<sup>+</sup>  
15 F4/80<sup>+</sup> Ly6C<sup>+</sup> DCs that are absent from steady-state tissues and lymphoid organs, and  
16 differentiate from monocytes during inflammation [4]. InfDCs have since been described  
17 during pathogenic inflammation (cutaneous *Leishmania major* infection [4, 5], systemic  
18 *Listeria monocytogenes* infection [6-8], systemic *Trypanosoma brucei* infection [9, 10],  
19 fungal infections [11-13], genital *Herpes simplex virus-2* (HSV-2) infection [14], lung  
20 Influenza infection [8, 15, 16], lung *Streptococcus pneumoniae* infection [8], oral *Salmonella*  
21 *Typhimurium* infection [8], *Mycobacterium tuberculosis* lung infection [17] and  
22 mycobacterial granuloma [18]), experimental sterile inflammation [19-23] and in models of  
23 inflammatory diseases, such as allergic asthma [24, 25], colitis [26, 27], rheumatoid arthritis  
24 [28] and experimental autoimmune encephalomyelitis (EAE) [8, 29].

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1 The phenotypic description of infDCs has been completed by several studies: in addition to  
2 MHC II, CD11b, CD11c, F4/80, Ly6C [4], infDCs express CD206 [22], CD115/GM-CSFR  
3 [5, 8], Mac3 [8, 19], FcεRI [24] and CD64 [8, 25]. Because of the promiscuous expression of  
4 some of these markers on myeloid cell populations, infDCs are not always easily identified  
5 (Box1). FcεRI is probably the best marker to distinguish infDCs from macrophages and cDCs  
6 (Table1), and a recent study proposed combined FcεRI and CD64 staining as the best gating  
7 strategy to analyze infDCs in both tissues and lymphoid organs [25].

8

9 A cardinal feature of DCs, as opposed to macrophages, is their ability to migrate from tissues  
10 to lymph nodes. InfDCs have been identified in lymph nodes draining the sites of infection in  
11 several studies [4, 11, 15, 20, 23-25, 28]. This migration appears to be CCR7-dependent  
12 because infDCs in lymph nodes express CCR7 [4, 23, 25], and infDCs from alum-injected  
13 muscle [23] and allergen-loaded lung-derived DCs (including infDCs) in allergic asthma [25]  
14 were absent from the draining lymph nodes of *CCR7<sup>-/-</sup>* mice. Consistent with this, the infDCs  
15 that are found in the lymph nodes of *plt* mice (that do not express CCR7 ligands) have been  
16 proposed to derive from monocytes that enter directly from the blood rather than from  
17 lymphatics [21].

18 Finally, infDCs are characterized by their ability to activate T cells, a key property of DCs  
19 (see below). By contrast, macrophages purified from inflamed tissues can not activate  
20 antigen-specific T cells *ex vivo* in vaginal HSV-2 infection [14], in a model of EAE [29] or a  
21 model of allergen-induced asthma [25], although in the latest they were shown to capture the  
22 allergen very efficiently.

23

24 **Development of infDCs**

1 InfDCs were initially described to differentiate *in situ* from monocytes recruited to the sites of  
2 inflammation [4]. Several lines of evidence support a precursor-product relationship between  
3 monocytes and infDCs. *In vivo* transfer experiments have shown that injected monocytes  
4 differentiate into infDCs in different inflammation models [4, 8, 9, 11, 19, 20, 25-27, 30]. A  
5 similar conclusion was drawn using a reporter mouse expressing fluorescent CCR2 (a  
6 chemokine receptor expressed by monocytes and required for their migration), in which  
7 infDCs that express CCR2 appear during *Aspergillus fumigatus* infection [11]. In addition, in  
8 the absence of monocyte migration in CCR2<sup>-/-</sup> mice [5, 10-12, 14, 16, 21], infDC numbers are  
9 greatly reduced in inflamed tissues and draining lymph nodes. Consistent with this, infDCs  
10 are not affected in Flt3L<sup>-/-</sup> mice [25] whereas cDCs are dramatically reduced [1], suggesting  
11 that infDCs do not derive from pre-cDCs (Fig1).

12  
13 Although most DCs in the steady-state derive from pre-cDCs, some DC subpopulations, such  
14 as intestinal CD103<sup>-</sup>CD11b<sup>+</sup> DCs, originate from monocytes [31, 32]. Recent evidence,  
15 however, suggests that this population is heterogeneous and includes macrophages [33].  
16 Moreover, in addition to cDCs some monocyte-derived DCs are also found in skeletal muscle,  
17 but these cells do not migrate to the lymph nodes in the steady-state [23]. Therefore, only  
18 monocyte-derived DCs appearing during inflammation should be termed infDCs.

19  
20 Little is known about the factors that drive infDC differentiation. Because bone marrow  
21 monocytes cultured with GM-CSF differentiate into DCs that phenotypically resemble  
22 infDCs [34], GM-CSF was initially proposed to be involved in infDC development. In  
23 addition, infDCs were described in several GM-CSF-dependent inflammation models [19,  
24 28]. However, a recent study using GM-CSFR<sup>-/-</sup> bone marrow chimeras showed that GM-CSF  
25 was dispensable for infDCs development during pathogen-induced lung inflammation or

1 systemic inflammation [8]. By contrast, infDC numbers were reduced in the absence of M-  
2 CSFR [8]. These results do not exclude a role for GM-CSF in infDC maintenance or survival,  
3 especially during chronic inflammation. Although MyD88 and IFN $\gamma$  signaling are required for  
4 infDC activation [5, 7, 10, 20], it seems that they are not required for their actual  
5 differentiation from monocytes [5, 10]. No transcription factor has been described so far to be  
6 essential for infDC development from monocytes. Of note, the DC lineage-specific  
7 transcription factor *zbtb46* is expressed in *in vitro*-generated monocyte-derived DCs [33] and  
8 in *in vivo*-generated infDCs [30].

9

### 10 **infDCs and T cell activation**

11 Several studies demonstrated that infDCs can present antigens to CD4<sup>+</sup> T cells. InfDCs  
12 purified from lymphoid organs [4, 11, 15, 22-25] or tissues [14] can activate antigen-specific  
13 CD4<sup>+</sup> T cells *ex vivo*. Indirect evidence also suggests that infDCs can activate CD4<sup>+</sup> T cells *in*  
14 *vivo* in peripheral tissues [35]. In addition, CD4<sup>+</sup> T cell activation *in vivo* is abrogated during  
15 *Aspergillus fumigatus* infection in mice depleted of CCR2<sup>+</sup> cells [11] and strongly decreased  
16 in CCR2<sup>-/-</sup> but not in Flt3L<sup>-/-</sup> mice during allergen-induced asthma [25], indicating a dominant  
17 role for infDCs in CD4<sup>+</sup> T cell stimulation *in vivo* in these models.

18

19 In terms of T helper (Th) cell polarization, infDCs induce Th1 cell-mediated responses during  
20 CFA-induced inflammation [21] (a setting known to induce strong Th1 responses), and in  
21 *Leishmania major* or *Aspergillus fumigatus* infections [4, 11]. However, in the Th2 response-  
22 dominated experimental settings of alum-induced inflammation [20] or allergen-induced  
23 asthma [24, 25], infDCs induce Th2 cell-mediated responses. In addition, infDCs produce IL-  
24 12 [7, 21], IL-23 [25-27], type I interferon [6], inflammatory chemokines [25] or the pro-  
25 inflammatory cytokines IL-1 $\alpha$  and IL-1 $\beta$  [17] in different inflammatory environments.

1 Therefore, infDCs appear to be plastic and the type of T cell response that they induce  
2 depends on the inflammatory environment and type of infection.

3

4 InfDCs can also present exogenous antigens to CD8<sup>+</sup> T cells, a process known as cross-  
5 presentation. In a model of HSV-1 reactivation, the stimulation of antigen-specific memory  
6 CD8<sup>+</sup> T cells in the inflamed tissue is decreased when monocytes are depleted, indicating a  
7 role for infDCs [35]. In addition, purified infDC that have captured antigens *in vivo* are able  
8 to cross-present to CD8<sup>+</sup> T cells *ex vivo* [15, 16, 22, 23]. A recent study suggests that infDCs  
9 cross-present antigens *in vivo* during EAE, even if the infDC population analyzed may be  
10 heterogeneous [29]. Regarding the intracellular mechanisms involved, infDCs use both the  
11 cytosolic and vacuolar pathways for cross-presentation, in contrast to resident DCs that  
12 mainly use the cytosolic pathway [22].

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14 Several studies have addressed how infDCs fit in the DC network and cooperate with other  
15 DC subsets during immune responses. In some settings, infDCs play a major role in antigen  
16 uptake and transport to lymphoid organs where they can present antigens to T cells. In  
17 *Leishmania major* infection, infDCs are the main infected cells [4], and in *Aspergillus*  
18 *fumigatus* infection antigen transport to the draining lymph nodes is abrogated in CCR2<sup>+</sup>  
19 cells-depleted mice, indicating that infDCs are the main transporter of antigens [11]. This  
20 predominant role in antigen uptake might be due to differential expression of pathogen-uptake  
21 or pathogen-recognition receptors as compared to cDCs.

22

23 Other studies showed a role for infDCs in the stimulation of antigen-specific T cells directly  
24 in inflamed tissues. In a model of HSV-1 reactivation, infDCs initiate memory responses in  
25 the tissue via stimulation of CD4<sup>+</sup> and CD8<sup>+</sup> tissue-resident memory T cells [35]. In mucosal

1 HSV-2 infection, effector T cell stimulation in infected tissues is impaired in the absence of  
2 infDCs (in  $CCR2^{-/-}$  mice) while T cell priming in lymph nodes is unaffected [14]. In addition,  
3 infDCs directly purified from the central nervous system of mice with EAE display antigen-  
4 MHC II complexes on their surface, as evidenced by specific antibody staining [29]. InfDCs  
5 purified from peripheral inflamed tissues also stimulate antigen-specific T cells *ex vivo*,  
6 suggesting that they present antigenic peptide on their MHC molecules *in vivo* [14, 16, 25].  
7 Whether infDCs stimulate T cells in the tissues or in the lymph nodes might depend on the  
8 antigen dose and the degree of inflammation. Indeed, it was recently shown in allergen-  
9 induced asthma that infDCs can prime T cells in lymph nodes at high dose of allergen, but at  
10 low dose only stimulate T cells in the lungs [25].

11

## 12 **Human infDCs**

13 In humans, several DC subsets have also been identified, including lymphoid organ-resident  
14 and migratory DCs. "Inflammatory" DCs have been described in several pathological  
15 inflammatory situations: atopic dermatitis, psoriasis, rheumatoid arthritis and tumor ascites.  
16 "Inflammatory dendritic epidermal cells" (IDEC) were first described in the skin of atopic  
17 dermatitis patients [36]. These cells express surface markers different from Langerhans cells  
18 and dermal DCs from healthy skin. Recently, we identified infDCs in synovial fluid from  
19 arthritis patients and in tumor ascites, and showed by transcriptomic analysis that these cells  
20 represent a distinct DC subset [37]. A population of HLA-DR<sup>+</sup> CD11c<sup>+</sup> cells observed in the  
21 skin of psoriasis patients, but absent from healthy skin, was also proposed to represent  
22 "inflammatory dermal" DCs [38]. However, these cells were recently proposed to be similar  
23 to a population of blood CD16<sup>+</sup> cells expressing 6-sulfo LacNAc (slanDC) [39], which have  
24 been shown by transcriptomic and functional analysis to be a subset of CD16<sup>+</sup> monocytes  
25 rather than *bona fide* DCs [40]. In addition these "inflammatory dermal" cells resemble



1 dermal macrophages, in particular in the expression of phenotypic markers and inflammatory  
2 cytokines [41, 42]. Further studies are therefore required to clarify the identification of  
3 infDCs in psoriatic skin.

4 Human infDCs express HLA-DR, CD11c, BDCA1, CD1a, FcεRI, CD206, CD172a, CD14  
5 and CD11b [37, 43, 44]. Similar to murine infDCs, human infDCs also express M-CSFR and  
6 *ZBTB46* [37]. The ontogeny of human infDCs is difficult to address, even if transcriptomic  
7 analysis showed that infDCs from tumor ascites and *in vitro* GM-CSF-cultured monocyte-  
8 derived DCs share transcriptomic signatures [37], suggesting that human infDCs derive from  
9 monocytes rather than from DC precursors.

10 There is limited data on the functional properties of human infDCs. Atopic dermatitis is an  
11 inflammatory disease initiated by a Th2-type inflammation, with a chronic phase dominated  
12 by a Th1-type response [45]. Using *in vitro*-generated monocyte-derived DCs as a model of  
13 IDEC, it has been proposed that these cells could initiate Th1 cells differentiation [46].  
14 However, the T cell responses induced by naturally-occurring IDEC remains to be analyzed.  
15 By contrast, rheumatoid arthritis is a Th17-mediated disease [47] and infDCs from  
16 rheumatoid arthritis synovial fluid induce Th17 cell polarization *ex vivo* [37]. InfDCs from  
17 tumor ascites also induce Th17 responses *ex vivo* through the secretion of the Th17-polarizing  
18 cytokines TGFβ, IL1β, IL-6 and IL-23. Of note, only infDCs, but not macrophages from the  
19 same samples, secrete IL-23 [37]. Human infDCs are therefore likely to be monocyte-derived  
20 and very plastic, similar to their murine counterparts.

21

## 22 **Perspectives**

23 Recent work has shed new light on the development and functions of infDCs. Important  
24 questions, however, remain open for future investigation. Although the ontogeny of cDCs and

1 pDCs has been dissected in much detail in the past few years, we still do not know what  
2 factors drive infDC differentiation from monocytes. Recent studies have analyzed the  
3 molecular signatures of steady-state DC subsets and macrophages, but the identification of a  
4 molecular signature for infDCs is still lacking. This might open new avenues for the targeted  
5 depletion of infDCs in mouse, which would enable a more refined analysis of the function of  
6 infDCs in different pathological situations. With the identification of human infDCs that  
7 resemble their murine counterparts, infDCs could become targets of interest for  
8 immunotherapies in inflammatory diseases.

9

## 10 **Summary**

11 InfDCs are a distinct subset of DCs that appear during inflammation and derive from  
12 monocytes that differentiate *in situ* at the site of inflammation. InfDCs can migrate to the  
13 draining lymph nodes and activate CD4<sup>+</sup> and CD8<sup>+</sup> T cells. InfDCs have also been shown to  
14 stimulate effector or memory T cells directly in the inflamed tissue. Human equivalents of  
15 infDCs have been identified in several inflammatory diseases and in tumor ascites.

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**Box1. Cases of mistaken identity**

An early study described a population of monocyte-derived cells in *Listeria monocytogenes* infection that expressed CD11c and MHC II and were termed "Tip-DC" for TNF $\alpha$ /iNOS-producing DC [48]. In this study however, the T cell stimulatory activity of these cells was not analyzed. In subsequent studies, the term "Tip-DC" has sometimes been used to designate infDCs, and has generated some confusion. Indeed, production of iNOS and TNF $\alpha$  is also observed in monocytes and activated macrophages, populations that can both express low levels of CD11c and MHC II. It has been argue that "Tip-DC" are actually inflammatory monocytes [49] and it was recently shown that these "Tip-DC" in *Listeria*-infected mice did not express the DC-specific transcription factor *zbtb46* [33]. Because of overlapping phenotypic markers, other myeloid cells are sometimes mistaken for infDCs. For instance, DCs that are recruited to the skin-draining lymph nodes after LPS systemic injection were proposed to be infDCs [50], but later shown to be skin-derived migratory cDCs [51]. The reverse situation also occurs: skin DCs that appear after UV inflammation have been referred to as "inflammatory" Langerhans cells, but display characteristics that closely resemble that of infDCs [52].

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**Figure 1. Current model of DC ontogeny.** CMP = common myeloid precursor; MDP = monocyte/DC precursor; CDP = common DC progenitor. In the bone marrow, CMP give rise to MDP that differentiate into CDP and monocytes. Monocytes and the progeny of CDP (pDC and pre-cDC) circulate in the blood, through which they reach peripheral tissues and lymphoid organs. There, cDC undergo a final differentiation stage that generates CD11b-like DCs and CD8-like DCs. During inflammation, monocytes give rise to inflammatory DCs and macrophages. Resident macrophages are also present in peripheral tissues and lymphoid organs and are thought to originate from seeded embryonic precursors that renew locally.

**Table 1. Phenotype of murine infDCs as compared to other myeloid populations**

	CD8 lineage DC	CD11b lineage DC	pDC	infDC	Macrophage	Ly6C+ Monocyte
CD11b	-	+	-	+	+	+
Ly6C	-	-	++	+	+	++
CD206	-	- (resident) + (migratory)	-	+	+	-
FcεRI	-	-	-	+	-	-
CD64	-	-	-	+	++	+/-
CD11c	++	++	+	+	+/-	+/-
CD172a	-	+	-	+	+	+
F4/80	-	+	-	+	+	+

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