Antigen presentation by mouse monocyte-derived cells: Re-evaluating the concept of monocyte-derived dendritic cells

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Abstract

Antigen presentation is a key feature of classical dendritic cells (cDCs). Numerous studies have also reported in mouse that, upon inflammation, monocytes enter tissues and differentiate into monocyte-derived DCs (mo-DC) that have the ability to present antigens to T cells. However, a population of inflammatory cDCs sharing phenotypic features with mo-DC has been recently described, challenging the existence of in vivo-generated mo-DC. Here we review studies describing mouse mo-DC in the light of these findings, and evaluate the in vivo evidence for monocyte-derived antigen-presenting cells. We examine the strategies used to demonstrate the monocytic origin of these cells. Finally, we propose that mo-DC play a complementary role to cDCs, by presenting antigens to effector T cells locally in tissues.

Keywords

Dendritic cell, monocyte, monocyte-derived dendritic cell, antigen presentation, inflammation

1. Introduction

Characteristic features of dendritic cells (DCs) include their ability to present exogenous antigens on MHC molecules and to activate naive T cells. Numerous studies have shown that DCs can be separated into 3 main subsets based on their phenotype and molecular ontogeny: plasmacytoid DCs, type 1 classical DCs (cDC1) and type 2 classical DCs (cDC2) (Guilliams et al., 2014). All three subsets depend on the growth factor Fms-like tyrosine kinase 3-ligand (Flt3-L) and can be derived from a committed common DC precursor (CDP) (Naik et al., 2007). An additional population of antigen-presenting cells has been identified in mouse models of infection and sterile inflammation (Kool et al., 2008; León et al., 2007). These cells were demonstrated to originate from monocytes using adoptive cell transfer, and were termed monocyte-derived DCs (mo-DCs) owing to their DC-like ability to present antigens and to stimulate T cells. Mo-DCs, characterized by their expression of CD11b, Ly6C and/or CD64, were subsequently reported in other inflammatory contexts, as well as in steady-state mucosal tissues (Bonnardel et al., 2015; Tamoutounour et al., 2013) and peritoneal cavity (Goudot et al., 2017). Despite obvious methodological limitations, equivalent mo-DCs were also identified in human tissues (Coillard and Segura, 2019). However, recent findings showing that mouse cDC2 upregulate Ly6C and CD64 during inflammation (Bosteels et al., 2020; Min et al., 2018) have challenged the concept of monocyte-derived cells capable of antigen presentation.

In this review, we re-examine the published literature on mouse mo-DCs in light of these findings, and evaluate whether there is sufficient evidence to support the existence of bona fide antigen-presenting cells derived from monocytes.

2. Comparative features of mo-DCs and CD64^{+} cDC2

Mo-DCs have been described in peripheral tissues as well as in inflamed lymphoid organs. They are usually characterized by the surface expression of CD11c, MHCII, CD11b,

Ly6C, CD64, and have also been shown to express F4/80, CD115, CD206 and CCR2. Their monocytic origin has been documented using adoptive transfer of purified monocytes or depletion of monocytes using clodronate liposomes, which deplete monocytes and macrophages but not cDCs (Leenen et al., 1998). Using deficient mice or bone marrow chimeras, their differentiation was shown to require CCR2, a chemokine receptor essential for monocyte migration from the bone marrow (Serbina and Pamer, 2006; Tsou et al., 2007). Their ontogeny has also been indirectly addressed by showing their independence on Flt3-L.

'Inflammatory' cDC2 have been described in lung and lung-draining lymph nodes during inflammation, but are absent in the steady-state (Bosteels et al., 2020). They express surface molecules previously thought to be specific mo-DC markers such as Ly6C, CD64, MAR1 and CD209a. However, they do not express CCR2, CD115 or F4/80. They also upregulate IRF8, a transcription factor highly expressed in steady-state cDC1. This phenotype is induced in cDC2 by exposure to type I interferon. Their cDC identity has been demonstrated by adoptive transfer of pre-cDC and dependence on Flt3-L. Consistent with this, they express high amounts of *Zbtb46*, a transcription factor specifically expressed in cDCs (Meredith et al., 2012; Satpathy et al., 2012). Importantly, their presence in inflamed tissues, but not in lymphoid organs, was shown to be partially dependent on CCR2 in a mixed bone marrow experiment. Of note, $CD64^+$ cDCs have also been reported in steady-state kidney (Schraml et al., 2013). Kidney $CD64^+$ $MHCII^+$ $CD11b^+$ $F4/80^{low}$ cells display functional and transcriptomic similarities with cDC2 (Salei et al., 2020). Their cDC identity was demonstrated using genetic lineage tracing and adoptive transfer of CDP (Schraml et al., 2013), and dependence on Flt3-L (Guilliams et al., 2016).

Overall, these observations indicate that the phenotypic markers previously used to identify mo-DCs cannot distinguish them from $CD64^+$ cDC2. cDCs can be separated from monocyte-derived cells by the expression of CD26 (Bosteels et al., 2020; Guilliams et al., 2016), but this marker has not been extensively used so far. Because DC precursors

transiently express the monocyte genes CD115, CCR2 and CX3CR1, strategies based on these fluorescent reporters to track monocytes and their progeny can also be misleading if not carefully controlled, as peripheral cDCs display some level of fluorescence (Hohl et al., 2009; Jung et al., 2000; MacDonald et al., 2005; Satpathy et al., 2013). In addition, because both mo-DCs and $CD64^+$ DCs are decreased in the peripheral tissues of $CCR2^{-/-}$ mice, results obtained using this approach cannot be considered an absolute proof of monocyte origin. Therefore, we argue that, in the absence of CD26 staining, true mo-DCs can only be reliably identified in the published literature when their origin has been specifically probed, in particular using adoptive transfer or targeted depletion of monocytes.

3. Evidence for antigen presentation by in vivo-generated monocyte-derived cells

The initial observation that monocytes can differentiate into DC-like cells was made in a model of *Leishmania major* infection (León et al., 2007). Adoptive transfer of monocytes showed that they upregulate DC markers CD11c and MHCII upon entry into inflamed skin or lymph nodes. Two populations of $CD11b^+$ 'inflammatory' DCs were identified, $F4/80^{high}$ $Ly6C^{high}$ and $F4/80^-Ly6C^{int}$, likely corresponding to monocyte-derived cells and $CD64^+$ cDC2 respectively. Because both populations were pooled for antigen presentation experiments in this study, it is not possible to conclude whether monocyte-derived cells are indeed antigen-presenting cells.

Subsequently, a number of studies have analyzed antigen presentation by putative mo-DCs, but using strategies that we now know cannot separate them from contaminating cDC2 (Table). Conclusions from these studies will need to be confirmed with more appropriate methods to evaluate the respective contributions of mo-DCs and $CD64^+$ cDC2.

However, other studies have provided formal evidence that monocyte-derived cells are capable of antigen presentation. In a model of sterile inflammation, DC depletion after

Diphteria Toxin (DT) injection in CD11c-DTR mice abrogated CD4 T cell activation (Kool et al., 2008). It could be restored after adoptive transfer of monocytes, showing that monocyte-derived cells were capable of antigen presentation on MHC class II molecules and CD4 T cell stimulation. In a model of local viral reactivation, recruited DCs stimulated resident memory CD8 and CD4 T cells, which was dependent on MHC expression by the DCs indicating bona fide antigen presentation (Wakim et al., 2008). Recruited DCs were strongly decreased by injection of clodronate liposomes. Therefore, these observations show that mo-DCs present the viral antigens to resident T cells after virus reactivation. In a *Salmonella typhimurium* infection model, clodronate liposomes injection also decreased the activation of CD4 T cells in infected spleens, indicating antigen presentation by mo-DCs (Flores-Langarica et al., 2011).

Two other studies support the identification of antigen-presenting monocyte-derived cells in inflammed tissues, although their cellular ontogeny will need to be further confirmed. In experimental autoimmune encephalomyelitis, stainings with an antibody specific for peptide-MHC class I complexes identified a population of antigen-presenting DCs in the central nervous system displaying a mo-DC phenotype (Ji et al., 2013). Although complementary experiments were not performed to address the ontogeny of these cells, their characterization as $CD11b^{+}Ly6C^{+}F4/80^{+}CCR2^{+}$ DCs with low expression of *Irf8* and *Zbtb46* strongly suggests that they are mo-DCs, rather than 'inflammatory' cDC2. In a colitis model, $CD11b^{+}Ly6C^{+}$ DCs were increased in the colon upon inflammation, and their monocyte origin was evidenced using adoptive transfer and lack of *Zbtb46* expression (Zigmond et al., 2012). After gavage with a model antigen, these cells could stimulate antigen-specific CD4 T cells ex vivo, indicating their ability to present antigens on their MHC class II molecules. Of note, mo-DCs were less efficient for T cell stimulation than CCR2-dependent $CD11b^{+}Ly6C^{low}$ DCs, which were likely 'inflammatory' cDC2.

Monocytes are also known to infiltrate tumors and several studies have identified populations of mo-DCs after immunostimulatory treatments. $CD11b^+CD64^+Ly6C^+$ DCs were increased in the draining lymph nodes of tumor-bearing mice that were locally treated with a combination of monosodium urate crystals and *Mycobacterium smegmatis* (Kuhn et al., 2015). Adoptively transferred monocytes were recruited to tumor-draining lymph nodes of treated mice and adopted this phenotype, showing that at least a portion of these cells could derive from monocytes. The accumulation in the tumor of antigen-specific CD8 T cell was abrogated upon DC depletion in CD11c-DTR bone marrow chimeric mice, however it was restored upon transfer of monocytes. This observation confirms that monocyte-derived cells were capable of presenting tumor antigens to T cells. Treatment of tumor-bearing mice with chemotherapy also favored the appearance in the tumor of a population of $CD11b^+Ly6C^+$ DCs also expressing CD103 and CCR2 (Ma et al., 2013; Sharma et al., 2018). Adoptive transfer experiments showed that these cells did not differentiate from CDP, but derived from monocytic precursors (Ma et al., 2013; Sharma et al., 2018). These mo-DCs could stimulate efficienly antigen-specific CD8 T cells ex vivo, showing they had captured and presented tumor antigens on their MHC class I molecules (Ma et al., 2013; Sharma et al., 2018).

Finally, antigen presentation is not limited to 'inflammatory' mo-DCs and can also be performed by mucosol mo-DCs. Because they differentiate in the steady-state, these mo-DC populations are easily distinguished from cDC2 based on their phenotype and dependence on CCR2. Skin mo-DCs could present a model antigen to CD4 and CD8 T cells when cultured in vitro, although less efficiently than cDCs (Tamoutounour et al., 2013). Similarly, mo-DCs from Peyer's patches were capable of antigen presentation to CD4 T cells in vitro (Bonnardel et al., 2015), and were observed interacting with CD4 T cells in situ by microscopy (Wagner et al., 2020).

4. Complementary roles for mo-DCs and cDCs in T cell activation

A characteristic feature of DCs is their ability to migrate from peripheral tissues to draining lymph nodes where the activation of naïve T cells takes place. However, monocyte-derived cells have been shown to have a low migratory capacity. In a model of lung inflammation, $CD11b^{+}Ly6C^{+}CD14^{+}$ DCs were non-migratory and lacked expression of CCR7, a chemokine receptor required for DC migration to lymph nodes (Nakano et al., 2013). Their monocyte origin was confirmed by adoptive transfer and independence on Flt3-L (Nakano et al., 2013). In a model of lung infection, only $CD26^{+}CD11b^{+}CD64^{+}$ cDC2 were found in draining lymph nodes, while monocyte-derived cells did not migrate (Bosteels et al., 2020). Consistent with this, other studies in which mo-DCs and 'inflammatory' $CD64^{+}$ cDC2 cannot be formally distinguished have reported a lack of detection or low numbers of these cells in draining lymph nodes (Aldridge et al., 2009; Langlet et al., 2012; Lim et al., 2020; Plantinga et al., 2013). Of note, putative mo-DCs have been observed in lymphoid organs, but lack of CCR7 expression or independence on CCR7 suggests that these cells originated from monocytes directly recruited from blood to inflamed lymph nodes, rather than from migratory mo-DCs (Langlet et al., 2012; Nakano et al., 2013, 2009). Supporting this idea, monocytes have been shown to enter lymph nodes through the high endothelial venules during adjuvant-induced inflammation (Leal et al., 2021; Palframan et al., 2001).

The efficient activation of effector T cells requires interactions between antigen-presenting cells and T cells in peripheral tissues, which provides signals to maintain their polarisation and effector functions (Honda et al., 2014; Ley, 2014; Natsuaki et al., 2014; Veres et al., 2017). Several lines of evidence support a role for mo-DCs in this process through the presentation of antigens directly in inflamed tissues. In tumor-bearing mice treated with chemotherapy, surgical removal of draining lymph nodes did not abolish CD8 T cells activation in the tumor, indicating that antigen presentation occurred in situ (Ma et al., 2013). Mo-DCs were identified as the antigen-presenting cells in the tumor (Ma et al., 2013). Consistent with these findings, cognate interactions between $CD11b^{+}Ly6C^{+}$ DCs and T cells

have been observed by imaging in inflamed tissues in models of lung infection (Lim et al., 2020) and kidney allograft (Zhuang et al., 2016). In addition, in a model of vaginal infection, CCR2-dependent DCs were dispensable for priming CD4 T cells but were involved in the in situ restimulation of effector T cells (Iijima et al., 2011). Finally, this peripheral antigen presentation can also be involved in the activation of autoreactive T cells, as shown in models of multiple sclerosis (Greter et al., 2005; Kivisäkk et al., 2009; Odoardi et al., 2007). In this setting, although antigen presentation was not directly addressed, mo-DCs but not cDCs were shown to be responsible for pathogenic CD4 T cells activation (Croxford et al., 2015).

Local antigen presentation by mo-DCs can also allow the activation of tissue-resident memory T cells, as shown in experimental virus reactivation (Wakim et al., 2008). In this model, herpes simplex virus was reactivated upon transplantation into a naïve mouse of peripheral tissues of a previously infected mouse. Virus-specific donor CD4 and CD8 T cells both proliferated locally and were not found recirculating in the host mouse. This phenomenon was dependent on recruited host mo-DCs (Wakim et al., 2008).

Collectively, these observations support a model in which migratory cDCs and non-migratory mo-DCs play complementary roles for the optimal induction of adaptive immune responses (figure). While cDCs transport antigens to draining lymph nodes to prime naïve T cells, mo-DCs would present antigens in tissues to boost effector functions of newly recruited T cells or to rapidly activate tissue-resident memory T cells.

5. Conclusion and perspectives

The recent description of inflammatory cDC2 challenged the existence of antigen-presenting cells derived from monocytes. These inflammatory cDC2 express numerous markers previously used to identify mo-DC and are partially dependent on CCR2. Therefore, these two strategies are no longer sufficient to assign a mo-DC identity. Nevertheless, we argue that studies based on monocyte depletion or adoptive transfer of monocytes have demonstrated the

presence in tissues of bona fide antigen-presenting cells derived from monocytes. These cells do not migrate to lymph nodes and can present antigens to effector T cells directly in tissues. Collectively, the work discussed here supports a model in which cDCs and mo-DC play complementary roles for the optimal induction of T cell responses, by presenting antigens in lymphoid organs or inflamed tissues respectively.

More work is needed to re-evaluate the contribution of mo-DC to antigen presentation, in particular in fungal infections, chronic inflammatory diseases and allograft rejection. In the absence of unique markers for mo-DC, the minimal set of phenotypic markers should include CD26 to distinguish cDC2 from mo-DC. New fate-mapping models will also be useful to track monocyte-derived cells in a more specific way, such as the Ms4a3 reporter mouse (Liu et al., 2019).

Finally, future studies should aim at translating these findings to human. Numerous studies have provided evidence for the in vivo differentiation of mo-DCs in human (Coillard and Segura, 2019). However, inflammatory cDC2 have not been identified in clinical samples yet. In addition, a population displaying mixed features of monocytes and DCs has been recently characterized in human, termed DC3 (Villar and Segura, 2020). How this population relates to mo-DC remains to be investigated. Addressing these questions will be essential for deciphering the role of mo-DC in the context of cancer or chronic inflammatory diseases.

Author Contributions

AC and ES wrote the manuscript.

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Competing interests statement

The authors declare no competing interests.

Figure Legend

Proposed model of the respective roles of classical DCs and monocyte-derived DCs in T cell stimulation. Upon inflammation, classical DC1, classical DC2 and inflammatory classical DC2 migrate to lymph nodes, where they present antigens to naive T cells. In parallel, monocytes enter inflamed tissues and differentiate into monocyte-derived DCs that further stimulate effector T cells. Thick and thin arrows represent differentiation and migration respectively. moDC, monocyte-derived DCs; cDC1, classical DC1; cDC2, classical DC2; inf cDC2, inflammatory classical DC2.

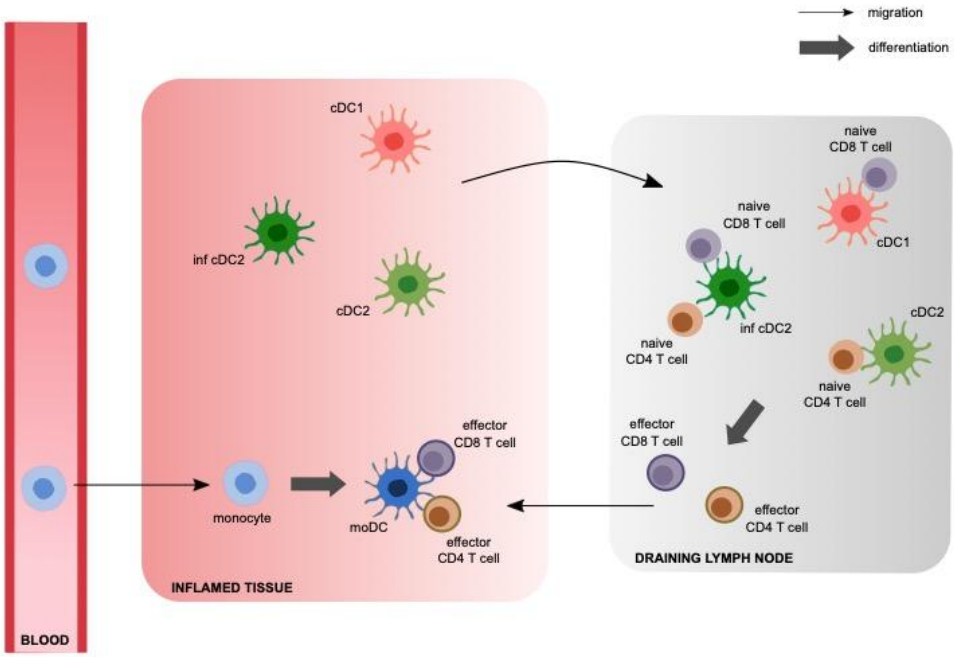

Table. Studies in which antigen-presenting cells cannot be resolved between mo-DCs and CD64$^+$ cDC2

Reference	Context	Experimental strategy	Type of Antigen presentation
(Aldridge et al., 2009)	Viral infection	Isolation of CD11b$^+$Ly6C$^+$ DCs	Cross-presentation
(Bedford et al., 2020)	Viral and bacteria infection	Isolation of CD11b$^+$CD64$^+$MAR1$^+$ DCs	Cross-presentation
(Chakarov and Fazilleau, 2014)	Adjuvanted vaccination	Detection of peptide-MHC complexes by flow cytometry (gated on CD11b$^+$ CD64$^+$DCs)	MHC II presentation
(Chang et al., 2017)	Chronic viral infection	Isolation of CD11b$^+$CD64$^+$MAR-1$^+$ DCs	MHC II presentation
(Hohl et al., 2009)	Fungal and bacteria infection	In vivo depletion in *Ccr2*-DTR mice	MHC II presentation
(Iijima et al., 2011)	Viral infection	CCR2 KO mice in vivo and isolation of CD11c$^+$ CD11b$^+$ DCs	MHC II presentation
(Ko et al., 2014)	Inflammatory disease (EAE) Bacteria and parasite infection	Isolation of CD11b$^+$Ly6C$^+$ DCs	MHC II presentation
(Langlet et al., 2012)	Sterile inflammation	Isolation of CD11b$^+$CD64$^+$Ly6C$^+$ DCs	Cross-presentation MHC II

			presentation
(León et al., 2007)	Parasite infection	Isolation of $CD11b^{+}Ly6C^{+}$ DCs	MHC II presentation
(Lim et al., 2020)	Viral infection	Imaging in *Csf1r*-EGFP reporter mouse	Cross-presentation
(Nakano et al., 2009)	Viral infection	Isolation of $CD11b^{+}Ly6C^{+}$ DCs	MHC II presentation
(Plantinga et al., 2013)	House Dust Mite Allergy	Isolation of $CD11b^{+}Mar1^{+}CD64^{+}$ DCs	MHC II presentation
(Segura et al., 2009)	Sterile inflammation	Isolation of $CD11b^{+}Ly6C^{+}$ DCs	Cross-presentation MHC II presentation
(Zhuang et al., 2016)	Allograft	Imaging in *Cx3cr1*-GFP reporter mouse Isolation of $CD11b^{+}$ DCs	Cross-presentation MHC II presentation

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