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Article *in* Immunology and Cell Biology · March 2008

DOI: 10.1038/icb.2008.14 · Source: PubMed

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Immunology and Cell Biology (2008) 86, 320–324

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REVIEW

Monocyte-derived dendritic cells in innate and adaptive immunity

Beatriz León and Carlos Ardavín

Monocytes have been classically considered essential elements in relation with innate immune responses against pathogens, and inflammatory processes caused by external aggressions, infection and autoimmune disease. However, although their potential to differentiate into dendritic cells (DCs) was discovered 14 years ago, their functional relevance with regard to adaptive immune responses has only been uncovered very recently. Studies performed over the last years have revealed that monocyte-derived DCs play an important role in innate and adaptive immunity, due to their microbicidal potential, capacity to stimulate CD4$^+$ and CD8$^+$ T-cell responses and ability to regulate Immunoglobulin production by B cells. In addition, monocyte-derived DCs not only constitute a subset of DCs formed at inflammatory foci, as previously thought, but also comprise different subsets of DCs located in antigen capture areas, such as the skin and the intestinal, respiratory and reproductive tracts.
Immunology and Cell Biology (2008) **86,** 320–324; doi:10.1038/icb.2008.14; published online 25 March 2008

Keywords: dendritic cells; monocytes; inflammation; infection; Langerhans cells; immune responses

Monocytes develop in the bone marrow and enter the blood stream until they are recruited to extravascular compartments not only during inflammatory processes but also under steady-state conditions, to maintain the homeostasis of the monocytic cell system. Monocytes were originally described as key elements of the mononuclear phagocytic system, due to their capacity to differentiate into different subsets of tissue macrophages with specific functions.[1] More recently, monocytes have been demonstrated to be endowed also with the potential to differentiate into dendritic cells (DCs) *in vivo* during inflammation.[2] This discovery has led to the concept that monocyte-derived DCs differentiated locally in inflammatory foci could play an important role with regard to the induction and regulation of immune responses against pathogens and the development of inflammatory and autoimmune diseases. However, so far only a few reports have addressed specifically the role of monocyte-derived DCs in innate and adaptive immunity that nevertheless has become recently an active research area. These studies, carried out over the last few years, have revealed that monocyte-derived DCs have the capacity to induce Th1-polarized CD4$^+$ T-cell responses,[3] crossprime antigen-specific CD8$^+$ T cells[4] exert a microbicidal action by producing tumour-necrosis factor-α (TNF-α) and iNOS,[5] and regulate IgA production by B cells.[6] Monocyte-derived DCs have been considered to constitute an independent category of DCs arising during inflammatory processes, with no role in the generation of DCs in noninflammatory conditions.[7] However, recent studies have revealed that monocytes are the precursors for some important DC subsets found in the steady state, such as Langerhans cells[8] and DC subsets present in the intestinal and respiratory mucosas.[9,10] Because of the lack of relevant information on the role of human monocytes in T-cell responses, this review will be focused on the available information on the role played by mouse monocyte-derived DCs in innate and adaptive immune responses.

MONOCYTE SUBSETS

In the murine system, circulating monocytes can be divided in two subpopulations, based on the expression of the myeloid markers, Ly-6C and Gr-1, the chemokine receptors, CCR2 and CX3CR1, and the rolling receptor L-selectin.[11] A major subset of mouse monocytes is composed of Ly-6C$^+$ Gr-1$^+$ CCR2$^+$ CX3CR1^{low} L-selectin$^+$ cells and corresponds to the classical monocytes. Therefore, the term 'monocyte' will be used in this review to describe this major monocyte subset, although we will term them 'Ly-6C$^+$ monocytes' when needed. The second and minor subset of mouse monocytes, constituting around 20–30% of all circulating monocytes, is composed of Ly-6C$^-$ Gr-1$^-$ CCR2$^-$ CX3CR1^{high} L-selectin$^-$ cells and will be hereafter named 'Ly-6C$^-$ monocytes'. Mouse Ly-6C$^+$ and Ly-6C$^-$ monocytes have been claimed to be functionally equivalent to the CD14^{high} CD16$^-$ and CD14^{low} CD16$^+$ human monocyte subsets, respectively.[11] Since only a few reports have addressed the functional properties of Ly-6C$^-$ monocytes, this review will be primarily focused on the role played by Ly-6C$^+$ monocytes in innate and adaptive immunity, although a special section will be dedicated to their Ly-6C$^-$ counterparts. Ly-6C$^+$ and Ly-6C$^-$ monocytes were originally termed Gr-1$^+$ and Gr-1$^-$ monocytes, respectively. However, since Gr-1, in fact, describes a specificity of monoclonal antibodies that recognize both the Ly-6C and Ly-6G molecules,[12] and since monocytes express Ly-6C but not Ly-6G, it seems more accurate to use Ly-6C expression to define the two monocyte subsets.

Departamento de Inmunología y Oncología, Centro Nacional de Biotecnología, Universidad Autónoma, Madrid, Spain
Correspondence: Dr Carlos Ardavín, Departamento de Inmunología y Oncología, Centro Nacional de Biotecnología, Universidad Autónoma, Madrid 28049, Spain.
E-mail: ardavin@cnb.csic.es
Received 10 February 2008; accepted 20 February 2008; published online 25 March 2008

MONOCYTE RECRUITMENT AND DIFFERENTIATION INTO DCs DURING INFLAMMATION

During the development of inflammatory reactions caused by external aggressions, microbial infections or autoimmune responses, monocytes are recruited to inflammatory foci, where they have been demonstrated to differentiate into macrophages.[1] Inflammatory macrophages have a crucial role in defense against infection by participating in innate immune responses against pathogens, but can also have a damaging effect by contributing to the development of inflammatory or autoimmune diseases. Mouse monocyte recruitment to inflamed organs, such as the dermis, lymph nodes, spleen, liver, lungs, buccal mucosa, brain, peritoneum and atherosclerotic plaques, is essentially controlled by the chemokine receptors CCR2, CCR5 and CCR6.[13] However, CCR2 has been reported to be only required for monocyte egress from the bone marrow, but not for their recruitment to inflamed foci.[14] Data regarding the integrin receptors involved in inflamed monocyte recruitment are controversial, because a number of reports have proposed that β2 integrins are essential for this process,[15,16] whereas others have concluded that β2 integrins are not required for monocyte recruitment during inflammation, a process that would be controlled by the β1 integrin VLA-4.[17] Finally, a recent report addressing the identity of the molecules controlling monocyte rolling during an infection-induced inflammatory process has revealed that migration through inflamed dermal venules was dependent on PSGL-1 and L-selectin, whereas monocyte migration to the lymph nodes through high endothelial venules relied essentially on L-selectin.[18]

Inflammatory macrophages can fulfill multiple effector and regulatory functions that reflect the existence of different inflammatory macrophage subsets whose functional specialization is largely dictated by the local environment that promoted their recruitment, differentiation and activation. This topic has extensively covered on a recent review on macrophage activation and the functional properties of macrophages subsets,[1] and thus will not be discussed in the present review.

On the other hand, the recent discovery of the monocyte potential to differentiate *in vivo* into DCs has opened a new field of research, aiming to explore the function of monocyte-derived DCs in the induction and regulation of immune responses. The capacity of monocytes to behave as DC precursors was originally revealed by *in vitro* studies performed in the human system 14 years ago.[19] These studies were subsequently confirmed 5 years later by *in vivo* studies in mice based on the subcutaneous injection of latex microspheres that aimed to reproduce an infection-mediated inflammatory process.[20] These experiments suggested that during infectious processes, inflammatory monocytes could differentiate in the dermis into DCs and subsequently migrate to the draining lymph nodes. This hypothesis was later challenged in a report demonstrating, using the same experimental set, that DC differentiation from monocytes was blocked if bacteria or lipopolysaccharide were present in the area where latex microspheres were injected.[21] However, the concept that monocytes differentiate into DCs during infection was conclusively demonstrated in a recent study describing the differentiation of DCs from monocytes recruited to the infected dermis and draining lymph nodes in *Leishmania major*-infected mice.[3] This notion was further supported by a number of articles analyzing the immune response to model antigens, viruses and bacteria, suggesting that monocytes recruited to infection-induced inflammatory sites can differentiate locally into DCs.[4,5,22–24] The apparent contradiction between these results and those describing the blockade of DC differentiation from monocytes caused by bacteria or LPS might be explained by the fact that a high concentration of pathogens or pathogen-derived compounds could inhibit monocyte differentiation into DCs. In this sense, the blockade observed in the experiments based on the injection of latex microspheres was probably due to high bacteremia levels or high LPS concentration, whereas the physiological conditions that allowed monocyte differentiation into DCs during viral, bacterial and parasitic infections probably involved low viremia, bacteremia and parasitemia levels in the area where monocyte were recruited. Monocyte differentiation into DCs is known to be controlled by the cytokine granulocyte–monocyte colony-stimulating factor and has been shown to be blocked by pathogen receptors, such as TLR receptors,[25,26] complement receptors[27] and C-type lectin receptors (León and Ardavín, unpublished). In addition, *in vitro* studies have revealed that the cytokines present during granulocyte–monocyte colony-stimulating factor-driven monocyte differentiation into DCs strongly influence the functional properties of monocyte-derived DCs, particularly with regard to their Th1/Th2 polarization capacity.[28] Although these studies need to be validated by *in vivo* experimental approaches, cytokines and other local mediators appear to contribute essentially to the acquisition of the functional specialization of monocyte-derived DCs formed at inflammatory foci induced by infections or autoimmune responses. On the other hand, the mechanisms regulating how monocytes differentiate into macrophages or DCs during *in vivo* inflammatory processes remain to be addressed in depth.

ROLE OF MONOCYTE-DERIVED DCS IN THE INDUCTION AND REGULATION OF INNATE AND ADAPTIVE RESPONSES

Several reports published over the last years have led to the notion that the differential expression of antigen receptors, functional properties, location and migratory behaviour of DCs, determine the identity of the DC subsets responsible for the induction of T-cell immunity against different pathogens. In this sense, specific roles have been ascribed to the main DC subsets described in mice, that is, Langerhans cells, dermal DCs, interstitial DCs, $CD8^-$ DCs and $CD8^+$ DCs, with regard to the establishment of T-cell responses against a variety of viral, bacterial or parasitic infections.[29] However, only a few reports have provided direct evidence on the role played by monocyte-derived DCs in the induction of immune responses (summarized in Table 1). The analysis of monocyte differentiation during infection by *Leishmania major* revealed that monocytes were recruited to the dermis and to the draining lymph nodes, and differentiated into DCs in both locations.[3] Interestingly, DCs derived from monocytes recruited to the dermis, that subsequently migrated to the draining lymph nodes, were responsible for the induction of protective Th1 responses against the parasite. After migration to the lymph nodes, these dermal monocyte-derived DCs were $CD11c^{intermediate}$ $Ly\text{-}6C^{intermediate}$ MHC II^{high} cells, $CD86^{high}$ $CD8\alpha^{low}$ $DEC\text{-}205^+$ cells and, therefore, expressed CD11c/Ly-6C levels that reflected their monocyte signature and MHC II/CD86 levels indicating that they had undergone a maturation process. In contrast, DCs differentiated from the monocytes recruited directly to the lymph nodes were $CD11c^{intermediate}$ $Ly\text{-}6C^{high}$ MHC $II^{intermediate}$ $CD86^-$ $CD8\alpha^{low}$ $DEC\text{-}205^-$ cells, and thus also displayed a monocytic signature, but represented immature DCs. These lymph node monocyte-derived DCs did not appear to contribute significantly to T-cell immunity against *Leishmania*; their function remains to be explored, although preliminary data suggest that they could be involved in the innate immune response against *Leishmania* (León and Ardavín, unpublished), as described for monocyte-derived DCs formed after *Listeria* infection.[5] Monocyte recruitment to the lymph nodes caused by a dermal inflammatory process was also described in a model of adjuvant-induced skin

inflammatory response, although these authors did not analyze the fate of recruited monocytes.[30]

In addition, a number of reports have supplied indirect evidence on the role of monocyte-derived DCs on T- and B-cell immunity. In a recent report, accumulation of DCs in the buccal mucosa, induced by the administration of the proinflammatory haptens 2,4-dinitrofluorobenzene or measles virus nucleoprotein that have intrinsic adjuvant properties, was claimed to depend on CCR6-dependent recruitment of monocytes; interestingly these newly formed DCs, that most likely correspond to monocyte-derived DCs, were essential for the cross-priming of OVA-specific $CD8^+$ T cells.[4] Induction of antigen-specific $CD4^+$ T-cell responses during *Salmonella* infection have also been claimed to rely on the recruitment of monocytes to the dermis, by a CCR6-dependent mechanism.[24] In addition, monocytes have been reported to capture antigens in the bone marrow and present them to antigen-specific $CD4^+$ T cells after migration and differentiation into DCs in the lymph nodes and spleen.[31] During infection by *Listeria monocytogenes*, newly formed splenic DCs, claimed to derive from monocytes recruited to the spleen by a CCR2-dependent mechanism, displayed a high capacity to produce TNF-α and nitric oxide-mediated microbicidal mediators and, therefore, had an important role in the innate immune response against *Listeria*.[5] Interestingly, these monocyte-derived DCs, that have been named Tip DCs (for TNF-α/iNOS-producing DCs) were not involved in the induction of *Listeria*-specific T-cell responses. The functional relevance of this DC subset that displayed a similar phenotype than monocyte-derived DCs differentiated in the lymph nodes of *Leishmania*-infected mice[3] was demonstrated in CCR2-deficient mice in which uncontrolled bacterial replication and host death occurred.[5] Moreover, TNF-α/iNOS-producing DCs present in the intestinal lamina propria have been recently demonstrated to be required for the iNOS-dependent induction of IgA class-switch recombination and IgA production by B cells located in the intestinal mucosa.[6] In line with these findings, newly recruited DCs that differentiated in the splenic marginal zone in response to *Streptococcus pneumoniae* infection displayed a similar phenotype that Tip DCs and were shown to participate in the induction of T-cell-independent B-cell responses and the differentiation of IgM-producing plasma cells by a mechanism dependent on the production of the transmembrane activator and calcium modulator cyclophilin ligand interactor (TACI) ligands, BlyS and APRIL by monocyte derived-DCs.[32] Finally, accumulation of DCs in the spleen with similar phenotypic characteristics as that of Tip DCs was also reported to occur after adjuvant treatment; this DC subset was also shown to promote antigen-specific B differentiation into Ig-producing cells.[33]

DO MIGRATORY DCS REPRESENT MONOCYTE-DERIVED DCs?

Monocyte-derived DCs are considered to constitute a specialized subset of inflammatory DCs different from the DCs present in antigen capture areas and the lymphoid organs, in the steady state. However, recent data suggest that migratory DCs that comprise Langerhans cells, dermal DCs and interstitial DCs (that in turn mainly include DCs present in the mucosa of the intestinal, respiratory and reproductive tracts) might also be derived from monocytes. In this sense, monocytes have been demonstrated to represent precursors for mouse epidermal Langerhans cells both in steady state and inflammatory conditions.[8] Moreover, Langerhans cells located in the vaginal epithelium were demonstrated to derive from monocytes during herpes virus infection, but not in the steady state.[23] Although consequently Langerhans cells represent monocyte-derived DCs, it is beyond the scope of the present review to discuss in depth the role played by Langerhans cells in immune responses. Nevertheless, it is noteworthy to mention that the functional relevance of Langerhans cells with regard to the induction of T-cell responses is a matter of debate. Several studies support the hypothesis that Langerhans cells are required for the induction of T-cell responses to model antigens expressed specifically by keratinocytes[34] and in contact hypersensitivity responses.[35,36] In contrast, a number of reports have challenged this paradigm by demonstrating that Langerhans cells are not required for the induction of T-cell responses during viral and parasitic infections of the skin, a function that appears to be fulfilled by dermal DCs and dermal monocyte-derived DCs.[37–40]

On the other hand, a number of reports analyzing the phenotypic features, functional properties and physiological relevance of dermal and interstitial DCs during infection[29] support the hypothesis that these two DC subpopulations represent monocyte-derived DCs. Therefore, when evaluating the function of monocyte-derived DCs in innate and adaptive immunity, it is important to take into account the important role played by dermal and interstitial DCs in the induction of *in vivo* immune responses against virus, bacteria and parasites. In this regard, dermal DCs and interstitial DCs have been demonstrated to be responsible for the induction of $CD4^+$ and $CD8^+$ T-cells responses against influenza or herpes virus infection of the dermis, lung and vaginal mucosa.[38,40,41] These reports have also revealed that induction of antiviral $CD8^+$ T-cell responses by dermal DCs and interstitial DCs could result from direct antigen presentation to antigen-specific T cells, or antigen transfer from these migratory DC subsets to resident DCs.[40,41] More recently, monocyte transfer experiments performed after diphtheria toxin-mediated DC depletion have revealed that monocytes were the precursors for lung parenchyma and intestinal lamina propria DCs.[9,10]

Finally, regarding whether monocytes can behave as precursors for resident DC subsets, such as $CD8^+$ and $CD8^-$ DCs present in lymphoid organs, including the lymph nodes, spleen, Peyer's patches and lymphoid tissues present in the intestinal, respiratory and reproductive tracts, a number of studies have characterized non-monocytic precursors that specifically generate $CD8^-$ and $CD8^+$ DCs under steady-state conditions.[7,42–45] However, the notion that monocytes could differentiate into resident DCs under inflammatory conditions remains to be clarified, since monocyte transfer experiments performed into irradiated mice[46] or *Leishmania*-infected mice[3] support the concept that monocytes might represent immediate precursors for $CD8^-$ and $CD8^+$ DCs during inflammatory processes.

Globally, these data challenge the hypothesis that monocyte differentiation into DCs only contributes to the generation of an independent subset inflammatory DCs and further support the concept that monocytes can also behave as precursors for interstitial DC subsets present in the steady state and can differentiate into defined resident DCs during inflammatory responses.

FUNCTIONAL RELEVANCE OF LY-6C$^-$ MONOCYTES

The origin of Ly-$6C^-$ monocytes was addressed in a report analyzing the repopulation of the different monocytes subsets after depletion of monocytes by intravenous injection of chlodronate-loaded liposomes, by injecting 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindodicarbocyanine (DID)-loaded fluorescent liposomes, allowing to track the cells that had internalize them.[47] It was concluded that Ly-$6C^-$ monocytes were derived from Ly-$6C^+$ monocytes through a transitional population expressing intermediate levels of Ly-6C that constituted around 15% of total circulating monocytes. Regarding their function, Ly-$6C^-$ monocytes were originally considered to behave as DC precursors under noninflammatory conditions. By using $CX3CR1^{gfp/+}$ transgenic mice, expressing green fluorescence protein under the control of the

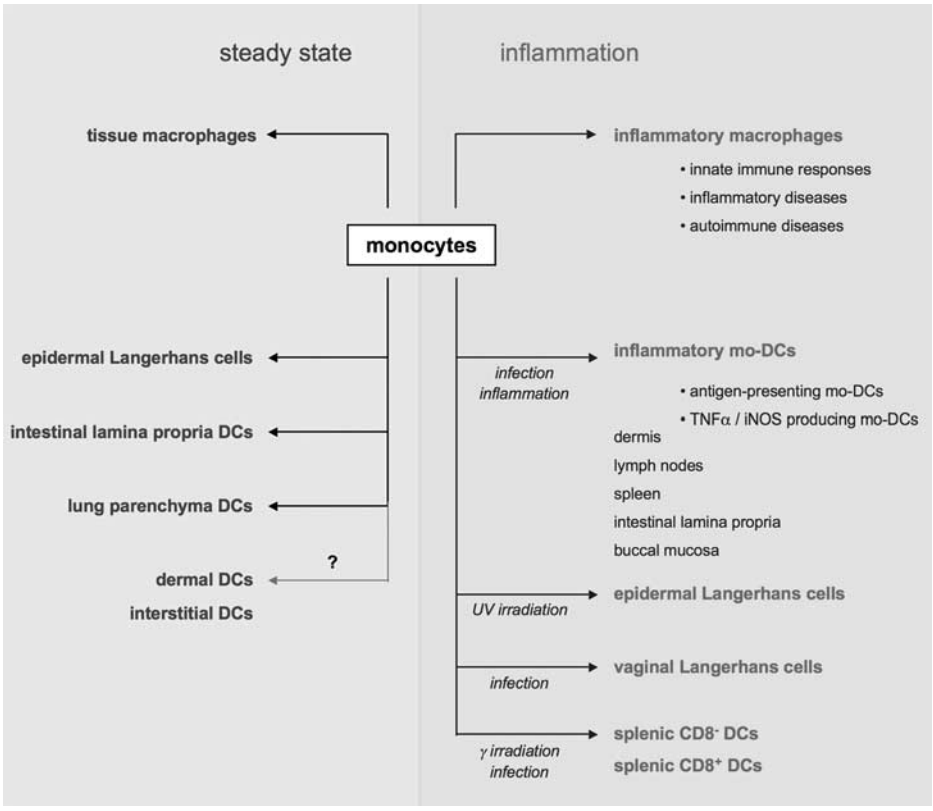

Figure 1 Diagram summarizing the potential of monocytes to differentiate into dendritic cells (DCs) under steady state and inflammation. The different locations in which monocyte-derived DCs have been described to differentiate during inflammation, the function described for them and the corresponding experimental conditions are indicated.

Table 1 Experimental evidence on the role of monocyte-derived dendritic cells in innate and adaptive immunity

Experimental model	*Location of monocyte recruitment*	*mo-DC subset*	*Immune response induced*	*Reference*
Leishmania infection	Dermis (PSGL-1 and L-selectin dependent)	Dermal mo-DCs	$CD4^+$ T-cell activation	León *et al.*[3]
OVA-latex bead immunization	Lymph node, spleen	Lymph node and spleen mo-DCs	$CD4^+$ T-cell activation	Tacke *et al.*[31]
Salmonella infection	Dermis (CCR6 dependent)	Dermal mo-DCs	$CD4^+$ T-cell activation	Ravindran *et al.*[24]
OVA-DNTB or OVA-NP immunization	Buccal mucosa (CCR6 dependent)	Interstitial mo-DCs	$CD8^+$ T-cell cross-priming	Le Borgne *et al.*[4]
Listeria infection	Spleen (CCR2 dependent)	Tip DCs	Bacteria killing by TNF-α/iNOS production	Serbina *et al.*[5]
Commensal bacteria	Intestinal lamina propria	Tip DCs	iNOS-dependent help for IgA production	Tezuka *et al.*[6]
Streptococcus infection	Spleen	Spleen mo-DCs	TACI-L-dependent help for IgM production	Balázs *et al.*[32]

Abbreviations: DNTB, 2-4 dinitrofluorobenzene; mo-DC, monocyte-derived dendritic cells; NP, measles virus nucleoprotein; OVA, ovalbumin; TACI-L: TACI-ligands (BLyS and APRIL); Tip DCs, TNF-α and iNOS-producing dendritic cells; TNF-α, tumour-necrosis factor-α.

CX3CR1 promoter, Ly-$6C^-$ monocytes were shown to generate splenic $CD11c^+$ MHC II^+ DCs upon adoptive transfer into non-irradiated recipients.[11] No information was nevertheless provided in this report regarding the functional properties of DCs derived from Ly-$6C^-$ monocytes or concerning their possible physiological counterparts. Whether Ly-$6C^-$ monocytes represent an immediate precursor for migratory or resident DCs remains to be explored. A recent report has challenged the initial hypothesis regarding the functional relevance of Ly-$6C^-$ monocytes, by proposing that this monocyte subset would be involved in patrolling the blood vessels allowing them to extravasate, differentiate into macrophages and initiate an innate immune response, in case of infection or tissue damage.[48]

FUTURE RESEARCH DIRECTIONS

The discovery of the potential of monocytes to differentiate into DCs during *in vivo* infection has dramatically changed our perception of the role played by monocytes in the immune system, as illustrated in Figure 1. A few years ago, monocytes were exclusively considered to participate in innate immune responses through the effector and regulatory functions of monocyte-derived macrophages. However,

recent studies have demonstrated that monocyte-derived DCs could be responsible for the induction of $CD4^+$ and $CD8^+$ T cell responses, participate in innate immunity and contribute to the regulation of immunoglobulin production by B cells. Moreover, monocytes not only differentiate into inflammatory DCs, but also represent the precursors for DCs located in antigen capture areas. Therefore, future research should be focused on investigating in depth the potential relevance of monocyte-derived DCs in the immune system, as well as the mechanisms controlling monocyte decision to differentiate into macrophages and DCs (Figure 1 and Table 1).

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