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Review

The role of monocytes in models of infection by protozoan parasites

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ABSTRACT

The confirmation of developmental differences between tissue macrophages and peripheral monocytes has changed our view of the functions and dynamics of these two important components of the innate immune system. It has been demonstrated conclusively that homeostasis of tissue resident macrophages is maintained by a low proliferative turn over. During an inflammatory response, bone marrow derived monocytes enter the tissue in large numbers and take part in the defense against the pathogens. After the destruction of invading pathogens, these cells disappear and tissue resident macrophages can be detected again. This new appreciation of the innate immune response has not only answered many outstanding questions regarding the role of the different myeloid cell types in inflammation, but also opened up new areas of research relating to the tissue- and pathogen-specific fate of the inflammatory macrophages or dendritic cells (DCs), and the transfer of this knowledge from mouse models to the human immune system. Nevertheless, there is still confusion in infection models, and especially in studies of human infections, as to what extent these recent observations and findings influence previous interpretations of data. This review will focus on insights from mouse models, summarize the literature on the ontogeny of macrophages and monocytes, explain the role of frequently used monocyte markers and effector molecules, and finally, discuss the role of inflammatory monocytes/macrophages/DCs in two experimental parasitic diseases.

1. Introduction

The origin of the cellular components of the innate immune system and their role in immune defense are a topic of great interest. Recently, a clear distinction of ontogenetically and functionally different cell subtypes has been made possible by the use of modern genomics (Gautier et al., 2012), proteomics (Luber et al., 2010) and gene modification techniques that have allowed the fate mapping of cell populations throughout the lifespan of an animal (Yona et al., 2013). We appreciate now that these innate cells are of hemopoietic origin, belong to the mononuclear phagocyte system (MPS) and comprise several blood monocyte populations, dendritic cells (DCs) and a variety of organ-specific macrophage subtypes. Furthermore, it has become clear that these cell types are highly dynamic and plastic, and central for the initiation, regulation and contraction of the immune response.

During the immune response to protozoan parasites, the contributions of monocytes and macrophages are crucial. This fact has been recognized early because macrophages represent an important target of many species of invading parasites and are therefore, central for the control of these pathogens. However, the descriptions of the monocyte/macrophage/DC populations that participate in the innate response are frequently sketchy and not well aligned with markers, especially in the light of new insights into macrophage ontogeny. Therefore, we will briefly explore recent findings and discuss the changing perception of some classic, frequently used myeloid markers. Subsequently, we will summarize research into the innate response during two protozoan parasite infections, toxoplasmosis and leishmaniasis, which have a wealth of information relating to the involvement of myeloid cells in host defense and disease.

1.1. Differentiation and ontogeny of cells of the MPS

The notion of a specialized MPS with committed precursor cells that leave the bone marrow, enter the peripheral circulation as monocytes and finally, enter the tissues to differentiate to tissue macrophages was based on early work by Ralph van Furth (van Furth et al., 1972; Hume, 2006). However, fate mapping experiments employing genetically modified mouse strains that express developmental marker molecules tagged with a fluorochrome (Yona et al., 2013) and the elucidation of underlying molecular mechanisms of myeloid cell differentiation

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(Geissmann et al., 2010; Gordon and Taylor, 2005; Hashimoto et al., 2011) allowing for a separation into a variety of cell types (DeKoter and Singh, 2000; Guerriero et al., 2000) have added considerable complexity.

The origin of tissue resident macrophages such as Kupffer cells and alveolar macrophages has been traced back to embryonic hemopoietic progenitor cells that seed the tissues of the embryo late during embryogenesis (Gomez Perdiguero et al., 2015; Ginhoux et al., 2010). Microglia and Langerhans cells have an even earlier ontogenetic origin and descent from yolk-sac-derived primitive macrophages (Ginhoux et al., 2010; Sheng et al., 2015). These long-lived populations of tissue resident macrophages proliferate slowly and are, with a few exceptions, maintained independently or with only minimal monocytic immigration (Ginhoux and Jung, 2014; Hashimoto et al., 2013).

In contrast, blood monocytes have been shown to have a variety of immunological fates. In a recent study a surprising heterogeneity of monocytic precursor cells has been identified within the bone marrow that clearly indicates that independent of inflammatory cues predetermined monocytes subsets exist at this stage (Menezes et al., 2016). These monocyte populations leave the adult bone marrow with the help of the CC-chemokine receptor CCR2 (Serbina and Pamer, 2006). They can enter peripheral, steady-state tissues and support homeostasis (Jakubzick et al., 2013; Tamoutounour et al., 2013) or develop to inflammatory cells with specific effector capabilities after being recruited rapidly to a site of inflammation, (Menezes et al., 2016; De Trez et al., 2009; Serbina et al., 2003) releasing pro-inflammatory cytokines such as TNF and effector molecules such as NO, and contributing to the clearance of pathogens (Ritter et al., 2004). Alternatively, they can develop into MHC class II expressing monocytic DCs (mo-DC) (Menezes et al., 2016). Consequently, this establishes peripheral, monocytic subsets as immune cell populations separate from classical DCs and macrophages (Yona et al., 2013; Tamoutounour et al., 2012) with unique physiological properties. The constant presence of large numbers of monocytes in the periphery and the diversity of their response to inflammatory cues makes them important contributors to the early immune response. During the contraction phase of the immune response, monocytes can replenish tissue macrophages in some organs, such as liver (Bleriot et al., 2015), and can differentiate to support wound healing after an injury and restore homeostasis (Swirski et al., 2009). Interestingly, one exception are macrophages of the intestine where embryonic precursor cells are replaced in an ongoing process by bone marrow derived Ly6C^{high} monocytes that differentiate locally (Bain et al., 2014).Fig. 1

The separate development of monocytes as a distinct line of cells and the crucial fate decisions in the bone marrow are dominated by the master transcription factor PU.1. This transcription factor induces the commitment of cells to the myeloid linage during early myelopoiesis (Dakic et al., 2005; Iwasaki et al., 2005; Nerlov and Graf, 1998) and controls further early developmental pathways of these cells by antagonizing other transcription factors, thus, preventing a deviation from monocytic development. This begins with an interaction with GATA-1 and −2 that shuts down the megakaryocytic/erythroid and the mast cell pathways, respectively (Walsh et al., 2002), as well as interactions with C/EBPα that prevent the granulocytic pathway (Dakic et al., 2005; Dahl et al., 2003). In the bone marrow, differences in the expression of PU.1 are responsible for the establishment of precursor populations with a predetermined fate as microbicidal phagocyte or as antigen-presenting mo-DC (Menezes et al., 2016).

1.2. Murine monocytes in homeostasis and inflammation

1.2.1. Cell surface molecules used in the identification of myeloid cell populations

Generally, monocyte, macrophage and DC populations have been identified primarily using cell surface receptors that are involved in a wide variety of functions from cell migration to differentiation and scavenging, and have been reviewed extensively in the past (Taylor et al., 2005).

The evolving insight into the role and ontogeny of cells of the MPS has changed our perception of commonly used markers such as CD11b/c, F4/80, Ly6C/G, CCR2 and CX3CR1. It is not sufficient for a clear distinction of different cell subsets if the markers are used in isolation. However, in combination, these markers can be employed to identify distinct cell populations of the innate response. Unfortunately, in infection experiments, there has been a lack of conformity in the numerous attempts to characterize cellular infiltrates after an infection.

1.2.1.1. CD11b/c. Frequently used first markers in the investigation of an inflammatory infiltrate are the expression of the heterodimeric adhesion molecules $\alpha_m\beta_2$ (CD11b-CD18) and $\alpha_x\beta_2$ (CD11c-CD18). Both molecules are broadly aligned with either monocytes/macrophages or DCs, respectively (Imhof and Aurrand-Lions, 2004). Importantly, while CD11b is expressed on myeloid lineage cells, it is also present on some lymphoid cells such as nature killer (NK) cells (Ross and Vetvicka, 1993) and is therefore, not conclusive if used alone. On a similar note, the integrin CD11c is commonly recognized as a marker of DC, including conventional DC, inflammatory monocytic DC and plasmacytoid DC, but can also be present on macrophages and monocytes *in vivo* (reviewed in (Hashimoto et al., 2011)) as well as T cells. Therefore, it is contentious to identify all inflammatory myeloid cells that express CD11c as DCs (Hume, 2008).

1.2.1.2. CD115. CD115 or monocyte-colony stimulating factor receptor (CSF-1 R) is encoded by the c-*fms* proto-oncogene. The receptor is expressed on many cell types of MPS (Sasmono et al., 2007) and has been studied extensively using MacGreen (Sasmono et al., 2003) and MacBlue transgenic reporter mice (Sauter et al., 2014). It has been shown that the receptor is expressed by the majority of blood monocytes, but is lost on many tissue resident macrophages (Sauter et al., 2014). Therefore, the reliance of cells of the myeloid linage on this receptor for their development and survival was tested using an anti-CSF-1R antibody to block the receptor. Interestingly, treated mice showed only a very specific reduction in subpopulations of blood monocytes after three weeks of treatment (F4/80^{high}CSF1-R^{high}, GR1$^-$, but not F4/80^{int}CSF1-R^{int}, GR1$^+$) and some tissue macrophages (liver, gut and kidney but not brain, lung, ovary and uterus) (MacDonald et al., 2010). Furthermore, CD115 can be used to follow the maturation or differentiation of inflammatory monocytes. Under inflammatory conditions, for example after infection with *L. monocytogenes*, CD115$^+$Ly6C^{hi}CCR2$^+$ monocytes can be recruited into spleen, where they differentiate into monocyte-derived DCs (termed TIP-DCs) and loose CD115 (Drevets et al., 2010).

1.2.1.3. F4/80. Macrophages are often distinguished from DCs and monocytes cells by a differential expression of the surface marker F4/80, which is encoded by an EGF-like module containing, mucin-like hormone receptor-like sequence 1 (Austyn and Gordon, 1981), and constitutively expressed on many cells of the myeloid linage (Guilliams et al., 2013). Recent work has shown that only yolk-sac-derived macrophages that can be found in liver (Kupffer cells), skin (some Langerhans cells) and brain (microglia) are F4/80^{high} while monocyte-derived cells in peripheral tissues such as inflammatory macrophages are predominantly F4/80^{intermediate} (Schulz et al., 2012).

1.2.1.4. Ly6 family. Two molecules of the Ly-6 family, Ly6C and Ly6G, are constitutively expressed on a proportion of myeloid cells. Both molecules share one epitope that is recognized by the mAb RB6-8C5. This mAb was originally described as being able to bind to an antigen present on mature granulocytes (neutrophils and eosinophils) (Tepper et al., 1992). Subsequently, it was shown that the epitope recognized by RB6-8C5 was also present to a lower extent on monocytes (Fleming et al., 1993). Only the generation of newer, more specific antibodies,