Cellular Immunology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Reprint of: Monocyte subsets in man and other species ☆

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ARTICLE INFO

Article history:
Received 25 March 2014
Accepted 31 March 2014
Available online xxxx

Keyword:
Innate immunity

ABSTRACT

Monocytes are white blood cells that belong to the mononuclear phagocyte system. They derive from precursors in bone marrow, from there they go into blood, where they have a half-life of 1–2 days, and then they migrate into the various tissues. Monocyte subsets were discovered by means of flow cytometry in human blood some 20 years ago and their phenotype and function has been characterized in detail in health and disease. The subset classification as classical, intermediate and non-classical monocytes appears to apply to other species as well, as reviewed in here by comparing data on human monocytes with the respective cells in the mouse, the rat, the pig, the cow and the horse. The data show that the subsets are homologous between the species but there are important differences in subset-specific gene expression such that findings in a given species cannot be directly translated to man.

1. Introduction

This review gives an overview of monocyte subpopulations in man and other species.

2. Monocyte subsets in man

Early on monocytes were deemed to be a homogenous cell population, which circulates in blood in order to replenish macrophages in various tissues under homeostatic and pathological conditions. The first evidence for heterogeneity was provided for man in that in the late 1980s the CD16-positive monocytes were discovered [34]. The CD16-negative classical monocytes form the major population of about (90%) and the CD16-positive cells account for about 10% of all monocytes under physiological conditions at rest. The number of the CD16-positive monocytes can, however, increase or decrease strongly under various conditions. Increases have been reported for malignancy and for many inflammatory conditions with an increase to more than 50% of all monocytes for severe infection like sepsis [12,49]. Also, the numbers for the CD16-positive monocytes can increase temporarily with excessive exercise and stress and this is interpreted to result from mobilization of these cells from the marginal pool [39]. In this pool monocytes transiently attach to the vascular endothelium of post-capillary venules a process that can be overcome by the action of catecholamines [39].

A selective depletion of the CD16-positive monocytes has been reported after therapy with glucocorticoids (GCs) [11] and there is evidence that this involves a process of apoptosis [8]). While GC therapy depletes the CD16-positive monocytes the classical monocytes at the same time increase in absolute number. Of note, GCs have multiple actions in the immune system [4] and the relevance of the effect on monocyte subsets to the immunosuppressive action in vivo remains to be demonstrated. A clear reduction of the CD16-positive monocytes is also observed after infusion of IgG preparations at levels of 400 mg/kg bodyweight [38,21]. Finally in a pilot study blockade of the M-CSF-R pathway was shown to reduce CD16 monocyte numbers selectively [23].

Functional studies have revealed for the CD16-positive monocytes a higher level of TNF production [5] and of IL-12 production [41]. Based on a differential expression of chemokine receptors the CD16-positive monocytes show a migratory response to CX3CL1 but not to CCL2, while the classical monocytes selectively respond to CCL2 [2,42].

The role of human monocytes in infectious disease goes beyond their increase and activation induced by microbial infection. Monocytes can be infected by various viruses including HIV, HCV and Dengue virus. HIV can be detected in both classical and CD16-positive monocytes, but most patients show a preferential infection of the CD16-positive monocytes [19]. Also Dengue virus can infect both monocyte subsets but it induces inflammatory cytokines only in the CD16-positive monocytes [43]. Finally, HCV selectively infects the CD16 monocytes, which express the CD81 HCV receptor [7]. The viral infection of monocytes can enhance

DOI of original article: http://dx.doi.org/10.1016/j.cellimm.2014.03.019

☆ The article is reprinted here for the reader's convenience and for the continuity of the special issue. For citation purposes, please use the original publication details; Cellular Immunology, 289(1–2), (2014) 135–139.

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http://dx.doi.org/10.1016/j.cellimm.2014.06.008
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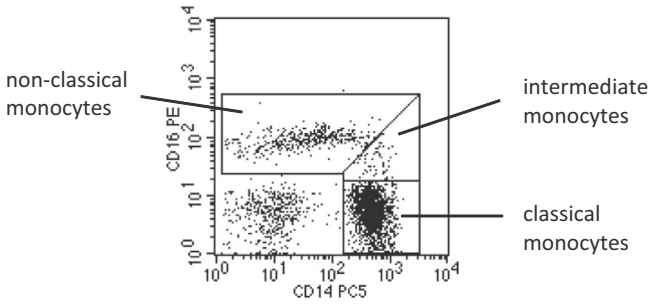

Fig. 1. Monocyte subsets in man as defined by flow cytometry.

spread of the virus in the body when monocytes migrate into tissue. Here the differential migratory potential of the monocyte subsets may determine the pattern of viral expression in the tissue.

A recent nomenclature proposal has further subdivided the CD16-positive monocytes into non-classical and intermediate cells ([50], see Fig. 1).

Molecular studies have shown that the intermediate monocytes have an intermediate phenotype between the classical and non-classical monocytes, but they show selectively higher levels of expression for MHC-Class II, CD74 and for receptors relevant to angiogenesis [44,47]. Functional studies of the intermediate monocytes had shown a higher antigen presenting activity [15] and a higher pro-angiogenic capacity [47]. Clinical studies documented an expansion of the intermediate monocytes in various settings including sarcoidosis, asthma, heart failure and colorectal cancer [16,28,45,36]. In time course studies in inflammatory disease an increase in intermediate monocytes is followed by an increase of non-classical monocytes suggesting a sequential developmental relationship [51]. Taken together, when looking at human monocytes in health and disease, we no longer study monocytes as such. Rather it is state of the art to define monocyte subsets using markers like CD14 and CD16.

3. Monocyte subsets in non-human primates

Monocytes have been studied in non-human primates using anti-human monoclonal antibodies and CD16 positive cells could be readily identified [31,30]. These studies in cynomolgus monkeys were also the first to demonstrate the induction of CD16-positive monocytes by M-CSF and here a gradual transition from classical monocytes via intermediate to non-classical monocytes was noted. Later on in Rhesus Macaques it was shown that classical monocytes account for about 80% of all monocytes with 10% each for intermediate and non-classical cells [22]. The analysis of monocyte phenotypes revealed patterns similar to what is seen in man in that non-classical monocytes had lower CCR2 and CD64 and higher CX3CR1 and CD68. In these analyses the intermediate monocytes again had an intermediate phenotype. The same study demonstrated that infection with SIV preferentially increased intermediate and non-classsical monocytes and this correlated with viral load in plasma [22]. Rhesus macaques were also studied by Kwissa et al. and it was shown that injection of the TLR7/8 ligand R-848 into non-human primates led to a strong increase in intermediate monocytes on day 1 followed by a peak of non-classical monocytes on day 2 [24]. Taken together the non-human primates show numbers and patterns of monocyte subsets similar to man.

4. Monocyte subsets in the mouse

In the mouse model the first evidence for different subsets was provided by Palframan based on the differential expression of a CX3CR1-promoter driven GFP transgene [33]. Subsequent reports have shown that the two subsets identified with this approach had different phenotypic and functional properties, including the higher ability of the GFP-high cells to attach to endothelium in vivo [14,3]. Also these GFP-high cells showed higher levels of TNF expression and emigrated in into tissue rapidly upon infection and inflammation [3]. Higher TNF production by the CD43++ Ly6C + CX3CR1high monocyte subset was seen for TLR4 ligands on a per cell basis [6]. Parallel research has defined mouse subsets via differential expression of Ly6C and has demonstrated informative patterns of receptor expression including low to absent CD62L on Ly6Clow monocytes [40]. The properties described for the CX3CR1high, Ly6Clow mouse monocytes resemble what had been reported for the CD16-positive human monocytes.

A side by side comparison of gene expression patterns supported the contention that these cells in man and mouse are homologous, but there were also important differences with a reverse pattern of gene expression for genes like CD64, CXCR4, TREM-1 and CD36 [18]. Hence it is clear that the CD16-positive human monocytes and the Ly6C-low mouse monocytes are similar but they are not identical. The reverse pattern for several important genes implies that in models of disease findings on mouse monocyte subsets cannot be directly applied to the human diseases. Of note there is a clear difference in the proportion of the two monocyte subsets in man and mouse in that in the mouse the two populations each account for about half of the total monocytes [33,6]. The higher proportion of the Ly6Clow in the mouse may be explained by the fact that blood is drawn from these animals under extreme stress, like cardiac puncture under terminal anesthesia, such that these monocytes are mobilized from the marginal pool. Studies to substantiate this point have, however, not been published.

Work by Sunderkotter et al. was the first to characterize of population of Ly6Cmed monocytes and these cells had features intermediate between the Ly6C high and low monocytes [40].

Based on the similarities in phenotype and function between man and mouse the nomenclature for monocyte subsets proposed for the mouse a similar classification of classical, intermediate and non-classical monocytes [50]. This nomenclature unifies the human and the mouse system and avoids the confusion generated with terms like inflammatory and pro-inflammatory monocytes which refer to reciprocal cell populations.

Interventions to manipulate monocyte subsets in the mouse model include the treatment with anti-M-CSF receptor antibodies [26,25]. Blockade of the M-CSF-pathway with such antibodies led to a reduction of mouse non-classical Ly6Clow monocytes. Regarding the effects on tissue macrophages the two studies reported conflicting findings in that Lenzo et al. noted a decrease of peritoneal and alveolar macrophages in inflammation [25] while MacDonald et al. did not [26]. Both studies found a decrease of peritoneal macrophages by such antibodies under homeostatic conditions. As to whether the effects on tissue macrophages are dependent on the depletion of the non-classical monocytes or are due to a direct effect of the antibody on the tissue macrophages still needs to be resolved.

The effects of these antibodies on the non-classical monocytes in blood are in line with the clinical pilot study in rheumatoid arthritis patients where an anti-M-CSF antibody also depleted the non-classical monocytes [23].

5. Monocyte subsets in the rat

For the rat monocyte subsets have been defined based on high or low expression CD43 expression and phenotyping demonstrated high CD4 on the CD43++ cells [1]. Infusion of IFNgamma into rats

Please cite this article in press as: L. Ziegler-Heitbrock, Reprint of: Monocyte subsets in man and other species, Cell. Immunol. (2014), http://dx.doi.org/10.1016/j.cellimm.2014.06.008