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MINIREVIEWS

Modulation of monocyte subsets in infectious diseases

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Abstract

Monocytes are effector immune cells but a precise analysis of their role in immune response has been precluded by their heterogeneity. Indeed, human monocytes are composed of at least three different subsets with different phenotypic characteristics and functional properties, the so-called classical, intermediate and non-classical monocytes. A review of the literature shows that these monocyte subsets are differently affected during viral, bacterial, parasitic and fungal infections. The expansion of the CD16$^+$ compartment (intermediate and non-classical monocytes) is typically observed in the majority of infectious diseases and the increased proportion of CD16$^+$ monocytes is likely related to their activation through their direct interaction with the pathogen or the inflammatory context. In contrast, the number of non-classical and intermediate monocytes is decreased in Q fever endocarditis, suggesting that complex mechanisms govern the equilibrium among monocyte subsets. The measurement of monocyte subsets would be useful in better understanding of the role of monocyte activation in the pathophysiology of infectious diseases.

Key words: Monocytes subsets; Infection; Virus; Bacteria

Core tip: In this review of the literature we show that monocyte subsets are differently affected during viral, bacterial, parasitic and fungal infections. We observe that the CD16$^+$ compartment (intermediate and non-classical monocytes) is typically increased in the majority of infectious diseases. The measurement of monocyte subsets would be useful in better understanding of the role of monocyte activation in the pathophysiology of infectious diseases.

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INTRODUCTION

Human monocytes arise from bone marrow progenitors with myeloid-restricted differentiation potential and then circulate in the blood for a few days before migrating into tissues[1]. Monocytes differentiate into macrophages and dendritic cells (DCs) during inflammation and less efficiently in the steady state[2].

Monocytes play a pivotal role in the immune response as effector cells. These cells are equipped with pattern recognition receptors (PRRs) and phagocytic receptors necessary for the ingestion and elimination of microbes and damaged cells[3,4]. They express adhesion molecules and chemokine receptors, which are required to migrate toward inflamed or infected tissues[5]. Monocytes also initiate the adaptive immune response through their ability to produce cytokines and to differentiate into DCs, the major antigen-presenting cells (APCs)[6]. Finally, monocytes play critical roles in homeostasis and tissue repair[7].

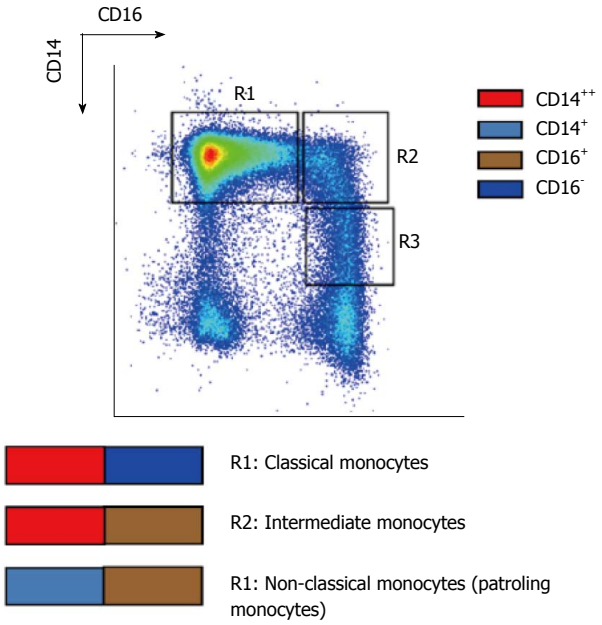

Figure 1 Expression of $CD14^{++}$ and $CD16^{+}$ cells.

A fundamental property of monocytes consists of their high plasticity[8]. They may adopt a biphasic response to a unique signal, first releasing inflammatory cytokines such as interleukin (IL)-6 and IL-1β[9] and then releasing immunoregulatory cytokines such as IL-10 and transforming growth factor (TGF)-β, thus an avoiding excessive inflammatory response[10]. We recently demonstrated that the gene expression program of human monocytes is determined by the time scale of the stimulation: although macrophage polarization genes are expressed in early stimulated monocytes, this expression is lost when the stimulation is sustained[11].

Another difficulty in analyzing the precise role of monocytes in the immune response is related to their heterogeneity, as they are composed of at least three different subsets with different phenotypic characteristics and functional properties. The aim of this review is to summarize what is known regarding the functions of monocyte subsets and to describe the evolution of these monocyte subsets during infectious diseases.

DEFINITION OF MONOCYTE SUBSETS

Human monocytes were initially defined as an homogeneous population on the basis of morphology, cytochemistry (monocyte-specific esterase) and flow cytometry measurements, such as light scattering and the expression of CD14, the receptor of bacterial lipopolysaccharides (LPS)[12]. Multi-color flow cytometry using antibodies against CD14 and CD16, the low affinity receptor for IgG, has revealed their heterogeneity, consisting of three subsets[12,13]. The "classical monocytes" that represent approximately 90% of circulating monocytes highly express CD14 but not CD16 ($CD14^{++}CD16^{-}$ cells). Other circulating monocytes express CD16: "non-classical monocytes" representing approximately 5% of circulating monocytes, express low levels of CD14 but highly express CD16 ($CD14^{+}CD16^{+}$cells) and "intermediate monocytes", which highly express CD14 with the concomitant expression of CD16 ($CD14^{++}CD16^{+}$ cells)[14] (Figure 1). However, the notion of intermediate monocytes is still debated. For Ziegler-Heitbrock and Hofer, they are only a transition from[14], conversely, for Hijdra *et al*[15], they consist of a true population of monocytes, as revealed by the expression of chemokine and Tumor Necrosis Factor (TNF) receptors. Because only the level of CD14 expression allows the distinction between non-classical monocytes and intermediate monocytes and many papers do not explicitly make this distinction, we propose referring to them collectively as $CD16^{+}$ monocytes[1] and precisely defining the type of monocyte subset when it is documented.

PHENOTYPIC AND FUNCTIONAL CHARACTERISTICS OF MONOCYTE SUBSETS

The phenotypic properties of $CD16^{-}$ (classical) and $CD16^{+}$ (intermediate and non-classical) human monocytes are summarized in Table 1. $CD16^{+}$ monocytes express lower levels of CD64 than $CD16^{-}$ monocytes but highly express HLA-DR, CD86, and CD49d compared with $CD16^{-}$ monocytes[16,17], demonstrating an activated phenotype. The expression of PRRs and chemokine receptors varies according to the monocyte subset. The intermediate monocytes express higher levels of Toll-like receptor (TLR)-2 and TLR4 than classical and non-classical monocytes[17,18]. The non-classical monocytes do not express CCR2, the membrane receptor of the chemokine CCL2, making them likely unable to migrate in response to CCL2. In contrast, classical and intermediate monocytes express CCR2 and migrate in response to CCL2[19,20]. Intermediate monocytes, but not classical and non-classical monocytes, express CCR5[19-21]. The responses to classical agonists of monocytes vary according to the monocyte subset. For instance Lipopolysaccharide (LPS) stimulation of classical monocytes, but not intermediate monocytes, decreases the membrane expression of CD163; hence, the majority of soluble CD163 found in plasma originates from classical monocytes[22,23].

The functional properties of monocyte subsets are also different (Table 2). The phagocytosis of Staphylococcus aureus and *Escherichia coli* is lower in non-classical monocytes than in intermediate monocytes and classical monocytes, a property likely related to the expression of CD14[18]. The non-classical monocytes produce less reactive oxygen species (ROS) in response to ligands of TLR4, TLR7 or TLR8 than the classical monocytes[24,25]. In addition non-classical and intermediate monocytes produce lower levels of cytokines, including granulocyte colony-stimulating factor, IL-6, IL-10 and CCL2 in response to LPS stimulation than classical monocytes[20].

Table 1 Major marker of monocyte subsets

Markers	Classical monocytes	Intermediate monocytes	Nonclassical-monocytes	Ref.
CD14	++	++	+	[1]
CD16	-	+	+	[1]
CD86	+	++	++	[17]
CD64	++	+	+	[17]
HLA-AB	+	++	+	[21]
HLA-DR	+	++	+	[21,25]
CCR1	++	+	-	[21]
CCR2	++	-	-	[15,20,21]
CCR5	+	++	-	[15,20,21]
CXCR1	++	-	-	[21]
CXCR2	++	-	-	[15,21]
CX3CR1	++	+	-	[15,20]
CD62L	++	-	-	[20,21]

++: High; +: Median; -: Low.

Table 2 Functional characteristics of monocyte subsets

Functions	Classical monocytes	Intermediate monocytes	Nonclassical-monocytes	Ref.
Phagocytosis	++	++	+	[25]
MHC Ⅱ processing	+	++	+	[25]
Antigen presentation	+	++	+	[25]
$CD4^+$ T cell proliferation	+	++	+	[25]
Transendothelial migration	-	-	++	[15]
Patrolling endothelium	-	-	++	[24]
Virus sensing	-	-	++	[24]
TNF production	+	-	++	[24]
IL-1β production	+	++	++	[24]
CCL2 production	++	-	-	[24]
IL-10 production	++	-	-	[24]

++: High; +: Median; -: Low. IL: Interleukin.

The monocyte subsets likely play different roles as APCs. $CD16^+$ monocytes express higher levels of HLA-DR than classical monocytes[12,26], suggesting that they are potent APCs. It has been shown that $CD16^+$ monocytes are more efficient in presenting tetanus toxoid to $CD4^+$ T cells than classical monocytes[27]. Taken together, these results suggest that $CD16^+$ monocytes are activated under homeostatic conditions but they are less responsive to monocyte stimuli than $CD16^-$ monocytes.

Interestingly, monocytes are known to act as precursors of macrophages or DCs. It has been shown that the ability of monocyte subsets to differentiate into DCs is different according the monocyte subset. Indeed, nonclassical monocytes are more prone to becominge DCs with a higher capacity to induce T cell proliferation and IL-4 production by $CD4^+$ T cells[28]. In addition, the functional properties of monocyte-derived macrophages are dependent on the type of monocyte subset. It has been recently shown that the macrophages derived from $CD16^+$ monocytes are more phagocytic than those derived from classical monocytes; they also exhibit a specific gene expression program[29].

The investigation of monocyte functions has benefited from the use of mouse models, though it remains unclear whether monocyte subsets are similar in humans and mice. Murine monocytes can be separated into at least two subpopulations, $Gr1^+$ and $Gr1^-$ monocytes. The major subset of murine monocytes is composed of "inflammatory" $Gr1^+$ monocytes that produce high levels of TNF, ROS and nitric oxide (NO) but low levels of IL-10 upon *in vivo* infection with bacteria such as Listeria monocytogenes or parasites such as Toxoplasma gondii[30]. $Gr1^+$ monocytes also produce type I interferons (IFNs) in response to viral ligands[31]. Murine $Gr1^+$ monocytes resemble human classical monocytes based on surface marker expression, gene expression and a reduced ability to produce inflammatory cytokines[32,33]. In contrast, the minor subset of murine monocytes does not express Gr1. These $Gr1^-$ monocytes patrol the blood vasculature, differentiate into macrophages after extravasation into tissues and are likely associated with tissue repair[34,35]. Murine $Gr1^-$ monocytes, which resemble human $CD16^+$ monocytes, are described as the main producers of inflammatory cytokines such as TNF and IL-1β in response to LPS[26].

The existence of different subsets of monocytes likely has pathophysiological consequences. An expansion of the CD16+ monocyte subsets inflammatory diseases including hemophagocytic lymphohistiocytosis[36], asthma[37], sarcoidosis[38], peridontitis[39], atopic eczema[40], pancreatitis[41] and alveolar proteinosis[42] has been observed. Despite immunosuppressive therapy, the $CD16^+$ monocyte compartment is also increased in kidney transplant patients, suggesting that this subset may be involved in the persistent, allograft-induced inflammatory reaction[43]. In patients with colorectal cancer, the percentage of intermediate monocytes is mainly increased at the onset of the disease[44], and this subset is also increased in adult survivors of childhood acute lymphoblastic leukemia[13].

MONOCYTE SUBSETS AND VIRAL INFECTIONS

Human immunodeficiency virus

Human immunodeficiency virus (HIV) is a lentivirus that efficiently infects $CD4^+$ T cells, leading to their apoptosis and a decreased number of circulating $CD4^+$ T cells. The antiretroviral therapies to date restore the number of circulating $CD4^+$ T cells but are unable to completely eliminate viral infection, as demonstrated by HIV persistence in tissues. Both *in vitro* and *in vivo* studies have clearly demonstrated that blood monocytes and tissue macrophages can be infected by HIV[45,46]. During the early phase of HIV infection, the proportion of $CD16^+$ monocytes is increased[47], and this increase in $CD16^+$ monocytes in treatment-naïve HIV-infected patients is correlated with high viral loads and low $CD4^+$ cell counts[48]. Convergent results have been obtained with the infection of non-human primates by simian immunodefi-

ciency virus (SIV), with SIV infecting both $CD4^+$ T cells and monocytes. Following the first description of $CD16^+$ monocytes in cynomolgus monkeys (Macaca fascicularis) nearly two decades ago, an increase in $CD16^+$ monocytes ten days after SIV infection has been observed. Note that increased levels of $CD16^+$ monocytes have also been reported in rhesus monkeys (Macaca mulatta) with lentiviral encephalitis[49]. The treatment of chronically infected macaques with high doses of corticosteroids decreased the proportion of $CD16^+$ monocytes (intermediate monocytes), whereas the other subsets of monocytes were found to be unresponsive to corticosteroids[50]. Highly active antiretroviral therapy (HAART) rescues the amount of intermediate monocytes[51]. The viral efficiency of HAART is also associated with insulin resistance, and it has been reported that the abundance of classical monocytes predicts the risk of insulin resistance and metabolic syndrome during the chronic phase of HIV infection[51].

HIV infection also affects the phenotype of monocyte subsets. The membrane expression of CD163, a receptor involved in the resolution of inflammation and M2 polarization[52] by classical and intermediate monocytes is increased in HIV-1 infection, but HIV-infection does not induce the membrane expression of CD163 in non-classical monocytes[53]. Note that plasma CD163 is not significantly altered by HIV-1 infection, demonstrating that CD163 shedding is not associated with the alteration of the membrane expression of CD163[53]. The exposure of whole blood to HIV enhances the expression of tissue factor (TF) on non-classical monocytes, whereas LPS-activated TLR-4 increases TF expression on all monocyte subsets[47]. The acquisition of such activated phenotypes by non-classical monocytes is reminiscent of the observation in acute coronary syndrome and suggests a potential role of non-classical monocytes in the cardiovascular risk of HIV infection. A recent study reported a decrease in the proportion of non-classical monocytes expressing TF in patients treated with rosuvastatin though anti-retroviral therapy has no effect on monocyte activation[54]. The functional alteration of monocyte subsets is associated with that of the programmed death-1 (PD-1) pathway known to limit the functions of virus-specific T cells during chronic infections such as HIV infection[55]. The expression of PD-1 by monocytes is increased in viremic subjects compared with healthy subjects, but the expression of PD-1 by $CD16^+$ monocytes is twofold higher than that of classical monocytes. The relationship between HIV infection and PD-1 expression likely involves an indirect mechanism in which inflammatory cytokines play a major role[56]. First, the expression of PD-1 by monocyte subsets is not related to viral load in patients with HIV infection. *In vitro*, viral material such as HIV single-stranded RNA (RNA40) fails to increase PD-1 expression by monocytes. Second, inflammatory cytokines such as TNF, IL-1β and IL-6 increase the expression of PD-1 by monocytes in a dose-dependent manner, and it has been largely demonstrated that the circulating levels of these cytokines are increased in HIV infection[57,58]. Taken together, these results suggest that HIV infection leads to the modulation of monocyte subsets.

Dengue virus

Dengue fever, a public health problem in tropical countries, is due to the dengue virus (DENV), a flavivirus that is transmitted to humans *via* the bite of an *Aedes* mosquito[59,60]. Monocytes are implicated in protection against DENV infection[61,62]. Indeed, monocytes infected *in vitro* with DENV produced IFN-α which is protective against viruses[63]. This is confirmed by the increase in DENV titers in mice deficient in IFN receptors[64]. Nevertheless, the role of monocytes is likely more complex. Monocytes are involved in dengue pathogenesis through virus propagation[65], and DENV-specific antibodies promote the infection of monocytes and thus increase the viral burden of individual monocytes[66].

It has been demonstrated that the number of $CD16^+$ monocytes is twofold higher in dengue patients than in healthy controls[67], but the relative role of monocyte subsets in dengue infection remain unclear. *In vitro* classical monocytes and $CD16^+$ monocytes are susceptible to DENV and produce molecules associated with dengue protection, such as IFN-α, CXCL10 and TNF-related apoptosis-inducing ligand (TRAIL), a cytokine known to induce cell apoptosis[68]. Taken together, these results suggest that classical monocytes and $CD16^+$ monocytes may potentially contribute to anti-dengue responses, however only $CD16^+$ monocytes appear to be affected by DENV infection *in vivo*.

Hepatitis C virus

Hepatitis C is due to an RNA virus (HCV) that affects 160 million individuals worldwide and is responsible for chronic hepatitis and hepatocellular carcinoma[69,70]. It has been recently demonstrated that HCV infects $CD16^+$ monocytes but not classical monocytes in individuals infected with HCV. This specific tropism is related to the expression of CD81, the receptor considered to be necessary for HCV entry into target cells. Hence, CD81 is highly expressed on $CD16^+$ monocytes but not on classical monocytes[71]. These results also suggest that the expression of CD81 by monocyte subsets is associated with the expression of CD16. Furthermore, we can suppose that the monocyte subsets that express CD16 may serve as HCV reservoirs. In hemodialyzed patients with chronic hepatitis, the $CD16^+$ monocyte subset is increased threefold compared with healthy donors[72], suggesting an impact of the viral infection on monocyte distribution. The frequency of $CD16^+$ monocytes is decreased and negatively correlated with viral load in chronic HCV infection. Furthermore the expression of PD-L1 allows the discrimination between chronic HCV infection and spontaneous HCV resolvers[73].

Cytomegalovirus

Cytomegalovirus (CMV) is a herpes virus of medical importance in immune-compromised individuals. CMV has

a tropism for immune and non-immune cells *in vivo* and *in vitro*, yet peripheral blood leukocytes are involved in viremia and latency, regardless of the immune status of the patient[74]. Monocytes are likely latent reservoirs and support viral dissemination by benefiting from the maturation of monocytes into permissive macrophages and dendritic cells. CMV encodes inflammatory viral chemokines required for viral dissemination. A recent study proposed that patrolling monocytes acquire the virus from the initial site of infection and deliver to the spleen and salivary glands where CMV can persist. Analysis of the recruitment of patrolling monocytes reveals two phases: the first phase is necessary for the activation of natural killer (NK) response; and the second phase, involving viral chemokine and CX3CR1, the marker of patrolling monocytes, is required for the amplification of monocyte recruitment. Although this study revealed a previously undescribed role for this minority monocyte subset as a latent reservoir, it is not clear whether this finding can be extrapolated to human disease[75].

MONOCYTE SUBSETS AND BACTERIAL INFECTIONS

The study of monocyte subsets in bacterial infections is in its infancy. In patients with severe bacterial sepsis, the number of $CD16^+$ monocytes is dramatically increased[76]. Another report shows that the proportion of intermediate and non-classical monocytes increases during sepsis. $CD16^+$ monocytes show a reduced ability to engulf a bacterium such as *E. coli*, express low levels of CD86 and HLA-DR, and poorly presents antigen to T cells[77]. The hemolytic uremic syndrome observed in children is due to bacterial toxins. The acute period of this disease is characterized by an increased proportion of $CD16^+$ monocytes that express higher levels of CD16 and lower levels of CD14 compared with those of healthy age-matched children. In addition, HLA-DR expression by classical monocytes is decreased in this patients, and this lower expression of HLA-DR is related to the severity of the disease[78]. In patients with tuberculosis, the percentage and absolute numbers of $CD16^+$ monocytes are increased[79]; nevertheless, some authors did not find changes in the proportion of $CD16^+$ and $CD16^-$ monocytes during tuberculosis[80]. When expanded, these monocytes exhibit decreased expression of markers associated with maturation and differentiation and also functional alterations. These alteration include a decrease in phagocytosis potential, a tendency toward cell death and an increased production of TNF after stimulation with live *M. tuberculosis*[79]. In addition, $CD16^+$ monocytes differentiate into cells that poorly express CD1a and CD209 (DC-SIN) and with a low capacity for presenting mycobacterial antigens. It is likely that this differentiated cell populations contributes to the impairment of DC maturation during tuberculosis[81]. The expansion of these monocytes is amplified in patients with HIV co-infection[82]. Q fever is an acute infectious disease caused by *Coxiella burnetii*, an obligate intracellular bacterium that targets monocytes and macrophages[83], in patients with valvular damage and in immunocompromised patients, the primo-infection may lead to a chronic disease that essentially manifests as endocarditis[83]. We recently found that the distribution of monocyte subsets is altered in patients with Q fever endocarditis, with a decreased number of $CD16^+$ monocytes (non-classical and intermediate monocytes) (submitted manuscript), which to our knowledge, is the first demonstration that minor monocyte subsets are decreased in an infectious disease.

MONOCYTE SUBSETS AND PARASITIC INFECTIONS

Only a few papers report the modulation of monocyte subsets in parasitic infections. It has been demonstrated that, the proportion of $CD16^+$ monocytes is increased in pregnant women infected with *Plasmodium falciparum*, the agent of malaria. These $CD16^+$ monocytes express higher levels of CCR5 than classical monocytes[84]. $CD16^+$ monocytes may play a major in the pathogenesis of maternal malaria because placental plasma concentrations of chemokines such as CCL3 and IL-8 are increased and are associated with placental monocyte infiltration[84,85]. Nevertheless, classical monocytes appear to be critical for the control of *Toxoplasma gondii* infection in mice[86] and *Leishmania brasiliensis* in humans *via* the generation of reactive oxygen species[87].

MONOCYTE SUBSETS AND FUNGAL INFECTIONS

Aspergillus fumigatus

Aspergillus fumigatus (*A. fumigatus*) is an environmental fungus that causes life-threatening infections in neutropenic patients. Inhaled *A. fumigatus* spores (conidia) germinate in the lung and form hyphae that invade blood vessels and disseminate to other tissues[88]. It has been clearly demonstrated that monocyte subsets contribute differently to the defense against *A. fumigatus* infection. Indeed, classical monocytes are efficient at restricting conidial germination *in vitro* whereas $CD16^+$ monocytes fail to suppress the germination of conidia. The efficiency of monocyte subsets in controlling *A. fumigatus* germination is likely dependent on inflammatory cytokines. Although classical monocytes do not secrete TNF following infection, $CD16^+$ monocytes produce high levels of TNF and IL-1β[89]. These results are rather surprising because $CD16^+$ monocytes are thought to be more mature and share features with tissue macrophages and, thus, might be expected to have stronger antimicrobial properties[26]. These data suggest that $CD16^+$ monocytes are the subset that is the most efficient in the control of *A. fumigatus* infection.

Candida albicans

Candida albicans (*C. albicans*) is responsible of the major-

ity of fungal infections. In 30% of healthy subjects, *C. albicans* is present as commensal yeast. However when host defense mechanisms are impaired, *C. albicans* can cause mucocutaneous infections, or disseminate into the bloodstream, thereby infecting multiple organs[90]. Monocytes are associated with systemic candidosis. While the uptake and killing of *C. albicans* by classical monocytes and $CD16^+$ monocytes are similar, classical monocytes stimulated with heat-killed yeasts produce higher levels of IL-1β and prostaglandin E2 (PGE2) than $CD16^+$ monocytes[91]. It has also been demonstrated that the production of IL-1β by classical monocytes favors the production of IL-17A by $CD4^+$ T lymphocytes and that PGE2 regulates inflammation[92-94]. In addition, the higher production of IL-1β and PGE2 by classical monocytes is associated with increased membrane expression of the mannose receptor (MR)[92,95], suggesting that classical monocytes instead play an immunoregulatory role. These results suggest that only classical monocytes are able to initiate antifungal Th17 responses in human $CD4^+$ T lymphocytes.

CONCLUSION

Circulating monocytes has been classically considered a homogeneous cell population, but in recent years it has become clear that they are composed of different subsets. A review of the literature shows that monocyte subsets are differently affected in infectious diseases caused by varied pathogens including virus, bacteria, parasites and fungi. In the majority of cases, an expansion of the $CD16^+$ compartment is observed, and the increase in $CD16^+$ monocytes is likely related to their activation through their direct interaction with the pathogen or through cytokines. More surprisingly, it has also been found that the relative number of non-classical and intermediate monocytes is decreased in Q fever endocarditis, suggesting that complex mechanisms govern the equilibrium between monocyte subsets. The measurement of monocyte subsets would be useful in better understanding of the role of monocyte activation in the pathophysiology of infectious diseases.

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