The Novel Subset of CD14+/CD16+ Blood Monocytes Is Expanded in Sepsis Patients

By Günter Fingerle, Almuth Pforte, Bernward Passlick, Matthias Blumenstein, Marion Ströbel, and H.W. Löms Ziegler-Heitbrock

Staining with CD14 and CD16 monoclonal antibodies will identify two monocyte subpopulations in human blood: a major population of regular monocytes, which strongly expresses the CD14 antigen (CD14+), and a minor population with weak expression of CD14 and expression of the CD16 antigen (CD14+/CD16+). As shown herein, the latter cells account for 45 ± 22% of all monocytes in 3 of 18 patients and for more than 500 cells in 4 of 18 cases. This subset of monocytes, designated CD14+/CD16+, exhibits a more mature phenotype compared to the CD14+ monocytes, characterized by lower levels of CD11b and CD33 antigens, consistent with a more mature nature of the CD14+/CD16+ cells. Levels of interleukin-6 (IL-6) were increased in septic patients; 3 of 5 patients with high numbers of CD14+/CD16+ cells (>200/μL) had high levels of IL-6 (>250/U/mL). These data suggest that sepsis may lead to substantial changes in blood monocyte composition and may be related to elevated levels of cytokines such as IL-6.

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SEPTICEMIA IS A life-threatening condition that occurs in patients with immunodeficiency due to inborn defects, to human immunodeficiency virus (HIV) infection, to malignancy, to chemotherapy, to major surgery, and to trauma. In such patients, massive flooding of the body with microbes and microbial products will activate several cellular systems, including endothelial cells and monocytes/macrophages. These cells will then produce and release prostanoids, platelet activation factor, reactive oxygen and nitrogen species, and cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and transforming growth factor β (TGFβ), which are responsible for many of the pathophysiologic mechanisms observed in sepsis. Blood monocytes, in addition to producing cytokines, are also responsive to these mediators, which may activate or deactivate monocytes and may induce maturation towards macrophages. We have recently identified a novel subset of blood monocytes,1,2,3 as opposed to the strongly CD14-posi-
tive regular monocytes (CD14+), these cells are characterized by low levels of the CD14 antigen (CD14+) and by the expression of the CD16 antigen. Therefore, these cells were designated CD14+/CD16+. Comparison with alveolar macrophages shows that these cells bear features of tissue macrophages, as evidenced by the pattern of additional cell surface molecules.3 In the present report, we have asked whether the CD14+/CD16+ cells may be expanded in sepsis. We can, in fact, show an increase in percentage and number coincident with high levels of IL-6 in some cases.

MATERIALS AND METHODS

Patients. Patients analyzed were treated at the intensive care units (ICUs) of the Department of Internal Medicine, Klinikum Innenstadt; the Department of Surgery, Klinikum Innenstadt; and the Department of Internal Medicine I, Klinikum Großhadern, Munich. The average age of the 18 patients was 59 ± 16 years (17 men and 1 woman). Diagnosis of sepsis syndrome was based on fever, infectious focus or positive blood culture, leukocytopenia or leukocytosis, and thrombocytopenia or a more than 30% decrease in thrombocyte count (3 of 4 required). Three patients had a positive blood culture, 15 patients had a defined focus of infection, 18 patients had fever, and 18 patients had leukocytosis at any time during their stay at the ICU. Two patients had leukocytopenia, 6 patients had absolute thrombocytopenia, and 9 additional patients had a more than 30% decrease in thrombocyte count within 1 week of the monocyte analysis presented. Patients received multiple drugs, including antibiotics, vasopressors, anticoagulants, diuretics, analgetics, sedatives, and muscle relaxants. Samples were obtained in 1- to 2-day intervals after diagnosis of sepsis syndrome had been established, and we report on highest values during an observation period of 2 weeks. Hematologic values at the time of monocyte analysis are given in Table 1. Control donors were apparently healthy volunteers recruited from laboratory personnel and from relatives (n = 35; average age, 56 ± 20 years).

Cells. For determination of CD14+/CD16+ cells, EDTA blood samples were immediately stored on ice and subjected to whole blood staining within 3 hours. For this purpose, 100 μL whole blood was admixed with 150 μL phosphate-buffered saline and then reacted with the CD14 antibody My4-fluorescein isothiocyanate (FITC) (1:20; Coulter Electronics, Krefeld, Germany) and the CD16 antibody Leu1-1c-phycoerythrin (PE) (1:4; Becton Dickinson, Heidelberg, Germany) for 20 minutes on ice, followed by lysis of erythrocytes and fixation of cells using commercial reagents according to manufacturer’s instructions (Coulter Electronics). Using a FACScan flow cytometer (Becton Dickinson), we first determined the percentage of monocytes among all leukocytes in the light scatter histogram and then the CD14 and CD16 staining within the
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age (yr)</th>
<th>Disease</th>
<th>Infectious Focus*</th>
<th>Temperature (°C)*</th>
<th>Leukocytes (cells/μL)*</th>
<th>Platelets (cells/μL)*</th>
<th>CD14+/CD16-</th>
<th>Serum IL-6 (U/mL)†</th>
<th>Outcome (died/survived)</th>
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<td>1</td>
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<td>Adenocarcinoma</td>
<td>—</td>
<td>40.0</td>
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<td>Cholangitis</td>
<td>BC: E coli</td>
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<td>68</td>
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<td>38.6</td>
<td>42,600</td>
<td>101,000</td>
<td>36</td>
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<td>Lo</td>
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<td>Ma</td>
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<td>38.8</td>
<td>15,700</td>
<td>347,000</td>
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<tr>
<td>18</td>
<td>Kr</td>
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<td>Lung: Klebsiella</td>
<td>36.6</td>
<td>16,900</td>
<td>71,000</td>
<td>24</td>
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Abbreviation: BC, blood culture.

* All of the patients fulfilled at least 3 of the 4 criteria (infectious focus, fever, leukocytosis or leukopenia, platelet decrease) for the diagnosis of septicemia. In some cases, the values for the day of monocyte analysis given here were in the control range again.

† Control donors had no detectable serum IL-6 (<15 U/mL).

‡ Patients had a decrease of more than 30% in platelet count within the previous week.
gates set around monocytes. Gates were set such that they allowed for some spill-over of lymphocytes, but not of granulocytes. For proper adjustment of fluorescence amplification and compensation, reciprocal isotype controls (My4-FITC/IgGl-PE and IgGl-FITC/CD11c-PE) were used. To exclude a spill-over of granulocytes, the CD14+/CD16 staining of these cells was assessed separately and the window for CD14+/CD16+ monocytes was adjusted accordingly. If granulocytes do show staining, they localize to the lower left corner of the CD14+/CD16+ monocyte window (see Fig 4). The percentage of CD14+/CD16+ and of CD14+ cells was determined and used to calculate the percentage among all (CD14+ and CD14+/CD16+) monocytes and the absolute number (cells per microliter) by taking into account the percentage of cells in the monocyte light scatter window and the leukocyte count. In the FACScan analysis, fluorescence is given on a logscale with 4 logs over 1024 channels. Here, 78 channels give one doubling of fluorescence intensity. Specific mean fluorescence intensity (sMFI) was determined by subtracting MFI for the isotype control from the MFI of the specific antibody.

For three-color immunofluorescence and for cell sorting, mononuclear cells were isolated from heparinized blood by ficoll-hyphaque (Pharmacia, Freiburg, Germany) density gradient separation, and cells were stored in liquid N2 after controlled freezing. For three-color immunofluorescence, cells were first reacted on ice with either anti-class II (I-2; Coulter), CD11b (IOM-1; Immunotech, Marseille, France), CD33 (My-9; Coulter), CD64 (anti-FcγRI; kindly provided by Dr P. Dadonna, Centocor, Malvern, PA), CD32 (anti-FcRII, 2E1; Immunotech), anti–VLA-4 (HP2/1; Immunotech), and CD54 (anti–ICAM-1; P.249; kindly provided by Dr J. Johnson, University of Munich, Munich, Munich Germany), or with the respective isotype control antibodies obtained from the same source as the specific antibody. After washing, cells were stained with goat antimouse-lg Texas red (M25003; Medac, Hamburg, Germany) as a standard was titrated in 20-μL volumes in threefold serial dilutions in duplicates with and without anti–IL-6 antibody (no. 27.2 15.55; Janssen Biochimica, Geel, Belgium). To this suspension, My4-FITC and LeulIc-PE were added directly. Cells were then analyzed in an EPICS V 753 flow cytometer equipped with one argon laser for direct excitation and one argon laser used to pump a Rhodamine 6 G dye laser. Cells were excited by 488 nm from the argon laser and 7 microseconds later by 600 nm from the dye laser. One thousand to 5,000 CD14+ / CD16+ cells were analyzed per sample. Fluorescence is given on a logscale with 3 logs over 256 channels. One doubling of fluorescence intensity results in a 26 channel increase.

For cell sorting, cells were stained with My4-FITC and Leu11c-PE, and the CD14+/CD16+ cells were isolated using the EPICS V 753 cell sorter to a purity of greater than 90%. Cytospin preparations of these cells were stained with May–Grünewald-Giemsa staining according to standard laboratory procedures.

IL-6 assay. IL-6 was measured in a bioassay using the 7TD1 cell line with MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide) as a read out as described. In brief, heparin plasma or recombinant IL-6 (2 × 106 U/mg; Boehringer Mannheim, Penzberg, Germany) as a standard was titrated in 20-μL volumes in threefold serial dilutions in duplicates with and without anti–IL-6 antibody (no. 27.215.55; Janssen Biochimica, Geel, Belgium). To this mixture, 5 × 105 7TD1 cells per well were added and grown for 3 days, followed by the addition of tetrazolium salt (MTT; no. M2128; Sigma), solubilization of crystals, and reading of optical density (OD) at 577 nm in an enzyme-linked immunosorbent assay (ELISA) reader. Units of IL-6 were calculated from the specific OD (OD of plasma sample minus 0D of plasma sample with anti–IL-6 antibody) with reference to the recombinant standard.

Statistics. For statistical analyses, the Student’s t-test, the Kruskal-Wallis ANOVA test, and Pearson correlation analysis were used.

RESULTS

Numbers of CD14+/CD16+ cells. In apparently healthy control donors, two-color immunofluorescence analysis with CD14 (My4) and CD16 (Leu11c) will identify two monocyte subsets. In the example in Fig 1, one subset that strongly stains for CD14 accounts for 82.5% of all monocytes, as defined by expression of CD14, whereas another subset that weakly stains for CD14 but strongly stains for CD16 accounts for 17.5%. On average, in 35 control donors, these CD14+/CD16+ cells form 9.3% ± 5.2% of all monocytes and the average absolute number is 45 ± 22 cells/μL.

In patients with septicemia, CD14+/CD16+ can become the predominant cell type. In the example in Fig 2A they account for 55% of all monocytes. However, in this patient, the absolute number is only slightly increased to 141 cells/μL. In a second example in Fig 2B, 68% of all monocytes are CD14+/CD16+ cells and here the absolute number is increased to 1,592 cells/μL.

Of note, these septicemia patients showed in addition a substantial decrease in CD14 staining intensity on the regular monocytes as well. Compared with the control donor with an sMFI of 427 channels (Fig 1), CD14 intensity was about sixfold and eightfold lower in these examples.

When looking at a group of 18 patients, increased percentages of CD14+/CD16+ cells with more than 30% of all monocytes were observed in 6 of 18 patients (Fig 3) and 3 of 18 patients had more than 50% CD14+/CD16+ cells. The absolute number of CD14+/CD16+ cells was dramatically increased in some patients, with more than 500 cells/μL in 4
Fig 2. Monocyte subpopulations in blood of sepsis patients. Whole blood from 2 sepsis patients was stained with directly conjugated antibodies and analyzed by gating on monocytes according to light scatter. (A) CD14+CD16+ cells, 55% with 141 cells/μL (patient no. 2). (B) Sixty-eight percent with 1,592 cells/μL (patient no. 3). Fluorescence intensity for CD14 on the regular monocytes was 201 channels (A) and 260 channels (B).

of 18 patients (Table 1). Two of these patients (nos. 7 and 8) had only a moderate increase in percentage to around 20%. Irrespective of the increase in CD14+/CD16+ cells, all patients showed a decrease in the CD14 antigen density on the regular monocytes. Nine of 11 patients studied had an sMFI of less than 300 channels. On average, in 11 patients, sMFI for CD14 on regular monocytes was 260 ± 85 channels, compared with 453 ± 22 in controls (n = 14). This difference of 200 channels in sMFI reflects a sixfold lower antigen density. The increase of CD14+/CD16+ cells in sepsis patients was not a persistent phenomenon, but usually lasted for only 1 to 3 days within a 2-week time span of screening. Low CD14 on monocytes was not a constant phenomenon either, but specific fluorescence intensity for CD14 was frequently still low when CD14+/CD16+ cells had returned to the control range (data not shown).

When comparing CD14+/CD16+ percentage and absolute number with clinical parameters (Table 1), there was no apparent correlation to sex, age, infectious focus, leukocyte count, or platelet count. This was confirmed by Pearson's correlation analysis (P > .05). Only CD14+/CD16+ percentage and body temperature showed a striking correlation (P = .013), whereas for the absolute number of CD14+/CD16+ cells no such correlation was detected (P = .499). Furthermore, Kruskall-Wallis analysis showed no correlation to patient outcome for CD14+/CD16+ cells, CD14++ cells, IL-6 levels, platelet count, leukocyte count, or temperature (P > .1). All patients received a large spectrum of drugs (antibiotics, vasopressors, anticoagulants, diuretics, analgetics, sedatives, and muscle relaxants) and there was no apparent correlation with CD14+/CD16+ cells.

To exclude the possibility that underlying disease, drug treatment, or intensive care treatment as such might induce the CD14+/CD16+ cells, we have screened a panel of 155 patients with various conditions. This included patients with cardiovascular disease, inflammatory disease, infectious disease (viral and bacterial), metabolic disease, and neoplastic disease. In addition, we have tested 113 ICU patients without sepsis syndrome. None of these patients exhibited increased CD14+/CD16+ cells.

Morphology. In control donors, CD14+/CD16+ cells
granulocytes due to high autofluorescence and to expression of CD14 and CD16, which may spill over into the CD14⁺/CD16⁺ window (Fig 4), we wanted to confirm the monocyte nature of CD14⁺CD16⁺ cells in septicemia. For this purpose, frozen peripheral blood mononuclear cells (PBMC) from 3 patients were thawed, stained, and sorted. Photomicrographs of cytopsin preparations in Fig 5 show that these expanded cells are, in fact, monocytes and not granulocytes.

**Three-color immunofluorescence.** Our previous studies in control donors show that CD14⁺/CD16⁺ cells exhibit high levels of class II and lower levels of CD11b and CD33. This is consistent with a development towards macrophages. An example of a three-color immunofluorescence analysis of a liquid nitrogen stored PBMC sample from a sepsis patient in Fig 6 shows for the CD14⁺/CD16⁺ monocytes a higher expression of class II and a lower expression of the CD11b and the CD33 antigens. This pattern was observed in all cases studied (Table 2). When looking at fluorescence intensity as a measure of antigen density, class II was, on average, threefold higher (34 channels on a log scale with 26 channels reflecting a doubling of intensity), CD11b was 1.5-fold lower, and CD33 was threefold lower. Hence, similar to CD14⁺/CD16⁺ cells in control donors, these cells in septicemia patients appear to exhibit features of tissue macrophages.

Additional cell surface molecules studied were the FcRII (CD32) with similar expression on CD14⁺ and CD14⁺/CD16⁺ cells and CD64, which was found to be clearly expressed on CD14⁺/CD16⁺ cells, as well, although at a lower level (Table 2). The adhesion molecule ICAM-1 was not found to be expressed on the regular CD14⁺ monocytes, but it was clearly expressed on CD14⁺/CD16⁺ cells in 2 of 6 patients (Table 2, last column and footnote). This finding suggests that these cells had been activated in vivo.

**Serum IL-6.** With the strong increase of these more mature CD14⁺/CD16⁺ cells, the question arises as to what then drives maturation of these monocytes. Several cytokines have been reported to be increased in septicemia, including TNF, TGFβ, and IL-6. We have assayed serum samples for IL-6 in 7 of our patients. Whereas control sera contained no detectable levels of IL-6 (<15 U/mL), sera from patients had IL-6 values ranging from 33 to 2,516 U/mL.

The 2 patients with normal numbers of CD14⁺/CD16⁺ cells (patients no. 15 and 16, Table 1) had low levels of serum IL-6 (69 and 72 U/mL), whereas 3 of 5 patients with high counts for CD14⁺/CD16⁺ cells (patients no. 5, 6, and 7, Table 1) had high IL-6 values. These data suggest that cytokines such as IL-6 might contribute to the expansion of CD14⁺/CD16⁺ blood monocytes.

**DISCUSSION**

In the present report, we have analyzed in sepsis patients the recently described subset of CD14⁺/CD16⁺ blood monocytes. These cells are characterized by low-level expression of the CD14 antigen and a high-level expression of the CD16 antigen, when compared with regular blood monocytes. These cells have been shown to express several typical monocyte antigens, such as class II, CD4, and CR3, and they show no expression of the T/NK-cell antigens CD2, CD8, or CD57. This monocyte subset appears to be distinct from other monocyte populations, such as the FcR⁺ monocytes, and it is distinct from the CD14⁺ dendritic cell.

However, a subpopulation of monocytes recently isolated by velocity sedimentation appears to be identical to the CD14⁺/CD16⁺ monocyte population.

CD14⁺/CD16⁺ cells in control donors form a minor subset, with about 10% of all monocytes. In an extensive screening of various patients in the departments of surgery, internal medicine, pediatrics, and dermatology, we did not find an increase of the CD14⁺/CD16⁺ cells. Therefore, we have turned to a disease with active involvement of monocytes, ie, sepsis. In sepsis, bacteria or other microbes are released into blood in high amounts. The monocytes/macrophages will respond to bacteria by producing and secreting various cytokines, including TNF and IL-6. The importance of these cytokines to the pathophysiology of sepsis is shown by neutralization studies with anticytokine antibodies, which can prevent the lethal outcome. Furthermore, clinical studies have shown TNF and IL-6 to be of prognostic importance for patients with septicemia. When comparing these two cytokines, IL-6 was reported to have a higher predictive value.

Hence, monocyte-derived cytokines are central to septicemia, but few studies have analyzed characteristics of these cells in such patients.

One study reported on reduced class II expression on monocytes in sepsis patients and found low expression (<20% of monocytes) to indicate bad prognosis. In our limited study we do not observe that low class II on monocytes indicates bad prognosis (Tables 1 and 2). However, it has to be taken into account that the study of Volk et al analyzed, at a defined time after admission, transplant patients with immunosuppression, whereas we report on class II expression in a heterogenous group of patients at a time when CD14⁺/CD16⁺ cells were highest.

In our studies using CD14 and CD16 antibodies, we...
found a strong increase in the percentage and number of the CD14+/CD16+ subpopulation in some patients. When studying inflammatory disease with CD14 and CD16 antibodies, care has to be taken to exclude granulocytes, because these cells may express low levels of CD14 in addition to the CD16 molecule.\textsuperscript{17,18} For our studies we have always determined the fluorescence pattern of granulocytes, defined by light scatter properties, and then have adjusted the gates for CD14/CD16 cells accordingly. That the CD14+/CD16+ cells determined in our studies were, in fact, monocytes is supported by morphology of sorted cells. Furthermore, the expanded CD14+/CD16+ cells in sepsis patients did show high levels of class II, and low levels of CD11b and CD33 antigens. This is similar to what is observed in monocytes of control donors, and it is similar to the pattern seen in alveolar macrophages.\textsuperscript{3} These findings support the idea that CD14+/CD16+ cells are circulating cells with the properties of tissue macrophages. If the CD14+/CD16+, in fact, were circulating macrophages, then the question arises as to what drives the maturation of monocytes to macrophages in blood of sepsis patients.

Cytokines may be involved in this process. IL-4, for instance, has been shown to downregulate CD14, and TGF\textbeta has been shown to induce the CD16 antigen in blood monocytes.\textsuperscript{19,20} We have tested serum levels of IL-6, a cytokine known to induce TGF\textbeta.\textsuperscript{31} Our finding of elevated levels of...
IL-6 in sepsis patients with high levels of CD14+/CD16+ cells suggests that either CD14+/CD16+ cells synthesize cytokines or cytokines induce the CD14+/CD16+ cells. Because the relationship between IL-6 and CD14+/CD16+ cells is not clearcut in every patient, other cytokines might be involved. In experiments by Mackensen et al., treatment of cancer patients with LPS resulted in induction of serum cytokines, but this response decreased with repeated LPS injections. These repeated injections, however, led to a strong increase of CD14+/CD16+ cells. Still, the relationship between cytokines and CD14+/CD16+ cells in our study is strengthened by the significant correlation of these cells with fever, a parameter controlled by pyrogenic cytokines such as TNF, IL-1, and IL-6.

Septicemia appears to be an informative model for answering these questions and anticytokine therapy in animal models or in humans may help to elucidate the relationship between cytokine production and the expansion of CD14+/CD16+ blood monocytes.

REFERENCES


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