Neutrophils from Patients with Advanced Human Immunodeficiency Virus Infection Have Impaired Complement Receptor Function and Preserved Fcy Receptor Function

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Interleukin (IL)-8 production by human polymorphonuclear leukocytes (PMNL) to Cryptococcus neoformans is related to complement activation. Generation of the bioactive fragments C3a and C5a is responsible for IL-8 release. IL-8 production was analyzed in response to C. neoformans by PMNL from persons with early- and late-stage (<400 and <200 CD4 cells/mm², respectively) human immunodeficiency virus (HIV) infection who were at high risk for cryptococcosis. IL-8 release by PMNL from persons with early-stage infection and from healthy donors was similar; however, PMNL from persons with late-stage HIV infection had significantly impaired IL-8 production, which correlated with reduced IL-8 response to C3a and C5a proteins and decreased CD88 expression. Addition of murine monoclonal antibody (MAb) 18B7 promoted phagocytosis and restored IL-8 release consistent with integrity of FcyRIII. These results provide evidence for a selective defect in CD88 expression on PMNL from persons with late-stage HIV infection. However, Fcy receptor expression in PMNL appears to be intact and allows MAb to glucuronoxylomannan to positively influence PMNL function.

Cellular immunity plays a dominant role in host defense against disseminated cryptococcal infection [1, 2]. Moreover, several studies have provided in vivo and in vitro evidence of a critical role for human polymorphonuclear leukocytes (PMNL) against Cryptococcus neoformans [3–6]. In vivo, PMNL depletion with cyclophosphamide enhances susceptibility to infection [3]; however, administration of recombinant granulocyte colony-stimulating factor (G-CSF) prolongs survival of lethally infected mice [4]. In vitro studies show that PMNL are potent anticytotoxic cell effectors [5, 6] and that killing of C. neoformans by neutrophils is most efficient when complement-derived opsonins [7, 8] or capsule-binding antibodies are present [5]. Humoral immunity also contributes to protection against C. neoformans. There is also considerable evidence that antibody to the capsule mediates protection by enhancing cellular immunity [9].

Recruitment of CD4 cells is important to contain primary infection of C. neoformans in the lung in murine models of infection [1]. Although the pathogenesis of initial human C. neoformans infection is poorly understood, one can anticipate that the paucity of CD4 T cells in persons with AIDS contributes to their marked predisposition for disseminated infection. Because PMNL are potent anticytotoxic cells and persons with AIDS have normal numbers of PMNL, it is possible that they counterbalance CD4 cell impairment and protect against C. neoformans. However, the functional status of PMNL may be compromised in human immunodeficiency virus (HIV)–positive persons. HIV-infected persons have reduced chemotaxis for PMNL [10] but preserved fungicidal mechanisms [11, 12].

The complex biology of PMNL involves the ability to sense chemotactic factors and to migrate, perform phagocytosis, and kill microbes. In recent years, several researchers have firmly established that the release of cytokines constitutes an important aspect of neutrophil biology [13]. Such cytokines as tumor necrosis factor–α, interferon (IFN)–α, macrophage-CSF, G-CSF, interleukin (IL)–1, IL-1 receptor antagonist, IL-6, and IL-8 are produced by PMNL [14–16]. IL-8, a small protein that is a member of a supergene family of chemotactic cytokines produced by PMNL, is important in promoting inflammatory responses. Biologic actions of IL-8 on neutrophils include the induction of respiratory burst and chemotaxis [17–19], promoting release of lysosomal enzymes, and enhanced killing of various microorganisms, including Mycobacterium tuberculosis [20].

We previously demonstrated that PMNL from normal persons release IL-8 in response to C. neoformans or capsular material, glucuronoxylomannan. This effect is related to acti-
vation of the complement system and release of biologically active complement cleavage fragments, such as C3a and C5a, that are involved in the induction of IL-8 release. C5a is also involved in the induction of protective immune response to C. neoformans [21].

Although many studies have assessed neutrophil function in patients with AIDS [10, 22–27], studies focusing on PMNL cytokines are scarce [28, 29]. The aim of this study was to determine the production of IL-8 by PMNL from patients with late-stage HIV infection in response to C. neoformans and to explore the mechanisms involved in this phenomenon. In particular, we studied the effect of monoclonal antibody (MAb) 18B7 to the capsular polysaccharide in regulating PMNL functions. This MAb is in advanced preclinical development for use in persons with cryptococcosis [30].

Materials and Methods

Subjects. Ten patients with early-stage and 10 with late-stage HIV infection, aged 24±42 years, were enrolled in the study. HIV-positive donors were recruited from the Clinic of Infectious Disease, University of Perugia, Perugia, Italy. Patients were classified according to absolute CD4 cell counts: >400 cells/mm³ (early-stage HIV infection; mean ± SD, 575 ± 289.46, CDC clinical category A) and <200 cells/mm³ (late-stage HIV infection; mean ± SD, 100.14 ± 53.5, CDC category C). The virus loads of patients with early- and late-stage infections were 126.609 ± 42.203 and 528.119 ± 132.029 copies/mL, respectively. Healthy HIV-seronegative donors, matched for age and sex, were included as controls. At the time of the study, no patients were receiving cytokine therapy.

Reagents and media. RPMI 1640 with glutamine and fetal calf serum were obtained from Gibco BRL (Paisley, UK). Human serum (HS) type AB, fluorescein isothiocyanate (FITC)-conjugated MAb anti-rabbit immunoglobulin (mouse IgG1 isotype), FITC-conjugated sheep anti-mouse IgG (whole molecule), FITC-conjugated anti-mouse isotype control IgG1, FITC-conjugated anti-rabbit isotype control IgG, and mouse isotype control IgG1,κ were purchased from Sigma (St. Louis, MO). Mouse anti-human CD16 MAb (IgG1) was provided by Ancell (Bayport, ME). Mouse anti-human CR3 MAb (IgG1; CD11b/CD18) was obtained from Monosan (Uden, The Netherlands). Rabbit anti-human CD88 (C5aR) MAb (IgG1) was provided by Serotec (Oxford, UK).

The characteristics of MAb 18B7 have been described [30]. MAb 18B7 was purified by protein G affinity chromatography (Pierce, Rockford, IL). The concentration of MAb 18B7 was determined by ELISA relative to isotype-matched standards of known concentrations. Human complement C3a (Cortex Biochem, San Leandro, CA), human complement recombinant C5a (Fluka Chimica, Sigma Aldrich, Milan, Italy), MAb anti-human C3a (Quidel, San Diego), and goat anti-human C5a (Quidel) were purchased. Polyclonal anti-human C5 shows strong reactivity to human C5a [31]. Monoiodoacetic acid (MIA) was purchased from Sigma. All reagents and media used in this study were negative for endotoxin as detected by Limulus amebocyte lysate assay (Sigma), which had a sensitivity of ∼0.05–0.1 ng/mL of Escherichia coli lipopolysaccharide.

Microorganisms. Candida albicans (strain PCA-2) was supplied by D. Kerridge (Department of Biochemistry, University of Cambridge, UK). This is an agrerminative strain that grows as a pure yeast form in vitro at 28°C or 37°C in conventional media. The 2 strains of C. neoformans used in this study were obtained from J. Orendi (Central Bureau Schimmel Cultures [CBS], Delft, The Netherlands). C. neoformans var. neoformans 6995 (CBS 6995; also known as NIH 37) is a thinly encapsulated isolate of serotype A. C. neoformans var. neoformans 7698 (CBS 7698; also known as NIH B-4131) is an acapsular mutant. The morphologic characteristics and conditions for growth of the 2 strains of C. neoformans and the C. albicans isolate have been described elsewhere [32, 33]. The cultures were maintained by serial passage on Sabouraud agar (BioMérieux, Lyon, France) and harvested by suspending a single colony in RPMI 1640. C. neoformans 6995 and 7698 and C. albicans were killed by autoclaving.

Preparation of PMNL. Heparinized venous blood from healthy donors or from patients with late-stage HIV infection was diluted with RPMI 1640, and mononuclear cells were separated by ficoll-hypaque density gradient centrifugation [34]. The pellet containing PMNL and erythrocytes was treated with hypotonic saline to lyse the erythrocytes. Granulocytes were collected by centrifugation, washed twice in RPMI 1640, and counted, and adjusted to the desired concentration. The purity of PMNL isolated by this method was always>98%, as determined by Giemsa staining. PMNL preparations contained ~0.5–1% eosinophils. PMNL viability, evaluated after 18 h of incubation, was >98% in all determinations by a trypan blue dye exclusion test.

Killing activity against C. albicans or C. neoformans (7698 or 6995). Killing activity was evaluated by colony-forming unit inhibition assay. In brief, PMNL (10⁵) in 0.1 mL of suspension/well were incubated in flat-bottom 96-well microtiter tissue culture plates (Falcon, Oxnard, CA) with 10⁵ C. albicans or C. neoformans (7698 or 6995) in 0.1 mL of RPMI plus 10% HS in the presence or absence of MAb 18B7 (10 µg/mL) or mouse isotype control IgG1 (10 µg/mL). Cells mixed with C. neoformans were incubated for 2 h. After incubation at 37°C with 5% CO₂, plates were vigorously shaken, cells were lysed by addition of Triton X-100 0.1% in distilled water (final concentration in the well, 0.01%), and serial dilutions were prepared in distilled water. Cell lysates (triplicate samples) were plated for cfu on Sabouraud dextrose agar. After incubation for 24 h at 37°C, we counted C. albicans colony-forming units. C. neoformans colony-forming units were counted after a 72-h incubation at 28°C. Colony-forming units in experimental wells were compared with colony-forming units for C. albicans or C. neoformans suspensions in RPMI 1640 plus 10% HS without effector cells. Killing activity against C. albicans or C. neoformans was expressed as the percentage of colony-forming unit inhibition by the following formula: % killing activity = [100 – (colony-forming units from experimental group/colony-forming units from control cultures)] × 100.

Production of PMNL culture supernatants. Isolated PMNL were distributed in 0.1-mL volumes into 96-well U-bottom tissue culture plates (Becton Dickinson, Oxnard, CA) at 4 × 10⁶ cells/mL and incubated for 18 h at 37°C in a 5% CO₂ atmosphere with RPMI containing 10% HS with different stimuli. Supernatant fluids
were harvested at the indicated times and stored at −20°C until use.

Cytokine level determination. Cytokine levels in culture supernatant fluids were measured by an ELISA kit for human IL-8 (Euroclone, Devon, UK).

Determination of surface expression of CD16, CR3, and CD88 molecules. Freshly isolated human PMNL were analyzed for CD16, CR3, and CD88 surface expression. PMNL (10⁶) were fixed with 2% paraformaldehyde in PBS for 10 min at room temperature, washed twice in PBS containing 0.5% bovine serum albumin (BSA) and 0.1% sodium azide, and mixed with MAb anti-human CD16 (5 µg/mL), MAb anti-human CR3 (dilution 1/5), or MAb anti-human CD88 (dilution 1/100). After 30 min of incubation on ice, the cells were washed twice and stained with FITC-conjugated sheep anti-mouse IgG (dilution 1/256) for 30 min or FITC-conjugated anti-rabbit immunoglobulin (IgG1). We used irrelevant FITC-conjugated antibodies as negative controls (isotype control, anti-mouse and anti-rabbit IgG, both diluted 1:256). CD16, CR3, and CD88 surface expression was measured by flow cytometry (FACScan; Becton Dickinson, Mountain View, CA). Autofluorescence was assessed using untreated cells.

Preparation of fluorescein-labeled C5a. A fluorescence derivate of human C5a (FI-C5a) was prepared with a fluorescein labeling kit (Boehringer Mannheim Biochimica, Mannheim, Germany).

Binding of FI-C5a to PMNL. The binding interaction of FI-C5a with human PMNL C5a receptor was defined by accepted methods [35]. In brief, freshly isolated human PMNL were incubated with FI-C5a (25 nM) for 20 min at room temperature. Cells were washed twice in PBS containing 0.5% BSA and 0.1% sodium azide and resuspended in 0.5 mL of PBS containing 0.5% BSA and 0.1% sodium azide. The binding of FI-C5a was assessed by flow cytometry.

Statistical analysis. Statistical analysis was performed by use of Student’s t test.

Results

IL-8, a cytokine involved in the inflammatory process, serves as a chemotactic factor to recruit immune cells to the site of infection. Our first series of experiments studied IL-8 release from PMNL of HIV-infected patients in response to C. neoformans. We enrolled 2 patient groups: persons with early-stage HIV infection (CD4 cells/mm³) and patients with late-stage HIV infection upon stimulation with encapsulated strain (6995) was rare. However, a significant increase of IL-8 secretion was observed using MAb 18B7 in combination with 6995 (figure 2).

Given that PMNL from patients with late-stage HIV infection are poor responders of IL-8 in response to encapsulated C. neoformans, we considered the possibility of a defect involving unresponsiveness to complement fractions. To test this possibility, we added MAb to C3a and polyclonal antibody to C5a separately to suspensions of C. neoformans and measured IL-8 production. As expected, addition of antibody to C3a and C5a produced a significant reduction in IL-8 secretion by PMNL from healthy donors incubated with the encapsulated strain (6995), regardless of the presence or absence of MAb 18B7. In contrast, antibody to C3a and C5a had little or no effect on IL-8 production by PMNL from patients with late-stage HIV infection (figure 3), suggesting that the reduced ability of these cells to secrete IL-8 after exposure to C. neoformans was related to unresponsiveness to C3a or C5a stimulation. Consistent with this hypothesis, addition of purified C3a and C5a to PMNL from persons with late-stage HIV infection resulted in little or no IL-8 production (figure 3).

Having established that PMNL from subjects with late-stage HIV infection are poor responders to active complement fractions, we considered the possibility that phagocytosis could be an alternative or adjunctive mechanism for PMNL IL-8 pro-
Figure 2. Interleukin (IL)-8 production by polymorphonuclear leukocytes (PMNL) from controls and from patients with late-stage human immunodeficiency virus (HIV) infection in response to *Cryptococcus neoformans*. IL-8 was determined in supernatant fluids of PMNL not stimulated (NS) or treated with lipopolysaccharide (LPS; 10 μg/mL), *Candida albicans* (CA), or acapsular (7698) or encapsulated (6995) *C. neoformans*. *C. neoformans* was added at an effector : target ratio of 1 : 5 in presence or absence of monoclonal antibody (MAb) 18B7 (10 μg/mL). Supernatant fluids were harvested after 18 h of incubation. Addition of isotype-matched MAb at 10 μg/mL did not affect IL-8 secretion. Results are mean ± SD of 8 separate experiments. *P < .05, MAb 18B7-treated vs. respective untreated cells.

Figure 3. Effect of monoclonal antibody (MAb) to C3a (anti-C3a) and polyclonal antibody to C5 (anti-C5) on interleukin (IL)-8 production by polymorphonuclear leukocytes (PMNL) from controls and from persons with late-stage HIV infection in response to *Cryptococcus neoformans*. IL-8 level was determined in supernatant fluids of PMNL not stimulated (NS) or treated with encapsulated *C. neoformans* (6995). *C. neoformans* was added at an effector : target ratio of 1 : 5 in presence or absence of monoclonal antibody to C3a (0.1 μg/mL) or polyclonal antibody to C5 (1 μg/mL). Some PMNL were treated with purified C3a or C5a. Supernatant fluids were harvested after incubation for 18 h. Results are mean ± SD of 7 separate experiments. *P < .05, 6995 + anti-C3a or 6995 + anti-C5a vs. respective 6995-treated cells. †P < .05, C3a- or C5a-treated vs. respective untreated cells (NS).

To test this hypothesis, we used MIA, a well-known inhibitor of phagocytosis [36], in our experiments. Figure 4 shows that appreciable levels of IL-8, produced in response to acapsular *C. neoformans* and to the encapsulated strain plus MAb 18B7, were abrogated by using MIA (500 nM), suggesting that the preserved phagocytic activity of PMNL may be important for the induction of appreciable levels of IL-8 in the absence of C3a or C5a responsiveness. The importance of the phagocytic process to mediate secretory activity by PMNL was confirmed using opsonized zymosan that was able to induce detectable levels of IL-8 (figure 5). These results indicate that IL-8 production by PMNL from persons with advanced HIV infection can be restored by Fcγ receptor activation and phagocytosis.

To study the effect of MAb 18B7-induced phagocytosis in enhancing the functional status of PMNL from persons with late-stage HIV infection, PMNL killing activity against *C. neoformans* was determined in the presence and absence of MAb 18B7. We recently reported that MAb 18B7 enhances anticytotoxic capacity of PMNL from HIV-infected persons [34]. In the present study, we show that MAb 18B7, by promoting the phagocytic process, augments killing capability of PMNL from patients with late-stage HIV infection.

In contrast to PMNL from persons with early-stage HIV infection, PMNL from those with late-stage infection had reduced antifungal activity against the encapsulated *C. neoformans* strain. Of interest, PMNL from patients with late-stage HIV infection retained killing activity against *C. albicans* and the acapsular *C. neoformans* strain (table 1). However, addition of MAb 18B7 restored the antifungal activity of PMNL from each of 8 patients with late-stage HIV infection against encapsulated *C. neoformans* (table 1).

Because PMNL from persons with late-stage HIV infection exhibited deficits in secretory activity despite maintaining phagocytic capacity, we investigated the expression of surface molecules involved in the phagocytic process. Analysis of several important molecules for phagocytosis revealed that CR3 expression (CD11b/CD18) and FcγRIII (CD16) in PMNL from persons with late-stage HIV infection and controls were similar (figure 6). However, the deficit in IL-8 production by PMNL of patients with late-stage HIV infection in response to C3a and C5a stimulation suggested defective expression in the molecules responsible for C5a ligation and expression. To test this hypothesis, we measured CD88 expression on PMNL from patients with late-stage HIV infection and found it was significantly lower than in controls (figure 6).
Figure 4. Effect of monoiodoacetic acid (MIA) addition on interleukin (IL)-8 production by polymorphonuclear leukocytes (PMNL) from controls and from patients with late-stage human immunodeficiency virus (HIV) infection in response to encapsulated *Cryptococcus neoformans* in presence or absence of monoclonal antibody (MAb) 18B7. IL-8 level was determined in supernatant fluids of PMNL not stimulated (NS) or treated with encapsulated *C. neoformans* (6995) in presence or absence of MAb 18B7 (10 $\mu$g/mL) or with acapsular strain (7698). MIA (500 nM) was added at time of culture preparation. Supernatant fluids were harvested after 18 h of incubation. Results are mean ± SD of 4 separate experiments. * $P < .05$ (MIA-treated vs. respective untreated cells).

Figure 5. Effect of zymosan addition on interleukin (IL)-8 production by polymorphonuclear leukocytes (PMNL) from controls and from patients with late-stage human immunodeficiency virus (HIV) infection. IL-8 was determined in supernatant fluids of PMNL not stimulated (NS) or treated with encapsulated *C. neoformans* (6995) or acapsular strain (7698) or zymosan. Supernatant fluids were harvested after 18 h of incubation. Results are mean ± SD of 4 separate experiments. * $P < .05$ (zymosan-treated vs. untreated cells).

To investigate whether C5a ligation was impaired in PMNL from patients with late-stage HIV infection, C5a FITC conjugate was added, and flow cytometry was done. We found that the reduced expression of CD88 was strictly correlated with impairment of C5a ligation (data not shown).

Discussion

PMNL are the first cells recruited to sites of infection, and their functional status is critical in containing infections. PMNL possess effector and secretory functions and play a critical role in the early response against microbial infections. There is an emerging consensus that PMNL function is preserved during the early stages of AIDS. PMNL integrity, despite severe immune impairment in persons with late-stage HIV infection, may provide the major line of defense against some opportunistic infections (e.g., systemic *C. albicans*). This suggests the possibility that PMNL may be useful in containing other opportunistic infections, provided that they could be recruited. We previously demonstrated that IL-8 production of PMNL in response to *C. neoformans* is dependent on the generation of C3a and C5a. Here we extend those studies to compare the antifungal function of PMNL from normal persons with that of PMNL from persons with early and late HIV infection in the presence and absence of specific antibody.

PMNL from persons with early-stage HIV infection secrete IL-8 at levels similar to those of normal subjects in response to *C. neoformans*. As expected from prior results, the encapsulated strain stimulated more IL-8 production than the acapsular strain, and addition of MAb 18B7 produced a modest, but significant, increase in IL-8 production. In contrast, PMNL from persons with late-stage HIV infection produced significantly less IL-8 after exposure to *C. neoformans*. PMNL from persons with late-stage HIV infection did not secrete IL-8 in response to direct stimulation with purified C3a and C5a. In contrast, addition of MAb 18B7 to suspensions of PMNL from persons with late-stage HIV infection resulted in a significant increase in IL-8 production. This suggests that PMNL from persons with late-stage HIV infection had preserved responsiveness through Fc receptors but not complement receptors.

Several studies have investigated the mechanism responsible for the differences in IL-8 secretion by PMNL from persons with early- and late-stage HIV infection [28, 37]. Flow cytometry revealed comparable expression of CR3 and FcγRIII receptors in PMNL from the 3 subject groups. However, there was a marked reduction in CD88 expression on PMNL from patients with late-stage HIV infection, suggesting an explanation for the reduced IL-8 secretion based on lower CD88 expression. The fact that MAb 18B7 enhanced IL-8 production from PMNL of persons with late-stage HIV infection suggests cytokine release in response to the phagocytic process. Consis-
MIA, a potent inhibitor of phagocytosis, impaired IL-8 release. Thus, phagocytosis appears to be an alternative or adjunctive mechanism to facilitate IL-8 expression in PMNL and may be with advanced HIV infection.

HIV infection displayed antifungal activity to acapsular and late-stage HIV infection were severely impaired in killing en-

\[ C. neoformans \]

results differ slightly from our previous observations that [25]. This discrepancy may be due to differences in the

function provide support for potential immunotherapeutic inter-
ventions to enhance PMNL function against \[ C. neoformans \].

In addition to enhanced PMNL antimicrobial function, MAb 18B7 also enhanced IL-8 release. The effect was significantly greater for PMNL from patients with late-stage HIV infection than for normal PMNL or PMNL from persons with early-stage infection. Presumably, Fc receptor cross-linking is a minor pathway for IL-8 release in the setting of normal complement receptor expression in PMNL. However, in subjects with late-stage HIV infection, Fc receptor cross-linking may be a major signal for IL-8 secretion, given the reduced expression of CD88.

The principal activators of IL-8 release remain active com-
plement fragments such as C3a and C5a, as previously observed in PMNL from healthy donors [8]. Of interest, CD88 has a major role in supporting PMNL function, including cytokine release [38], with respect to C3a. The presence of C3a receptors on PMNL is controversial. Some studies reported the presence of C3a receptors on PMNL [39]; others suggest that PMNL C3a-mediated activation is subsequent to activation of contaminating eosinophils that bind C3a and release PMNL activating factors [40]. However, there is general consensus on the in-

volvement of CD88 perturbation in regulating a variety of PMNL functions [38, 41, 42]. These effects include promotion of neutrophil chemotaxis [43, 44], superoxide formation [45], enzyme release [46], and cellular aggregation [47].

The consistent impairment of CD88 observed in PMNL from persons with late-stage HIV infection at high risk for cryptococcosis supports our hypothesis that PMNL are unable to respond to C5a-mediated stimuli. It is conceivable that the impairment of additional functions (e.g., chemotaxis) could be ascribed to CD88 impairment. It was recently shown that the copresence of immune complexes and C5a greatly increase chemokine generation in vitro [48]. Similarly, MAb 18B7 could augment IL-8 release through immunocomplex formation. This is consistent with the inability of MAb 18B7 to induce IL-8 release when used in combination with the acapsular strain.

There is convincing evidence for the ability of IFN-\( \gamma \) to up-regulate CD88 on phagocytic cells [49], raising the possibility that CD88 defect could be exacerbated in patients with late-stage HIV infection (<200 CD4 cells) because of the dramatic impairment of IFN-\( \gamma \) production. It would be of interest to verify whether CD88 on PMNL from patients with late HIV infection could be up-regulated by exogenous stimuli and whether restoration of C5a-related functions, such as cytokine production, is also possible.

Overall, our results show that PMNL from persons with late-

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<th>Subjects</th>
<th>CD4 ( \times 10^9 \text{/L} )</th>
<th>MAb 18B7</th>
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Mean ± SD | 46 ± 7 | 46 ± 7 | 54 ± 5 | 57 ± 4 | 16 ± 5 | 36 ± 6 |

NOTE. MAb 18B7 was used at the dose of 10 \( \mu \)g/mL. Isotype matched MAb added to PMNL from controls or patients with late stage HIV infection at the dose of 10 \( \mu \)g/mL did not affect killing activity against the indicated fungi. The percentage of killing activity was evaluated as the percentage of colony forming units inhibition.

\( ^a \) \( P < 0.001 \) (6995 C. albicans MAb-treated vs. 6995 C. albicans MAb-treated cells).

\( ^b \) All patients had late-stage HIV infection.
Figure 6. C5aR (CD88), FcyRIII (CD16), and CR3 (CD11b/CD18) expression on freshly isolated polymorphonuclear leukocytes from controls and from patients with late-stage human immunodeficiency virus (HIV) infection (% positive cells). Results are from 1 of 3 experiments with similar results. NS, staining profile with mouse isotype-matched antibody.

late-stage HIV infection have selected impairment of effector function against encapsulated C. neoformans but not against C. albicans or acapsular C. neoformans. Down-regulation of effector function is accompanied by impaired secretory function, likely ascribed to a selective defect of CD88 expression on PMNL. In contrast, the integrity of Fcy receptors ensures multiple beneficial effects of MAb 18B7 in restoring killing capability as well as cytokine production. Pharmacoimmunologic intervention to stimulate expression of CD88 could improve migration of PMNL to the site of infection and promote the inflammatory process, which appears to be rare in patients with late-stage HIV infection.

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