Lipopolysaccharide-Stimulated or Granulocyte-Macrophage Colony-Stimulating Factor-Stimulated Monocytes Rapidly Express Biologically Active IL-15 on Their Cell Surface Independent of New Protein Synthesis


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Lipopolysaccharide-Stimulated or Granulocyte-Macrophage Colony-Stimulating Factor-Stimulated Monocytes Rapidly Express Biologically Active IL-15 on Their Cell Surface Independent of New Protein Synthesis


Although IL-15 shares many of the biological activities of IL-2, IL-2 expression is primarily under transcriptional regulation, while the mechanisms involved in the regulation of IL-15 are complex and not completely understood. In the current study, we found that CD14+ monocytes constitutively exhibit both IL-15 mRNA and protein. IL-15 protein was found stored intracellularly and stimulation of CD14+ monocytes with either LPS or GM-CSF resulted in mobilization of IL-15 stores to the plasma membrane. This rapidly induced surface expression was the result of a translocation of preformed stores, confirming that posttranslational regulatory stages limit IL-15, because it was not accompanied by an increase in IL-15 mRNA and occurred independent of de novo protein synthesis. After fixation, activated monocytes, but not resting monocytes, were found to support T cell proliferation, and this effect was abrogated by the addition of an IL-15-neutralizing Ab. The presence of preformed IL-15 stores and the ability of stimulated monocytes to mobilize these stores to their surface in an active form is a novel mechanism of regulation for IL-15. The Journal of Immunology, 2001, 167: S011–S017.
mM sodium pyruvate (Life Technologies), and 0.1 mM nonessential amino acids (Life Technologies).

In some cases, PBMC (1.5 × 10^6/well) were allowed to adhere to plastic in 24-well flat-bottom plates (Falcon, Franklin Lakes, NJ) for 2 h at 37°C and 5% CO₂ in complete medium. Medium and nonadherent cells were then gently aspirated, adherent cells were washed three times with RPMI 1640, and fresh complete medium was added to the wells.

**RNA extraction**

PBMC (1.5 × 10^6/ml) were cultured in 24-well plates in the presence and absence of 1 μg of *Escherichia coli* LPS (Sigma, Oakville, Ontario, Canada). At various intervals (see individual experiment), the cells were lysed with a guanidinium-isothiocyanate solution and the total RNA was extracted using the MicroRNA isolation kit (Stratagene, La Jolla, CA) followed by a reverse transcription with the SuperScript III (Invitrogen). The cDNA synthesis and PCR amplification were performed using primers specific for IL-15 (5’ primer: 5'-CTGAAAGTGGGACTTCTGTCC-3’, and 3’ primer: 5'-GAGTTCATCATGCACCTGCTT-3’) and GAPDH (5’ primer: 5'-CCGAGACCATCAACCAACCTGAT-3’, and 3’ primer: 5'-AGCCCTTCCATGTTGTAAGAC-3’). PCR products were separated by electrophoresis in ethidium bromide-stained 1.4% agarose gels and visualized with UV illumination.

**Flow cytometry**

Resting PBMC (1.5 × 10^6/ml) were cultured in complete RPMI 1640 (Life Technologies) or medium containing 10 ng/ml recombinant human (rh)IFN-γ (R&D Systems, Minneapolis, MN), 30 ng/ml rhGM-CSF (R&D Systems), or 1 μg of E. coli LPS (Sigma) with or without 20 μg of cycloheximide (CHX) (Sigma). For cell-surface labeling, 1.5 × 10^6 PBMC were washed three times with PBS (1% FCS, 0.1% NaN₃) and incubated in the dark at 4°C with anti-IL-15 Ab or isotype-matched control Ab. Anti-IL-15 Abs were mAb 247, mAb 647 (both from R&D Systems), and 16E3-PE (BioSource International, Camarillo, CA). The control Abs were an unlabeled isotype-matched control Ab (R&D Systems) or a directly labeled isotype-matched Ab (BD Biosciences, Mountain View, CA). Cells were washed twice and incubated with goat anti-mouse IgG1-PE (Molecular Probes, Eugene, OR). Cells were washed three times and incubated with anti-CD3 PerCP, anti-CD14 FITC, anti-CD19 FITC, or anti-CD56 PE (BD Biosciences). For intracellular staining of resting PBMC, 1.5 × 10^6 cells were washed three times with PBS (1% FCS, 0.1% NaN₃) and permeabilized using the Cytofix/Cytoperm reagent (BD Pharmingen, San Diego, CA) according to the manufacturer’s instructions. Cells were washed twice in “perm wash” (BD Pharmingen) and incubated for 30 min at 4°C with mouse monoclonal anti-human IL-15 Ab (R&D Systems or BioSource International) or mouse isotype-matched control (R&D Systems or BD Biosciences). Cells were washed twice and incubated with goat anti-mouse IgG1-PE (Molecular Probes). For identification of cell populations expressing IL-15, cells were then washed three times with PBS (1% FCS, 0.1% NaN₃) and incubated with anti-CD3 PerCP, anti-CD14 FITC, anti-CD19 FITC, or anti-CD56 FITC (BD Biosciences).

**Cell-surface ELISA**

Adherent monocytes were fixed in 1% paraformaldehyde, washed, and suspended in 1% human AB serum, 1% BSA, and 0.01% NaN₃ in PBS. Cells were labeled with the IL-15-specific mAb 247 or isotype-matched control Ab (R&D Systems) followed by goat anti-mouse HRP (Amersham, Buckinghamshire, U.K.). The ELISA was developed using 200 μl of a 1/1 mixture of H₂O₂ and tetramethylbenzidine solutions (Genzyme Diagnostics, San Carlos, CA). Reaction was stopped with 200 μl of 1 M H₂SO₄ and read spectrophotometrically at 450 nm. The values are expressed as the fold increase in absorption over control cells (absorption from cells labeled with anti-IL-15 Ab / absorption from cells labeled with isotype-matched Ab). For comparisons between different culture conditions, net IL-15/A₁₀ values were obtained and expressed relative to control cells.

| Abbreviations used in this paper: rh, recombinant human; CHX, cycloheximide. |

**Immunoblotting**

Freshly isolated cells were lysed in hypotonic buffer (10 mM Tris-hydrochloric acid (pH 8.0), 10 mM KCl) with fresh protease inhibitors (1 mM PMSF, 10 μg/ml aprotinin, 10 μg/ml leupeptin (Sigma), followed by Dounce homogenization. The cellular lysate was isolated from the homogenate by centrifugation (1000 x g for 10 min) and resuspended in 1X Laemmli SDS sample buffer. The lysate was applied to 15%SDS-PAGE and transferred onto nitrocellulose paper (Bio-Rad, Hercules, CA). The membrane was blocked with 5% BSA in PBS/0.5% Tween 20 and probed with polyclonal rabbit anti-human IL-15 (P2; Immunex, Seattle, WA), followed by HRP-conjugated goat anti-rabbit IgG (Bio-Rad). Immunoreactive protein bands were visualized using ECL (Amersham).

**Surface IL-15 bioassay**

Freshly isolated PBMC (2 × 10⁶) were cultured in complete RPMI 1640 overnight and monocytes were obtained by adherence to plastic. Monocytes were stimulated for 1 h with 10 ng/ml GM-CSF, washed, and fixed with 0.05% glutaraldehyde. Cells were washed twice with cold PBS and then incubated in complete RPMI 1640 for 1 h. CTLL-2 cells (2 × 10⁶) were added to fixed adherent monocytes in the presence or absence of mAb 247 or an isotype-matched control Ab. For optimal CTLL-2 response, 0.4 ng of IL-2 was added to each group. After 48 h, 10 μl of a 5 mg/ml MT solution was added to each well and cells were incubated for an additional 4 h at which time 100 μl of isopropanol/0.04 N hydrochloric acid solution was added to each well and read spectrophotometrically at 570 nm.

**Statistics**

When applicable, data are presented as mean ± SE. Different experiments were performed on different subjects on different days. Statistical analysis was performed by use of the Scheffé test for analysis of variance, when allowed by the F test. For these tests, p < 0.05 was considered significant. For CTLL-2 proliferation, a Student t test was performed using the Bonferroni correction for the comparison of multiple groups.

**Results**

**IL-15 is constitutively expressed in resting human PBMC**

To characterize the regulatory stages controlling IL-15 protein expression, we examined IL-15 mRNA and protein expression in resting human PBMC. Semiquantitative RT-PCR was performed on freshly isolated cells that were left in culture for various lengths of time. Western blot for IL-15 was performed. IL-15 protein levels were compared to those in freshly isolated PBMC by semiquantitative RT-PCR. For these tests, p < 0.05 was considered significant.

**FIGURE 1.** Constitutive IL-15 mRNA expression in resting PBMC. a, PBMC were cultured in complete medium and at the times indicated cells were lysed and RNA was extracted. Detection of IL-15 mRNAs was done by semiquantitative RT-PCR. b, Freshly isolated PBMC were lysed and a Western blot for IL-15 was performed. IL-15 protein levels were compared with known concentrations of recombinant cytokine. The experiment was repeated four times with similar results.
of time. IL-15 mRNA was found constitutively expressed in PBMC, and there was no change in IL-15 mRNA expression with up to 72 h in culture (Fig. 1a). Immunoblotting revealed that freshly isolated PBMC also constitutively express cell-associated IL-15 protein, showing one strong immunoreactive band at ~19 kDa, and one weak band at ~15 kDa (Fig. 1b). These correspond to the previously described molecular mass of mature IL-15 and the variant with the short signal peptide (20).

**IL-15 protein is found in intracellular stores in resting PBMC**

Because both IL-15 mRNA and protein are constitutively expressed in resting PBMC, experiments were performed to determine whether PBMC display surface-bound or intracellular IL-15 protein. PBMC labeled with a mAb specific for IL-15 showed no surface-bound IL-15 protein (Fig. 2a). However, when PBMC were permeabilized before labeling, IL-15 protein was detected intracellularly (Fig. 2b). The specificity of IL-15 staining was demonstrated by adding excess rIL-15 to cells before addition of the anti-IL-15 Ab, which reduced the intensity of fluorescence to that of the cells labeled with an isotype-matched control Ab (Fig. 2c).

**Expression of IL-15 by different subsets of PBMC**

Having determined that PBMC express intracellular IL-15, experiments were performed to determine which subsets of PBMC express IL-15. Two-color flow cytometry revealed that IL-15 protein is expressed largely in CD14⁺ monocytes, but labeling also occurred in CD3⁺ T cells, and to a lesser extent in CD19⁺ B cells and CD56⁺ NK cells (Fig. 3a). Surface expression of IL-15 on the major populations of resting PBMC was not detected by two-color flow cytometry (Fig. 3b). Similar results were obtained using the mouse mAbs 247, 647, and 16E3. Monocyte IL-15 surface labeling was detected with the M112 Ab, but, consistent with previous reports (21), when rIL-15 was added before labeling, we were unable to reduce the level of binding by M112, suggesting that this IL-15 signal detected using M112 was nonspecific. Thus, subsets of PBMC do not constitutively express IL-15 on their surface but do express intracellular IL-15.

**IL-15 surface expression in freshly isolated and resting cells**

Because our inability to detect constitutive IL-15 surface expression on monocytes by flow cytometric analysis may have been due to a lack of sensitivity of the assay, we developed a highly sensitive ELISA to detect IL-15 on the surface of monocytes. This revealed that only one donor of four expressed trace amounts of IL-15 on the surface of resting adherent monocytes (Fig. 4a). Because previous studies had demonstrated constitutive surface expression of IL-15, studies were performed to determine whether the surface expression might be influenced by the PBMC purification process. Surface labeling of IL-15 was measured at various stages of cellular purification. Monocytes obtained from whole blood did not express IL-15 on their cell surface (Fig. 4b). However, monocytes tested immediately after Ficoll-Hypaque gradient centrifugation displayed membrane-bound IL-15 (Fig. 4c) that was quickly down-regulated when cells were allowed to rest in culture (Fig. 4, d and e).

**IL-15 protein is rapidly expressed on the surface of stimulated CD14⁺ monocytes**

To determine whether mediators of inflammation induce IL-15 surface expression, resting PBMC were stimulated with LPS, which is known to induce modest levels of IL-15 secretion (22). Resting PBMC cultured in medium alone showed no IL-15 surface expression on CD14⁺ monocytes (Fig. 5, a and b). In contrast, CD14⁺ monocytes stimulated with 1 μg of LPS displayed IL-15

![FIGURE 2.](image)

**FIGURE 2.** IL-15 protein expression in resting human PBMC. a. Unpermeabilized, or permeabilized PBMC incubated in the absence (b) or presence (c) of excess rhIL-15 (5 μg/ml) were labeled for IL-15. The filled curve represents cells labeled with an isotype-matched control Ab. The open curve represents cells labeled with anti-IL-15 Ab. The experiment was repeated four times with similar results.

![FIGURE 3.](image)

**FIGURE 3.** IL-15 expression in PBMC subsets. Freshly isolated PBMC were indirectly labeled for intracellular (a) or extracellular (b) IL-15, followed by surface staining for PBMC subset markers CD3, CD14, CD19, and CD56. The filled curve represents cells labeled with an isotype-matched control Ab. The open curve represents cells labeled with anti-IL-15 Ab. The experiment was repeated four times with similar results.

![FIGURE 4.](image)

**FIGURE 4.** IL-15 surface expression in freshly isolated and resting cells. Monocytes obtained from whole blood did not express IL-15 on their cell surface (a). After Ficoll-Hypaque gradient centrifugation (b), membrane-bound IL-15 was detected immediately after centrifugation (c) that was quickly down-regulated when cells were allowed to rest in culture (d and e).

![FIGURE 5.](image)

**FIGURE 5.** IL-15 surface expression in stimulated CD14⁺ monocytes. To determine whether mediators of inflammation induced IL-15 surface expression, resting PBMC were stimulated with LPS, which is known to induce modest levels of IL-15 secretion (22). Resting PBMC cultured in medium alone showed no IL-15 surface expression on CD14⁺ monocytes (a and b). In contrast, CD14⁺ monocytes stimulated with 1 μg of LPS displayed IL-15...
surface expression at both 30 and 60 min after stimulation (Fig. 5, c and d). The macrophage stimulus GM-CSF (Fig. 5 e), but not IFN-γ (Fig. 5 f), also induced IL-15 surface expression on monocytes. Although we detected surface expression of IL-15, ELISA did not detect IL-15 in the culture supernatants at these early time points (data not shown). Thus, both LPS and GM-CSF induced surface expression of IL-15, while IFN-γ did not, and surface expression was not accompanied by secretion of IL-15.

**IL-15 surface expression on monocytes does not require mRNA induction or de novo protein synthesis**

Because IL-15 surface expression occurred rapidly following LPS stimulation, we considered the possibility that surface expression was from pre-synthesized IL-15 rather than the result of transcriptional or translational up-regulation. To determine whether the transcript increased, IL-15 mRNA was assessed following LPS stimulation. PBMC stimulated with LPS did not up-regulate IL-15 mRNA (Fig. 6 a). To determine whether translation was required, PBMC were stimulated with LPS in the presence of the protein synthesis inhibitor CHX. Both flow cytometry (Fig. 6, b–d) and cell-surface ELISA (Fig. 6 e) demonstrated that monocytes stimulated with LPS in the presence of CHX expressed IL-15 on their cell surface similar to cells stimulated with LPS in the absence of CHX. There was no reduction in viability of cells due to CHX exposure as assessed by trypan blue exclusion or forward and side light scatter (data not shown), and the concentration of CHX used was capable of inhibiting protein synthesis, because CHX treatment abrogated the secretion of IL-10 by PBMC stimulated with Con A (data not shown). These results suggest that early IL-15 surface expression is not the result of de novo protein synthesis, but, instead, IL-15 is translocated to the cell surface from preformed intracellular stores.

**Surface-bound IL-15 has biological activity**

Because monocytes express IL-15 on their surface following activation, experiments were performed to determine whether the surface-expressed IL-15 was biologically active. To avoid the possibility that IL-15 was secreted into the medium, monocytes were stimulated, fixed, and washed before assessing the activity of surface IL-15. Fixed, stimulated monocytes induced proliferation of CTLL-2 cells, which was inhibited by an antibody against IL-15 (Fig. 7). After stimulation with GM-CSF and fixation, monocytes induced proliferation of CTLL-2 cells, which was inhibited by an antibody against IL-15.
These experiments were repeated four times with similar results.

Surface-bound IL-15 can support T cell proliferation. Resting or GM-CSF-activated monocytes were fixed and then incubated with the IL-15-responsive CD8 T cell line CTLL-2. Neutralizing IL-15 mAbs, or isotype-matched control Abs, were added as indicated. Proliferation was assessed by MTT assay. NS, not significant compared with resting monocytes plus CTLL-2 plus IgG1. *, p < 0.01 compared with resting monocytes plus CTLL-2 plus IgG1. #, Not significant compared with activated monocytes plus CTLL-2 plus IgG1. The experiment was repeated four times with similar results.

### Discussion

We have made five major observations: 1) resting human PBMC constitutively expressed IL-15 mRNA and protein; 2) PBMC had detectable levels of two isoforms of IL-15 with apparent molecular masses of 19 and 15 kDa; 3) CD14⁺ monocytes and other major subsets of PBMC contained intracellular stores of IL-15, with minimal surface-associated IL-15; 4) activated monocytes rapidly translocated preformed IL-15 stores to their cell surface; and 5) surface-bound IL-15 caused T cell proliferation.

Many cell types show constitutive expression of IL-15 mRNA (1, 23–29), suggesting that IL-15 is regulated through posttranscriptional mechanisms. Nevertheless, the purpose of this mRNA was not clear, because to date only a limited number of studies have demonstrated constitutive IL-15 protein expression. IL-15 protein is present in umbilical vein endothelial cells, renal cortical tubular epithelial cells, and human cancer cell lines (29–32). Using intracellular cytokine analysis, the current studies indicate that the constitutively expressed IL-15 mRNA is translated to protein in the major subsets of PBMC, which possess IL-15 protein stored intracellularly. Previously pulse/chase experiments have shown that cell-associated IL-15 protein has a slow turnover rate (20). Taken in conjunction with the present study, we conclude that monocytes store IL-15 protein in relatively long-lived intracellular stores that become rapidly exported to the plasma membrane following stimulation. Although we have demonstrated that some biologically relevant stimuli (LPS or GM-CSF) are sufficient to signal CD14⁺ monocytes to express IL-15 on their surface, while others (IFN-γ) are not, the downstream pathways required and their specificity are unknown.

Other type I T cell growth factors, including IL-2 (11–13) and IL-4 (12), are primarily under transcriptional regulation. Although this tight regulation prevents inappropriate growth factor signaling, it imposes a number of limitations on the expression of these cytokines, including the time and physiologic mechanisms required for transcription and translation before expression. Preformed cytokines circumvent these limitations and, in the case of IL-15, might permit immediate support for T cell responses and other T cell growth factor-dependent responses until additional growth factors can be synthesized. Although posttranslational regulation is atypical for other T cell growth factors, some monokines are regulated in this manner. For example, monocytes store TGF-α in secretory granules, and these stores are liberated following treatment with IL-10 and IFN-γ (33). The current studies indicate that IL-15 can bypass the requirement for transcriptional and translational control by existing as a mobile preformed cytokine in peripheral blood monocytes.

Although many cytokines are secreted proteins that allow action at sites distant from their elaboration, some other monokines have
membrane-associated forms. Membrane-bound IL-1 plays an important role in accessory cell support of anti-CD3-induced T cell proliferation (34). Surface TNF-α mediates macrophage contact-dependent cytotoxicity (35–38) and IL-10 induction (39). Macrophage-expressed surface IL-10 regulates both phagocytic function (40) and bactericidal activity (41), and membrane lymphoxygen-β contributes to lymphokine-activated killer cell cytotoxicity (42). Membrane retention provides an important level of control over immune responses, because cells must be in direct contact for these membrane-bound cytokines to exert their effects.

Monocytes have the capacity to support lymphocyte activity by a number of mechanisms that include accessory receptor-ligand interactions and the release of cytokines. Although soluble IL-15 can clearly promote T cell responses (6, 21), we have shown a potent capacity for membrane-bound IL-15 to promote T cell proliferation. Recent investigations suggest that a form of IL-15 that is not secreted confers a more protective effect than secreted IL-15 in vivo anti-vaccinia virus responses (19). In the current study we observed 4.4 ng of IL-15 activity on the surface of 100,000 monocytes. This concentration is higher than what we have estimated using other techniques (our unpublished observations). A potential explanation for the observation that a lower level of IL-15 protein was found on the surface of activated monocytes (<1 ng per 10^6 monocytes) despite a higher level of IL-15 activity detected (4.4 ng per 10^6 monocytes, Fig 7) may depend on the fact that membrane-localized IL-15 activity may be more potent than its soluble isof orm. That is, an additional feature of membrane-bound IL-15 may be its ability to promote clustering of its cognate receptor, thereby amplifying the effective dose of membrane IL-15, when compared with its soluble counterpart. This provides a potential mechanism for the protective effect of cell-associated IL-15. Additionally, because IL-15 is a potent T cell growth factor, cognate interactions between IL-15-expressing monocytes and Ag-specific T cells would limit the extent of bystander activation in the initiation of an Ag-specific immune response. Cognate roles for IL-15 may also be important in the developmental education of intraepithelial lymphocytes and NK cells, processes both known to be dependent on the IL-15 receptor (9).

We have shown that PBMC store IL-15 intracellularly. A recent study by Musso et al. (21) reported that monocytes and mononuclear cell lines constitutively express IL-15 on their surface. We have confirmed that some cell lines, such as THP-1, constitutively express IL-15 on their cell surface (data not shown), but, using multiple different IL-15 mAbs, we were unable to detect IL-15 on monocytes from the majority of healthy adults. We believe that differences in techniques are the explanation for these discrepant results. First, we have used four different mAbs. We have found that three commercially available mAbs consistently show IL-15 only on activated monocytes, while M112 used by Musso et al. (21) appears to have a level of nonspecific binding, which gives the appearance of constitutive surface expression (after stimulation, M112 does not reveal any rapid increase in surface labeling). Secondly, Musso et al. (21) purified monocytes from total PBMC by Ficoll-Hypaque followed by Percoll gradient centrifugation. We made similar observations concerning surface expression of IL-15 after Ficoll-Hypaque separation of PBMC. The transient surface expression may be due to the activation of cells during the purification process. Specifically, Percoll, which is a modified mixture of colloidal silica (43), has been shown to cause membrane disruption (44), decrease plasma membrane phospholipid levels (45), induce histamine release from human basophils (46), and induce random migration and elevated H2O2 production from neutrophils (47). In addition, we have shown that, while resting monocytes do not have active IL-15 on their cell surface, activated monocytes can readily support T cell proliferation, which is blocked by an anti-IL-15 Ab. Although Musso et al. (21) reported constitutive IL-15 membrane localization on resting monocytes, they failed to attribute biological function to this observation. Finally, our data corroborate the observation that healthy alveolar macrophages do not express surface IL-15 (48). Thus, our results suggest that IL-15 is not constitutively expressed on the membrane, but becomes rapidly expressed on the cell surface following monocyte activation. Although IL-2 is produced by Ag-specific T cells hours to days after Ag presentation (12, 49), and is not necessary until after the fifth round of division (50), IL-15 is required for the afferent phase of a T cell response in vivo (50) and surface expression is rapidly induced by monocyte activators like the cytokine GM-CSF or the innate T-independent immunostimulant LPS. This provides monocytes with the capacity to use LPS (and perhaps other signals) as an initial bridge between innate and acquired immunity, resulting in immediate IL-2-independent support for the initiation of an Ag-specific T cell response.

In summary, IL-15 is constitutively expressed in subsets of resting PBMC at the level of both message and protein. Therefore, mechanisms that regulate the cellular export of IL-15 protein are likely the limiting factor in IL-15 expression. Furthermore, monocytes rapidly express IL-15 on their surface following activation. The broad expression of preformed IL-15 stores, and the ability of the stores to be mobilized in a T-independent manner to a biologically active form, suggest that IL-15 is operationally ready to provide an initial bridge between innate and acquired immunity.

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References


