Impaired Protein Kinase C Activation/Translocation in Epstein-Barr Virus-infected Monocytes*

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Infection of human monocytes by Epstein-Barr virus (EBV) has been linked to a decrease in the production of proinflammatory mediators as well as an impairment of phagocytosis. Considering the key role of protein kinases C (PKCs) in many biological functions of monocytes, including phagocytosis, we investigated the effects of EBV on the PKC activity in infected monocytes. Our results indicate that infection of monocytes by EBV impairs both phorbol 12-myristate 13-acetate (PMA)-induced translocation of PKC isoforms α and β from cytosol to membrane as well as the PKC enzymatic activity. Similarly, the subcellular distribution of the receptor for activated C kinase (RACK), an anchoring protein essential to PKC translocation, was also found to be reduced in EBV-infected monocytes. Transfection of 293T cells with an expression vector coding for the immediate-early protein ZEBRA of EBV resulted in impaired PMA-induced translocation and activity of PKC. Using co-immunoprecipitation assays, the ZEBRA protein was found to physically interact with the RACK1 protein. Thus interaction of ZEBRA with RACK likely results in the inhibition of PKC activity, which in turn affects functions of monocytes, such as phagocytosis.

Epstein-Barr virus (EBV) is a human γ-herpesvirus exhibiting a strong tropism for pharyngeal epithelial cells and B lymphocytes. Some studies have shown that EBV infects other cell types, including thymocytes (1), T lymphocytes (2), natural killer cells (3) and Reed-Sternberg cells (4), which are found in Hodgkin’s disease. More recently, it has been reported that EBV infects phagocytes such as neutrophils (5) and monocytes (6) and modulates their biological functions such as cytokine production (7) and phagocytosis (6).

Involved in the clearance and destruction of microorganisms, phagocytosis is an essential process for host defense. Hence, several microorganisms have developed mechanisms to impair the phagocytic ability of human monocytes. For example, it was reported that murine cytomegalovirus (MCMV) (8) and human immunodeficiency virus (HIV) (9) decrease the Fc receptor-mediated phagocytosis of IgG-opsonized particles by a down-regulation of the Fc receptors expression. Regarding EBV, the mechanisms by which this virus impairs phagocytosis of human monocytes remain to be elucidated.

Phagocytosis is a complex process of particle ingestion involving the recognition of a target by specific cell surface receptors and the triggering of a signaling cascade, which allows the local reorganization of the actin-based cytoskeleton and internalization of the foreign particle. Reports indicate that inhibition of PKCs causes a decrease of phagocytosis by monocytes/macrophages (10–12). In addition, several studies demonstrated that selected PKC isozymes interact with components of cytoskeleton such as F-actin (13), involved in the engulfment of particles. In addition, PKCα was found associated with the phagosomal membranes, suggesting its importance in the phagocytic process (10, 14). Furthermore, a recent study reported that phagocytosis of latex beads by THP1 cells requires the activity of both PKCα and PKCβ, in support for a key role of these kinases in this biological event (14).

Phosphorylation and translocation of PKCs are two essential steps for activation of these enzymes (15–17). Previous reports have proposed that localization of activated PKC in the membrane fractions following agonist stimulation was mediated by the RACK (receptor for activated C kinase) anchoring protein (18, 19). RACK1 is localized in a specific organelle in resting cells and the activation of PKC leads a movement of RACK1 to cell periphery (20). At present, RACK1 co-localizes with the enzyme in response to PMA stimulation, a powerful PKC activator (20). Recently it was reported that the HIV-1 Nef protein binds to RACK1 and interferes with PKCα activity in T lymphocytes (21, 22). Interestingly, ZEBRA protein of EBV also binds RACK1 in vitro (23). However, the effect of this association on PKC activation remains undetermined. Thus, disruption of the association between PKC and RACK1, which is essential to PKC activity, could represent a strategy used by viruses to perturb cell signaling. Since EBV decreases the phagocytic ability of monocytes and such function is regulated in part by PKC, we investigated the possible mechanisms used by EBV to alter the activation of PKC. For this purpose, we analyzed the enzymatic activity and translocation of PKC as well as the subcellular localization of RACK1 in infected monocytes. The current study demonstrates that infection of monocytes by EBV impairs the activity and translocation of PKCα/β. Moreover, our results suggest that such disruption of PKC translocation/activation is caused by the ability of EBV-ZEBRA protein to interact with RACK.

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The abbreviations used are: EBV, Epstein-Barr virus; CMV, cytomegalovirus; MCMV, murine cytomegalovirus; HIV, human immunodeficiency virus; PKC, protein kinase C; RACK, receptor for activated C kinase; PMA, phorbol 12-myristate 13-acetate.
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**EXPERIMENTAL PROCEDURES**

**Purification of Human Monocytes**—Peripheral blood mononuclear cells were isolated by centrifugation of heparinized blood obtained from healthy donors over a Ficoll-Hypaque gradient (Amersham Biosciences, Uppsala, Sweden). Monocytes were enriched by Percoll density centrifugation and purified (>98%) by cell sorting (Epics Elite ESP, Coulter Electronics, Burlington, Ontario, Canada). Cell viability was >99% as estimated by trypan blue dye exclusion procedure (6).

**General Culture Conditions**—Purified human monocytes (10^6 cells/ml) were cultured in RPMI 1640 medium supplemented with 10% of heat inactivated fetal bovine serum and cultured at 37 °C under 5% CO2 in 15-ml polypropylene tubes. The culture medium contained less than 10 pg/ml endotoxin, as evaluated by Limulus amoebocyte assay (Becton Dickinson). To evaluate the activity and translocation of PKC, cells were stimulated with PMA (100 nM) (Sigma) at 37 °C for different periods of time.

**Infection Procedure**—Viral preparations of EBV (strain B95-8) were produced and titered as described previously (24). Monocytes (2.5 × 10^6 cells) were infected with infectious EBV (10^9 transforming units) in 250 μl of culture medium for 1 h at 37 °C and were washed twice in Hanks’ balanced salt solution (pH 7.4). Cells were subsequently resuspended in 4 ml of culture medium and cultured for varying period of times.

**Phagocytosis Assay**—The phagocytic activity of EBV-infected and uninfected monocytes was assessed by flow cytometry using carboxyfluorescin microspheres, as described previously (6). Briefly, 5 × 10^5 monocytes were washed with 500 μl of phosphate-buffered saline (pH 7.4) and resuspended in 350 μl of Hanks’ balanced salt solution supplemented with 5% fetal bovine serum. Where indicated, cells were pretreated for 1 h with the selective PKC inhibitor, calphostin C (500 nM) (Sigma) or RO-31-8220 (500 nM) (Sigma), to inhibit phagocytosis. Carboxylated fluoresceinated microspheres (1.87 μM: Fluoresbrite, Polyscience, Warrington, PA) were added to give a ratio of 12 beads per cell, and phagocytosis was allowed to proceed at 37 °C under constant agitation (150 rpm) for 2 h. Subsequently, monocytes were washed three times with 500 μl of cold phosphate-buffered saline to remove unphagocytosed microspheres and fixed in 500 μl of 0.5% paraformaldehyde. Monocytes were analyzed with an EPICS-XL flow cytometer and the percentage of fluorescent-positive monocytes determined.

**Plasmid DNA Transfection**—The CMV-Z expression vector contains the EBV-ZEBRA cDNA cloned downstream of the CMV immediate-early promoter (kindly provided from Dr. Shannon Kenney, University of North Carolina, Chapel Hill, NC). The human herpesvirus-6 IE1 expression plasmid was generated by the cloning of a full-length IE1 cDNA into the pBluescript vector, as described.2 Plasmid DNA was transfected into 293T (human embryonic kidney cells using the EXGEN-500 reagent (Upstate Biotechnology, Lake Placid, NY). The phagocytic activity of EBV-infected and uninfected monocytes, pHD1013-transfected 293T, or pCMV-Z-transfected 293T cells, untreated or PMA-treated, were assayed for PKC activity using a commercial PKC assay system according to supplier’s recommendations (Upstate Biotechnology, Lake Placid, NY).

**Statistical Analysis**—Statistical significance was determined using unpaired two-tailed Student’s t test. A p value of ≤ 0.05 was considered statistically significant.

**RESULTS**

**Both EBV and PKC Inhibitors Decrease Phagocytosis of Fluoresceinated Microspheres by Human Monocytes**—Considering that phagocytosis is important for host defense, an impairment of this function may lead to an increase susceptibility to infectious agents. As shown in Fig. 1, EBV inhibits (by 40%) the ability of human monocytes to phagocytose fluoresceinated beads as reported previously (6). Phagocytosis triggering is often associated with multimerization of cell surface receptors such as the Fc receptors (CD32, CD64) and complement receptors (9, 25). As a first step, we analyzed the expression of FcRI (CD64), FcRIIIa (CD32), and CR3 (CD11b/CD18) on the cell surface of EBV-infected monocytes. Results indicate that EBV has no effect on the expression of such molecules (data not shown), suggesting that this virus impairs phagocytosis through a yet to be defined mechanism. A previous study has reported that activation of PKC is crucial for the phagocytosis of latex beads and that pretreatment of THP-1 cells with specific PKC inhibitors abolished this activity (14). To investigate the involvement of protein kinases C on phagocytosis of latex beads by human monocytes, cells were pretreated with specific PKC inhibitors (calphostin C) or RO-31-8220 before the phagocytosis assay. In agreement with a previous study (14), our results (Fig. 1) show that pretreatment of monocytes with PKC inhibitors decreases the ability of monocytes to ingest microspheres, confirming the involvement of PKC in phagocytosis. Next, we investigated the effects of EBV infection on PKC activation in monocytes.

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Impaired PKC Activity in EBV-infected Monocytes—Activation of PKC results in the phosphorylation of various substrates. We first evaluated whether EBV infection affects PKC activation following PMA stimulation of monocytes. This assay was performed with cytosolic and membrane fractions obtained from uninfected or EBV-infected monocytes. As illustrated in Fig. 2A, the kinase activity of cytosolic PKCs from EBV-infected monocytes, in the absence or in the presence of PMA, is markedly decreased as compared with PKC activity measured in cytosols of uninfected cells. Similar results were obtained in testing PKC activity from membrane fractions (Fig. 2B). In addition, PKC activity in membrane fractions from PMA-treated monocytes was significantly suppressed by EBV (Fig. 2B). These results suggest that EBV may affect PKC activity but also that EBV can abrogate translocation of PKC from the cytosol to the membrane. While PKC activity is reduced by EBV infection, the protein levels of PKC were unaffected (data not shown). Thus, impairment of PKC activity in cytosol and membrane fractions of infected monocytes does not result from the degradation of the enzymes.

EBV Infection Inhibits the Translocation of PKCα and -β from Cytosol to Membrane Fractions in PMA-treated Monocytes—Activation of PKC involves its translocation from the cytosol to membranes. A failure in PKC translocation prevents triggering of PKC-dependent signaling cascade and impairs many biological functions. We next explored the impact of an EBV infection on the translocation of PKCα and -β from unstimulated and PMA-stimulated monocytes. Uninfected and EBV-infected monocytes were stimulated or not with PMA and proteins separated into cytosolic (C) and membrane (M) fractions. Western blot analysis indicates that PKCα remains sequestered in the cytosolic fraction of EBV-infected monocytes treated with PMA, while translocation of PKC from the cytosol to the membrane was easily detectable in uninfected monocytes (Fig. 3A). Similarly, EBV prevented PKCβ (Fig. 3B) and PKCγ (data not shown) translocation in PMA-activated monocytes, suggesting that this virus impairs the translocation of various PKC isoforms. In addition, it should be noted that the translocation process is not totally abolished by EBV, as detectable PKC proteins in membrane fractions from EBV-infected monocytes treated with PMA were observed. Interestingly, in PMA-untreated cells, greater levels of PKCα and -β were observed in the membrane fractions of EBV-infected monocytes compared with uninfected ones (Fig. 3, A and B). This may be explained by partial activation of PKC following binding of viral particles to the monocyte membrane, events preceding the synthesis of inhibitory viral proteins.

EBV Disrupts the Subcellular Localization of the RACK1 Anchoring Protein following PMA Treatment in Monocytes—Binding of activated PKC to RACK plays an important role in activation-induced translocation of PKC. Since translocation of PKCs is strongly reduced in EBV-infected monocytes, we evaluated the effects of EBV on the cellular localization of RACK1 upon PMA stimulation. Similar to the results obtained with PKC, the subcellular distribution of anchoring protein RACK1 is affected in EBV-infected monocytes (Fig. 4). In contrast to

![Fig. 1. Suppression of phagocytosis by EBV and PKC inhibitors.](http://www.jbc.org/) Monocytes (5 × 10⁵ cells) were infected with EBV (16 h) or pretreated with PKC inhibitors for 30 min (calphostin C (500 nM) or RO-31-8220 (500 nM)) before incubation with carboxylated fluoresceinated microspheres (at a ratio of 12 particles/cell) at 37 °C for 2 h. The percentage of cells having engulfed fluoresceinated beads was measured by flow cytometry, as described under “Experimental Procedures.” Similar results were obtained in three independent experiments. p values obtained from EBV-infected or PKC inhibitor-treated monocytes were compared with mock control (arbitrarily set at 100%). * = p ≤ 0.05.

![Fig. 2. Effects of EBV on PKC activity.](http://www.jbc.org/) Cytosolic (A) and membrane (B) fractions (50 μg of protein per sample) isolated from uninfected or EBV-infected monocytes were assayed for PKC activity as described under “Experimental Procedures.” Results are representative of three separate experiments, each carried out in triplicate. p values were calculated after comparison between EBV with mock control and EBV/PMA with PMA-treated cells. * = p ≤ 0.05.
uninfected cells, large amounts of RACK1 protein remain sequestered in the cytosolic compartment of EBV-infected cells treated or not with PMA. These results suggest that EBV inhibits the translocation process of RACK1 in human monocytes.

**EBV-ZEBRA Affects PKC Translocation and Binds RACK1 in 293T Cells**—ZEBRA has been linked with both the transactivation of lytic EBV genes, which favors viral replication, as well as the disruption of many cellular functions in B and T lymphocytes through interactions with the p53 (26) and NFkB p65 cellular proteins (27). While the ZEBRA transcript could be detected in infected monocytes, its translation product was not, suggesting that ZEBRA is expressed at low levels in EBV-infected monocytes. For this reason, PKC activity and the translocation process were evaluated in PMA-activated 293T cells transfected with a ZEBRA expression vector. Similarly to EBV-infected monocytes, ZEBRA-transfected 293T cells failed to adequately translocate PKCa following PMA treatment. In fact, the activity of PKC is reduced by 37% in membrane fractions of pCMV-Z transfected-293T cells following PMA treatment. Furthermore, PKCa levels in membranes from pCMV-Z transfected-293T cells stimulated with PMA are reduced as compared with mock or control cells (Fig. 5B), suggesting that the translocation process is affected by ZEBRA. However, since ZEBRA was found to be widely distributed in transfected 293T cells (e.g. cytosol and membrane), no significant changes were observed in cytosolic and membrane pools of ZEBRA following PMA treatment. Therefore, to evaluate whether the inhibition of PKC translocation observed could be caused through a physical interaction between ZEBRA and RACK1, a co-immunoprecipitation approach was considered. Interestingly, our results show that RACK1 co-immunoprecipitated ZEBRA, in support that both proteins physically interact (Fig. 5C). We were not able to co-immunoprecipitate PKCa/β using anti-ZEBRA antibodies, suggesting that ZEBRA does not bind to PKC. To ascertain that the ZEBRA-RACK1 interaction...
is not an artifact resulting from ZEBRA overexpression, we carried out a similar experiment using the immediate-early (IE1) gene of human herpesvirus-6. 293T cells were transfected with an expression vector for IE1 and 48 h later, IE1 was immunoprecipitated using rabbit anti-IE1 antibodies and protein A-Sepharose beads. No RACK1 protein could be detected in the IE1 immunoprecipitate despite large quantities of IE1 (data not shown). From these results we conclude that the interaction of ZEBRA with RACK1 is specific and does not result from overexpression of ZEBRA in transfected 293T cells.

**DISCUSSION**

It is well known that phagocytosis is crucial for the clearance of pathogens and represents a key step in antigen presentation (28). This process requires specific receptors on the cell surface (such as Fc and complement receptors) and activation of protein tyrosine kinases as well as PKCs, enzymes involved in foreign particles engulfment (28). We thus analyzed the effect of EBV infection on the expression of specific receptors and on the activation of protein kinases in monocytes. It has been reported that some viruses such as MCMV (8), HIV (29), and more recently EBV (6), have developed immunosuppressive strategies that target phagocytosis (8, 29). Our results indicate that EBV does not alter the expression of Fc (CD32, CD64) and complement (CR3) receptors but instead alters phagocytosis through an impairment of PKC activity in infected monocytes.

Since PKC isozymes carry out many cellular functions, it is not surprising that viruses target these enzymes to disturb cell signaling. A recent study reported that the HIV Nef protein interacts with PKCθ and inhibits its translocation from the cytosol to the membrane fraction (21, 22). Such a disruption may contribute to the impairment of T cell function associated with HIV infection. Moreover, it was demonstrated that NS3 protein of hepatitis C virus binds to PKC and suppresses its enzymatic activity and its subcellular distribution upon PMA stimulation (30, 31). According to Borowski et al. (30), NS3 protein is able to stop PKC-mediated functions within intact cells, supporting the possibility that NS3 disrupts PKC-mediated signal transduction. Similar to hepatitis C virus and HIV, EBV affects the activity of PKC in monocytes. Our results show that the PKC activity of cytosolic and membrane-bound protein extracts of infected monocytes is significantly lower than uninfected cells. Thus a reduction in PKC activity may affect several biological functions of monocytes such as phagocytosis, which are dependent on the activity of this enzyme. We previously reported that EBV suppresses tumor necrosis factor α and COX-2 gene expression in monocytes (7, 32), the likely result of impaired NFκB translocation (32) from cytosol to nucleus, regulatory events downstream of PKC activation (14, 33, 34). In contrast, D‘Addario et al. (35) have reported that binding of recombinant EBV gp350 envelope protein to monocytes leads to the up-regulation of tumor necrosis factor α gene expression via the activation of NF-κB, a process dependent of PKC and/or other kinase activation. The system used by D‘Addario and colleagues is somewhat artificial and does not take into account the events occurring during the infectious process such as viral protein synthesis. Binding of a protein to the cell membrane may induce cell signaling, leading to the activation of several cellular functions. Viral penetration and replication involve synthesis of different proteins having the potential to interact with host proteins and impair cellular function(s). We propose that infection of monocytes by EBV results in the inhibition of PKC translocation and activation, which suppresses other PKC-related events, including tumor necrosis factor α synthesis.

Translocation of enzymes from cytosol to particulate fractions upon cell stimulation is specific and often regulated by anchoring proteins, which bind selectively to enzymes allowing their subcellular relocalization. In the case of PKC, the anchoring protein RACK has been identified to be mostly responsible for both specific localization and the function of PKC isozymes (18, 36). RACKs are membrane-associated proteins located in various subcellular compartments (18, 37). Through co-factors such as calcium and diacylglycerol, RACK1 binds the active form of PKCs and moves the enzymes toward specific location in the cellular membrane following stimulation with agonist (18). Disruption of protein-protein interactions between RACKs and PKCs prevents agonist-mediated subcellular distribution of the enzymes and inhibits their function (19). According to Stebbins et al. (38), when the interaction between RACK1 and PKCβII is prevented by blocking peptides (which compete with PKCβII for RACK1 binding), the translocation of PKCβII is inhibited and cellular functions are affected. Our results show a reduced level of RACK1 in the membrane compartment of PMA-activated EBV-infected monocytes, a likely consequence for the reduction in PKC activity observed.

An EBV protein likely responsible for impaired PKC activa-
tion in monocytes is ZEBRA (39). In contrast to B cells (40), EBV infection of human monocytes is lytic with BZLF-1 transcripts, which encode for the ZEBRA protein, expressed at early times (6). It has been reported that complete activation of ZEBRA is dependent on Ser186 phosphorylation, an event catalyzed by PKCα and related kinases (41). Depending on the nature of PKC isoenzymes in the infected-cells, ZEBRA could recruit cellular proteins, like RACK, for its own activity and/or to affect cell signaling. Using the yeast two-hybrid system, EBV ZEBRA was reported to bind RACK1 in vitro (23). However, this study did not report the impact of ZEBRA expression on PKC activity. ZEBRA can thus possibly disturb the interaction between RACK1 and PKCα/β, resulting in an inhibition of PKC translocation. In fact, our results indicate that the activity and the translocation of PKCα is affected in ZEBRA-expressing cells. However, PKC inhibition in ZEBRA-transfected cells is less pronounced than in EBV-infected monocytes. This is possibly due to the very high PKC activity in 293T cells or alternatively due to other PKC isoenzymes in 293T cells that may be unaffected by ZEBRA. At the present time, we cannot exclude the possible role of other EBV proteins, whose transcripts were detected in infected monocytes (16). In fact, establishment of a lytic infection in monocyte leads to the expression of several viral genes, which could result in the inhibition of PKC activity. It is not surprising that in PMA-stimulated ZEBRA-transfected 293T cells, the activity of cytosolic PKCs is unaffected while that of membrane fractions is reduced. Such results suggest that translocation of PKCs from cytosol to membrane fractions is impaired in the presence of ZEBRA. Consistent with this result is the analysis of PKCα translocation in ZEBRA-transfected 293T cells, which shows that translocation of this isoenzyme from cytosolic to membrane fractions is disturbed in PMA-stimulated cells, supporting the hypothesis that ZEBRA, through its interaction with RACK1, impairs the translocation of PKCs. In agreement with Baumann et al. (23), who suggested that RACK1 interacts with ZEBRA, we have detected RACK1 in ZEBRA immunoprecipitates. Furthermore, binding of RACK1 to ZEBRA could prevent the association of RACK1 to PKC in the cytoplasm and inhibit the translocation of PKC to membranes. Since RACKs are adaptor proteins that mediate recruitment of various protein kinases (36, 37, 42), blocking activation of such protein may down-regulate phosphorylation of target protein and therefore cause impairment of various signaling pathways. The interaction between ZEBRA and RACK1 (a PKC anchoring protein) may represent another strategy used by EBV to affect cellular functions of human monocytes.

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