APOBEC3G is incorporated into virus-like particles by a direct interaction with HIV-1 Gag nucleocapsid protein

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APOBEC3G belongs to the family of cellular cytidine deaminase-editing enzymes with a potent antiretroviral activity, which is counteracted by the Vif protein expressed by lentiviruses. Antiretroviral activity of APOBEC3G requires its packaging into assembling virions, presumably to ensure its close association with nascent retroviral cDNA. Here, we demonstrate that APOBEC3G is encapsidated through a direct interaction with the HIV-1 Gag polyprotein which likely takes place on the membranes of the multivesicular bodies (MVB)/late endosomal compartments. This interaction is mediated by the Gag nucleocapsid protein NC, and the N-terminal part of NC is most critical for this interaction. Binding to the NC domain would ensure that APOBEC3G will be concentrated in the viral core of mature HIV-1, in close proximity to the reverse transcription complex.

PRODUCTIVE INFECTION BY HIV-11 requires the virus-encoded accessory protein called virion infectivity factor, Vif (1), the primary role of which is to counteract the action of a cellular antiretroviral protein APOBEC3G. APOBEC3G belongs to a family of cytidine deaminase genes that in humans includes APOBEC1, APOBEC2, seven genes (or pseudogenes) designated APOBEC3A to 3G and the activation-induced deaminase (AID) gene (2, 3). Recently another member of the APOBEC family, APOBEC3F, was shown to inhibit HIV-1 replication by a mechanism similar to that of APOBEC3G (4). The antiretroviral activity of APOBEC3G is attributed, at least partially (5), to deamination of cytosine to uracil on the newly synthesized minus strand of viral DNA that may lead to corresponding changes of guanidines to adenines on the coding strand (6–8). The mutations generated by APOBEC3G in HIV-1 DNA showed that single DNA strand specificity of APOBEC3G is responsible for deamination of the HIV DNA minus strand (9). Antiretroviral activity of APOBEC3G requires its encapsidation into assembling virions, presumably to ensure its close association with the retroviral reverse transcription complex and nascent retroviral cDNA. In the absence of Vif, APOBEC3G is specifically incorporated into the assembling HIV-1 virions, reducing infectivity of the newly produced virus (7, 10, 11). However, expression of HIV-1 Vif reduces incorporation of APOBEC3G into virions (10, 12–16), possibly by binding to APOBEC3G and promoting its degradation via the ubiquitin-proteasome pathway (13, 15, 17–19). The ability of Vif to block the antiviral activity of APOBEC3G is species-specific (10), and a region of APOBEC3G determining this specificity has been localized to a single amino acid residue (19–23). The mechanism by which APOBEC3G is incorporated into assembling virions is unknown. Analysis of the molecular mechanism(s) by which this antiviral protein is targeted to virus assembly sites may suggest an alternative approach to increase its virion levels in the presence of Vif. The precise cellular distribution of APOBEC3G has not yet been investigated but may provide an insight into the mechanism of its incorporation into virions. Results presented herein suggest that APOBEC3G is encapsidated through a direct interaction with the nucleocapsid of HIV-1 Gag. Moreover, we suggest that binding of APOBEC3G to abundantly produced Gag during infection may lead not only to its encapsidation but also result in degradation of APOBEC3G complexed with Gag. Both mechanisms may significantly deplete APOBEC3G levels independently of Vif.

EXPERIMENTAL PROCEDURES

Reagents—Recombinant APOBEC3G and anti-APOBEC3G monoclonal antibodies were from ImmunoDiagnostics. Mouse anti-GFP 3E6, rabbit anti-GFP, Lysotracker Red, and transferrin Alexa Fluor 594 were from Molecular Probes. Mouse anti-α-tubulin, anti-C6/33/LAMP3, anti-Rab7 antibodies, and protein A/G plus-agarose were from Santa Cruz Biotechnology. Anti-HA, mouse monoclonal 12CA5, and rat monoclonal 3F10 antibodies were from Roche Applied Science. Mouse anti-CD71 was from Beckman Coulter. Mouse anti-His and anti-EEA1 antibodies were from Invitrogen and BD Transduction Laboratories, respectively.

virion encapsidation assay—4 or 10 ml of culture supernatant from transfected 293T cells were filtered through 0.45-μm filters and concentrated by ultracentrifugation in a SW 60 or SW 41 rotor (Beckman) at 25,000 rpm for 2 h through a layer of 20% sucrose in phosphate-buffered saline. The pelletted virus-like particles were solubilized in 50–100 μl of RIPA buffer (50 mM Tris, pH 7.5, 10 mM EDTA, 150 mM NaCl, 1% Nonidet P-40, 0.1% SDS, 0.5% sodium deoxycholate) supplemented with protease inhibitors (Complete; Roche Applied Science), and 40 μl was analyzed by Western blotting.

Western blotting and immunoprecipitation—Western blot analysis was performed as described (24). For immunoprecipitation, postnuclear cell lysates in RIPA buffer were prepared from transfected 293T cells. Cell lysates (0.5–1 mg of protein) were immunoprecipitated overnight with anti-GFP 3E6 monoclonal antibody and protein A/G plus-agarose. After extensive washing, the precipitates were subjected to SDS-PAGE and analyzed by Western blotting. In vitro binding experiments—HIV-1 Gag and various Gag mutants (constructed using the QuickChange site-directed mutagenesis kit; Stratagene) were expressed as GST fusion proteins in Escherichia coli and purified from bacterial lysates using glutathione-Sepharose beads (25). Recovery of the GST and GST-Gag fusion proteins was monitored by staining the gels with Coomasie Blue. The glutathione-Sepharose beads with associated GST (negative control) or GST-Gag proteins were incubated overnight at 4 °C with recombinant

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APOBEC3G or with cell lysates prepared from transfected 293T cells expressing APOBEC3G tagged with GFP, His, or HA. After washing, bound proteins were eluted by boiling in SDS Laemmli buffer, resolved by SDS-PAGE, and visualized by Western blotting.

Confocal Microscopy—293T cells were grown on glass chamber slides (Nalgene Nunc International) and transfected with GFP-APOBEC3G and Gag or Gag-GFP expression vectors, and 24 h later, the cells were fixed with 4% paraformaldehyde, washed, and analyzed by confocal microscopy (24). For labeling of the early or late endosomes, the transfected cells were incubated for 30 min at 37 °C with transferrin conjugated with Alexa Fluor 594 or with LysoTracker Red, respectively (Molecular Probes), according to the manufacturer’s protocols. The images were taken with a LSM 510 META confocal microscope (Zeiss).

Biochemical Analysis of APOBEC3G Binding to Cellular Membranes and Lipid Rafts—Transfected 293T cells were harvested in 20 mM Tris, pH 7.5, 1 mM EDTA buffer supplemented with protease inhibitors and disrupted by Dounce homogenization. The postnuclear supernatant was separated into total membrane and cytosolic fractions by centrifugation at 40,000 × g for 30 min (26). Endosomal membranes were prepared from transfected cells by centrifugation of the postnuclear supernatant on a discontinuous sucrose gradient (27). Lipid rafts were prepared using 0.5% Triton X-100 as described in detail (24, 28).

RESULTS AND DISCUSSION

Transfection of GFP-APOBEC3G with increasing amounts of HIV-1 Gag reduced intracellular GFP-APOBEC3G steady-state levels in a concentration-dependent manner (Fig. 1A). Since Gag itself is sufficient to drive the assembly of virus-like particles (VLPs), we reasoned that reduction of GFP-APOBEC3G expression in cells resulted from APOBEC3G packaging into VLPs, most likely through the interaction with Gag. To test this hypothesis, 293T cells were transfected, and 24 h later culture supernatants were collected, filtered, and ultracentrifuged to pellet VLPs. Cell lysates were prepared from the same transfected cells, and both VLPs and lysates were analyzed by Western blotting for the presence of Gag and GFP-APOBEC3G (Fig. 1B). The results show that decreasing steady-state levels of GFP-APOBEC3G in cell lysates correlated with the increasing amount of transfected Gag expression vector. This increased amount of Gag resulted in greater accumulation of APOBEC3G in VLPs. Moreover, in the presence of Gag, GFP-APOBEC3G redistributed into a discrete punctate pattern localized close to, or at, the cell surface (Fig. 2A) and most likely represents coaggregating Gag and APOBEC3G (Fig. 2B). These results suggest that APOBEC3G interacts with Gag in the absence of other viral proteins. This possibility was further substantiated by the observation that Gag and APOBEC3G were bound to cell membranes pelleted from postnuclear supernatants prepared from transfected 293T cells in the absence of detergent (Fig. 2C). Interestingly, APOBEC3G localized to Triton X-100-resistant lipid rafts (Fig. 2D), which probably are not of plasma membrane origin, since APOBEC3G did not noticeably localize to the plasma membrane (data not shown). Thus, we hypothesize that APOBEC3G associates with intracellular membrane rafts. Since Gag concentrates both in the plasma membrane and multivesicular bodies (MVB)/late endosomal compartments (29–31) enriched in lipid rafts and both Gag and APOBEC3G colocalize (Fig. 2B), we speculate that APOBEC3G may interact with Gag at the membranes of the MVB/late endosomal compartments. Indeed, APOBEC3G partially cofractionated with the late endosomal/lysosomal markers, Rab7 and CD63/LAMP-3 (Fig. 3A). Solubilization of APOBEC3G as well as Rab7 and CD63 with the mild nonionic detergent octyl glucoside shows that these proteins were indeed associated with membrane fractions. Coexpression of Gag-GFP and APOBEC3G-HA in 293T cells resulted in significant accumulation of APOBEC3G in Rab7-positive and EEA1-negative late endosomes (Fig. 3B), suggesting that accumulation of Gag on MVB/late endosomes may be responsible for bringing more APOBEC3G to this compartment. These results were confirmed by confocal analysis using fluorescent LysoTracker Red, a specific probe for labeling late endosomes and lysosomes (Fig. 3C). While Gag-GFP and GFP-APOBEC3G colocalized with the LysoTracker-labeled compartment, signifi-
A. APOBEC3G interacts directly with HIV-1 Gag and requires Gag NC domain. A, GST, GST-Gag, and GST-Gag deletion mutants expressing MA, MA-CA-p2, or MA-CA-p2-p1-p6 (Gag-ΔNC) were produced as GST fusion proteins as described under "Experimental Procedures" and visualized by Coomassie Blue staining following SDS-PAGE. Truncated forms of full-length GST-Gag were observed. The purified GST-Gag deletion mutants were assayed for the ability to bind APOBEC3G from two different sources: recombinant T-tagged APOBEC3G or His-APOBEC3G present in lysates of 293T cells transfected with His-APOBEC3G expression vector. Bound proteins were visualized by Western blotting with anti-T-tag or anti-His antibodies, respectively. B, coimmunoprecipitation of Gag-GFP and different Gag-GFP deletion mutants with APOBEC3G was performed as described under "Experimental Procedures." Cell lysates were immunoprecipitated with anti-GFP 3E6 antibody and precipitated proteins were visualized using anti-HA, to detect APOBEC3G, or anti-GFP antibodies, to detect different GFP-Gag deletion mutants (lower panel).

Fig. 4. Distribution of GFP-APOBEC3G and endosomal markers. A, APOBEC3G cofractionates with late endosomal membrane markers. Transfected 293T cells were disrupted in homogenization buffer (HB; 20 mM Hepes, pH 7.4, 0.25 M sucrose, 2 mM EDTA) supplemented with protease inhibitors. The postnuclear supernatants were divided into two parts; one part was left untreated while the other was incubated with 0.5% nonionic detergent octyl-β-d-glucopyranoside (octyl glucoside). Lysates were subsequently adjusted to 41% sucrose and overlaid with 35 and 25% sucrose and homogenization buffer. The gradient was centrifuged for 1 h at 100,000 × g. Fractions (0.5 ml) were collected from the top of the gradient and were analyzed by Western blotting for the presence of APOBEC3G and endosomal markers, Rab7 and CD63/LAMP-3. B, GFP-APOBEC3G and Gag-GFP colocalize with Rab7-positive and EEA1-negative late endosomes. Cells were cotransfected with Gag-GFP and APOBEC3G-HA plasmids and postnuclear supernatants (PNS) were prepared and fractionated as described in (A). Following centrifugation, all three interfaces were collected and designated as the heavy membrane fraction (HM), 41%/35% interface, early endosomes (EE, 35%/25%), and late endosomes (LE, 25%/HB) as described (38). Thirty μg of each fraction, including postnuclear supernatants, were analyzed by Western blotting for the presence of APOBEC3G, Gag, Rab7 (late endosome marker), and EEA1 (early endosome marker). C, colocalization of GFP-APOBEC3G and Gag-GFP with late endosomal/lysosomal marker LysoTracker Red. Transfected cells were incubated for 30 min at 37°C with red fluorescent LysoTracker, a specific probe for labeling of late endosomes and lysosomes or transferrin-Alexa Fluor 594 are shown.

Fig. 3. Distribution of GFP-APOBEC3G and endosomal markers. A, APOBEC3G cofractionates with late endosomal membrane markers. Transfected 293T cells were disrupted in homogenization buffer (HB; 20 mM Hepes, pH 7.4, 0.25 M sucrose, 2 mM EDTA) supplemented with protease inhibitors. The postnuclear supernatants were divided into two parts; one part was left untreated while the other was incubated with 0.5% nonionic detergent octyl-β-d-glucopyranoside (octyl glucoside). Lysates were subsequently adjusted to 41% sucrose and overlaid with 35 and 25% sucrose and homogenization buffer. The gradient was centrifuged for 1 h at 100,000 × g. Fractions (0.5 ml) were collected from the top of the gradient and were analyzed by Western blotting for the presence of APOBEC3G and endosomal markers, Rab7 and CD63/LAMP-3. B, GFP-APOBEC3G and Gag-GFP colocalize with Rab7-positive and EEA1-negative late endosomes. Cells were cotransfected with Gag-GFP and APOBEC3G-HA plasmids and postnuclear supernatants (PNS) were prepared and fractionated as described in (A). Following centrifugation, all three interfaces were collected and designated as the heavy membrane fraction (HM), 41%/35% interface, early endosomes (EE, 35%/25%), and late endosomes (LE, 25%/HB) as described (38). Thirty μg of each fraction, including postnuclear supernatants, were analyzed by Western blotting for the presence of APOBEC3G, Gag, Rab7 (late endosome marker), and EEA1 (early endosome marker). C, colocalization of GFP-APOBEC3G and Gag-GFP with late endosomal/lysosomal marker LysoTracker Red. Transfected cells were incubated for 30 min at 37°C with red fluorescent LysoTracker, a specific probe for labeling of late endosomes and lysosomes or with the early endosomal marker transferrin-Alexa Fluor 594 and processed as described under "Experimental Procedures." Merged images of GFP-APOBEC3G or Gag-GFP with LysoTracker Red or transferrin-Alexa Fluor 594 are shown.

Significantly less colocalization was observed between APOBEC3G and the early endosomal marker transferrin-Alexa Fluor 594, suggesting that APOBEC3G was not randomly associated with intracellular membranes but specifically targeted to late endosomal vesicles. Together, these data strongly support the idea that APOBEC3G and Gag interact on intracellular membranes, most likely in the late endosomal compartment.

To test the potential interaction between Gag and APOBEC3G, in vitro binding assays were performed with recombinant proteins expressed in E. coli. HIV-1 Gag was expressed as a GST-Gag fusion protein, immobilized on glutathione-Sepharose beads (Fig. 4A, Coomassie Stain), and washed and assayed for the ability to bind recombinant APOBEC3G or His-APOBEC3G prepared from lysates of transiently transfected 293T cells (Fig. 4A, upper panels). Results show that APOBEC3G associated with GST-Gag but not with GST, indicating that the interaction was specific for Gag. Furthermore, to identify the Gag domain that interacts with APOBEC3G,
different Gag deletion mutants expressing MA, MA-CA-p2, or MA-CA-p2-p1-p6 (Gag ΔNC) were produced as GST fusion proteins (Fig. 4A, Coomassie Stain) and assayed for the ability to bind APOBEC3G. The results demonstrate that in the absence of the NC domain there is no binding to APOBEC3G. Thus, the Gag NC domain is likely to mediate the interaction with APOBEC3G. Since the purity of recombinant APOBEC3G and GST-Gag was greater than 95%, it seems unlikely that any contaminating proteins act as cofactors for the association between Gag and APOBEC3G in this assay. To confirm that the interaction between Gag and APOBEC3G occurs in vivo, a communoprecipitation experiment was performed (Fig. 4B). 293T cells were transfected with expression vectors for Gag-GFP or Gag-GFP deletion mutants and/or APOBEC3G-HA, and 24 h later, the cellular lysates were immunoprecipitated with monoclonal anti-GFP antibody. Immunoprecipitated proteins were analyzed by Western blotting for the presence of Gag and APOBEC3G using specific anti-tag antibodies. Results of the experiment show that APOBEC3G was immunoprecipitated with anti-GFP antibodies only when coexpressed with Gag-GFP and in the presence of Gag NC domain (Fig. 4B). Thus communoprecipitation experiments confirmed the requirement of Gag NC domain seen in GST pulldown assay. The significance of the NC domain in the interaction with APOBEC3G was further confirmed by showing that the NC domain fused with GST was sufficient to interact in vitro with APOBEC3G (Fig. 5A). However, in communoprecipitation experiments, binding of APOBEC3G to the NC-GFP domain was not as strong as in in vitro binding experiments. This may be due to the steric hindrance imposed by anti-GFP antibodies binding in close proximity to NC in the APOBEC3G-NC complex. Interestingly, when this paper was submitted, Cen et al. (32) showed that HIV-1 Gag alone is sufficient for packaging of APOBEC3G into Gag VLPs, and this incorporation requires the presence of Gag nucleocapsid. Thus, these findings corroborate our results. HIV-1 Gag NC is rich in basic residues and contains two zinc fingers. To determine more precisely which region of NC is responsible for the observed interaction with APOBEC3G, deletion mutants were produced as GST fusion proteins. The amino acid residues deleted were 1–28 in NC ΔN1 and 29–55 in NC ΔN2. Both in vitro GST fusion pull-down experiments (Fig. 5A) and immunoprecipitation experiments (Fig. 5B) show conclusively that although the N-terminal domain of NC (amino acid residues 1–28) is critical for the interaction with APOBEC3G, the C-terminal NC domain (amino acids 29–55) also contributes partially to the binding with APOBEC3G. Together, our results demonstrate that the antiretroviral protein APOBEC3G is incorporated into viral particles by direct binding to the NC domain of the Gag precursor p55 polyprotein. We hypothesize that the interaction with the NC domain ensures that APOBEC3G will be confined to the condensed HIV-1 core formed during virus maturation and containing HIV-1 RNA and reverse transcriptase and thus will have access to the reverse transcription products produced after virus entry. Our results also raise the possibility that abundant production of Gag proteins observed during infection (from which only a fraction will be incorporated into progeny virions, the rest most likely being degraded) may actually work as a decoy for APOBEC3G and deplete the cellular enzyme to levels insufficient for effective encapsidation and subsequent HIV-1 DNA editing activity. Another important implication of these results is that inhibition of the interaction between APOBEC3G and Vif by drugs (which may prevent APOBEC3G degradation) may not be sufficient to prevent depletion of APOBEC3G by HIV-1 Gag.

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