Human herpesvirus 7 U47 gene products are glycoproteins expressed in virions and associate with glycoprotein H

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The function of the human herpesvirus 7 (HHV-7) U47 gene, which is a positional homologue of the genes encoding glycoprotein O (gO) in human cytomegalovirus (HCMV) and human herpesvirus 6 (HHV-6), was analysed. A monoclonal antibody (mAb) against the U47 gene product reacted in immunoblots with proteins migrating at 49 and 51 kDa in lysates of HHV-7-infected cells and with 49 and 51 kDa proteins in partially purified virions. Digestion of the 49 and 51 kDa proteins with endoglycosidase H and peptide N-glycosidase F indicated that the U47-encoded proteins were modified with N-linked oligosaccharides. Therefore, the U47 gene and its product were named gO, as in HCMV and HHV-6. In addition, the anti-gO mAb co-immunoprecipitated glycoprotein H (gH) in HHV-7-infected cells, indicating an association between HHV-7 gO and gH. The results suggest that the HHV-7 gO–gH complex might have a similar function to that in HCMV or HHV-6, such as cell–cell fusion in virus infection.

INTRODUCTION

Human herpesvirus 7 (HHV-7) was first isolated from activated CD4+ T cells in the peripheral blood of a healthy donor (Frenkel et al., 1990) and was subsequently detected in and isolated from the blood and saliva of other individuals (Hidaka et al., 1993; Ihira et al., 2003; Sada et al., 1996; Wyatt & Frenkel, 1992; Yoshikawa et al., 1993). HHV-7 is reported to bind to the human CD4 molecule and to use CD4 as its host-cell receptor (Lusso et al., 1994). At present, however, the putative viral ligand for CD4 is still unidentified.

Herpesviruses encode several glycoproteins that are targeted to the virion envelope. They play critical roles in viral infection, including attachment, penetration, cell-to-cell spread and the maturation of nascent viral particles. In human herpesviruses, envelope glycoprotein H (gH) associates with glycoprotein L (gL) to form a gH–gL complex, which is a key participant in fusion events critical to herpesvirus infection. gH is thought to be important for virus cell fusion, whereas the role of gL is to serve as a chaperone, essential for the folding and transport of functional gH (Dubin & Jiang, 1995; Gompels et al., 1988; Gompels & Minson, 1989; Hutchinson et al., 1992; Kaye et al., 1992; Klupp et al., 1994; Liu et al., 1993; McGeoch & Davison, 1986; Roop et al., 1993; Scott et al., 1993; Spaete et al., 1993; Stokes et al., 1996; van Drunen Littel-van den Hurk et al., 1996; Yaswen et al., 1993; Yoshida et al., 1994). Similar to other herpesviruses, the HHV-7 gH and gL proteins form a complex in virus-infected cells (Mukai et al., 1997).

In some herpesviruses, a third viral glycoprotein associates with the gH–gL complex. Epstein–Barr virus gp42 (Li et al., 1995; Wang et al., 1998) and human herpesvirus 6 (HHV-6) glycoprotein Q (gQ) (Akkapai boon et al., 2004; Mori et al., 2003) have been identified as members of the gH–gL complex.

In human cytomegalovirus (HCMV), glycoprotein O (gO), which is unique to the subfamily Betaherpesvirinae, forms a tripartite complex with gH and gL, and this complex appears to play important roles in the viral entry into host cells (Huber & Compton, 1998; Kinzler et al., 2002; Paterson et al., 2002; Theiler & Compton, 2001, 2002). Recently, we reported that HHV-6 gO forms a tripartite complex with gH and gL on the viral envelope, as it does in HCMV (Mori et al., 2004).

In this study, we analysed the HHV-7 U47 gene, which is a positional homologue of the HCMV and HHV-6 gO genes, and identified its gene product as a glycoprotein that forms a complex with gH in infected cells.

METHODS

Cells and viruses. The KHR strain of HHV-7 was isolated from the peripheral blood mononuclear cells of a patient with exanthem subitum (Tanaka et al., 1994). The virus stocks were propagated in a CD4+ T-cell leukaemic cell line, Sup-T-1. The cells were infected with HHV-7 and cultured in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS). When HHV-7-infected Sup-T-1 cells showed evidence of more than 80% infection in an immunofluorescence assay...
The cells were lysed by freezing-thawing twice and spun at 2000 g for 10 min. The supernatant was used as cell-free virus. Partially purified virions were isolated as follows. SupT-1 cells were infected with HHV-7 and, at 7 days post-infection, the cells were spun at 2000 g for 15 min at 4°C. The supernatant from the cells was concentrated by centrifugation at 70,000 g for 2 h at 4°C through a 20% sucrose cushion in an SW28 rotor (Beckman). Virions were collected from the bottom. Phosphonoformic acid (PFA), which inhibits viral DNA synthesis, was used to determine whether the U47 gene encodes an early or a late protein. To observe the early proteins, SupT-1 cells were infected with HHV-7, cultured in medium supplemented with PFA (200 μg ml⁻¹) and harvested at 1, 8, 12, 24, 48 and 72 h post-infection. 293T cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% FCS.

**Expression of HHV-7 gO, gH and glycoprotein B (gB) in *Escherichia coli***. To obtain purified recombinant HHV-7 gO, named 7gO-C, the following procedure was used. The primer pair 7gO613bamF (5'-ACCGATCCGTTTACAATCGAAGATTGC-3') and 7gO942salR (5'-ACCGTGACTTATGTGCTTGTTACTATG-3') was used to amplify inserts from cDNA for the carboxyl terminus of the U48-encoded gO protein (corresponding to the codons for aa 205–313). The PCR products were inserted into the prokaryotic expression vector pQE30 (Qiagen) via the BamHI and SalI restriction sites. The resulting expression plasmid encoded the gO gene products with an N-terminal tag containing six histidine residues (MRGSHHHHHGS). 7gO-C. The recombiant proteins were expressed in E. coli and purified under denaturing conditions in accordance with the manufacturer’s (Qiagen) instructions. The same procedure was used to produce purified recombinant HHV-7 gH, named 7gH-C. The primer pair 7gH997bamF (5'-ACCGGATCCGTTTACAATCGAACAGATTGC-3') and 7gH1908salR (5'-ACCGTGACTTATGTGCTTGTTACTATG-3') was used to amplify inserts from HHV-7 cDNA for the carboxyl terminus of the U48-encoded gH protein (corresponding to the codons for aa 203–313). The PCR products were inserted into the prokaryotic expression vector pQE30 (Qiagen) via the BamHI and SalI restriction sites. The resulting expression plasmid encoded the gH gene product with an N-terminal tag containing six histidine residues (MRGSHHHHHGS). 7gH-C. The recombiant proteins were expressed in E. coli and purified under denaturing conditions in accordance with the manufacturer’s (Qiagen) instructions. The primer pair 7gH997bamF (5'-ACCGGATCCGTTTACAATCGAACAGATTGC-3') and 7gH1908salR (5'-ACCGTGACTTATGTGCTTGTTACTATG-3') was used to amplify inserts from HHV-7 cDNA for the carboxyl terminus of the U48-encoded gH protein (corresponding to the codons for aa 203–313). The PCR products were inserted into the prokaryotic expression vector pQE30 (Qiagen) via the BamHI and SalI restriction sites. The resulting expression plasmid encoded the gH gene product with an N-terminal tag containing six histidine residues (MRGSHHHHHGS). 7gH-C. The recombiant proteins were expressed in E. coli and purified under denaturing conditions in accordance with the manufacturer’s (Qiagen) instructions.

**Immunoblotting.** HHV-7-infected and mock-infected cells were lysed in radioimmunoprecipitation assay (RIPA) buffer [0.01 M Tris/HCl (pH 7.4), 0.15 M NaCl, 1% sodium deoxycholate, 1% Nonidet P-40, 0.1% SDS, 1 mM EDTA, 1 mM PMSF]. The lysed proteins were resolved by SDS-PAGE and electrotransferred onto a PVDF membrane for immunoblotting. Standard pre-stained molecular mass markers (Bio-Rad) were included in parallel lanes. After the blocking step, the membranes were incubated for 1 h with blocking buffer (PBS, 5% skimmed milk, 0.1% Tween 20) containing the mAbs or rabbit polyclonal antibodies. The reactive bands were visualized with a horseradish peroxidase-conjugated second antibody and enhanced chemiluminescence (ECL) detection reagents (Amersham Pharmacia Biotech).

**Immunoprecipitation and immunoblotting.** HHV-7-infected and mock-infected cells were lysed in RIPA buffer for 30 min on ice at 7 days post-infection. After centrifugation at 70,000 g for 1 h, the supernatants were incubated with the mAbs 7gO-A, 7gH-2, 24G7 or 33A7 coupled to protein G-Sepharose (Amersham Pharmacia Biotech) at 4°C for 4 h. The immunocomplexes were washed with RIPA buffer to remove unbound proteins. The precipitated proteins were solubilized with sample buffer [32 mM Tris/HCl (pH 6.8), 1.5% SDS, 5% glycerol, 2.5% 2-mercaptoethanol], separated by SDS-PAGE and electrotransferred onto a PVDF membrane for immunoblotting with the mAbs 7gH-2, 7gO-A or 24G7, or the rabbit polyclonal Ab 7gB-C.

**Immunohistochemical analysis.** The IFA was performed as described previously (Takeda et al., 1997). Specific immunofluorescence was observed with a confocal laser-scanning microscope (Carl Zeiss LSM 510).
RESULTS

Specificity of mAbs

To analyse the U47 gene products, we first produced an mAb against the U47 gene products (7gO-A), as described in Methods.

To examine the specificity of the mAbs, a plasmid containing each gene, pCAGGS/gH or pCAGGS/gO, was used. 293T cells were transfected with pCAGGS/gH, pCAGGS/gO or pCAGGS and the expression of gH or gO was examined by using mAbs for gH or gO. As shown in Fig. 1, the mAbs for gH and gO reacted with the gH and gO genes expressed in 293T cells, respectively.

Characterization of the U47 gene product gO in HHV-7-infected cells

To characterize the U47 gene products in HHV-7-infected cells using the mAb, lysates from HHV-7- or mock-infected cells were immunoblotted with 7gO-A. 7gO-A reacted with two specific species, with molecular masses of 49 and 51 kDa (Fig. 2a).

The HHV-7 U47 gene products are predicted to contain 11 potential N-linked glycosylation sites; therefore, we performed endoglycosidase digestion experiments to examine whether the U47 gene products were glycosylated. The proteins were treated with Endo H, which removes immature, high-mannose asparagine (N)-linked oligosaccharides but not the mature, complex oligosaccharides, and PNGase F, which removes both the high-mannose and complex N-linked oligosaccharides. As shown in Fig. 2(a), the 49 and 51 kDa proteins shifted in electrophoretic mobility to approximately 35 kDa after Endo H treatment and to 34 kDa after PNGase F digestion. These results indicate that the 49 and 51 kDa proteins contained both immature, high-mannose N-linked oligosaccharides and complex N-linked oligosaccharides. Because we identified the U47 gene products as glycoproteins, we named the U47 gene and its product gO.

HHV-7 gO protein is present in virions

The gO proteins of herpesviruses are expressed in the viral envelope. Therefore, we examined whether HHV-7 gO was present in virions. The presence of gO in the mature viral particle was verified by immunoblotting lysates from partially purified virions with the 7gO-A mAb. The 49 and 51 kDa proteins were detected in virions with 7gO-A (Fig. 2b). Next, we examined whether the gO products in the viral particles were glycosylated. The lysates of partially purified virions were digested with Endo H or PNGase F. Fig. 2(b) shows that the 49 and 51 kDa proteins shifted in electrophoretic mobility to approximately 35 kDa after Endo H treatment and to 34 kDa after PNGase F digestion.

N-linked oligosaccharides. Fig. 2(a) shows the digested proteins analysed by SDS-PAGE under reducing conditions. The 49 and 51 kDa proteins shifted in electrophoretic mobility to approximately 35 kDa after Endo H treatment and to 34 kDa after PNGase F digestion. These results indicate that the 49 and 51 kDa proteins contained both immature, high-mannose N-linked oligosaccharides and complex N-linked oligosaccharides. Because we identified the U47 gene products as glycoproteins, we named the U47 gene and its product gO.

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51 kDa was detected in virions (Fig. 3, Anti-gB). pp85 was detected in both infected cells and virions as an 85 kDa band (Fig. 3, Anti-pp85), as reported previously (Takeda et al., 2000) and by Stefan et al. (1997). Therefore, gB-51K and pp85 were both detected in purified virions; however, IE1 was not detected in purified virions (Fig. 3, Anti-IE1).

HHV-7 gO proteins appear late in infection

As shown in Fig. 4(a), gO expression was first detected at 48 h post-infection and became stronger until 120 h post-infection, similar to pp85, which has been reported to be a late protein (Takeda et al., 2000), although the immediate-early protein IE1 recognized by mAb 7IE1-A and the early protein U27 recognized by mAb 11H8 were first detected at 12 and 24 h post-infection, respectively. This expression pattern indicated that gO behaves like a late protein. In addition, gO expression in HHV-7-infected cells treated with PFA was examined at the same time (Fig. 4b). HHV-7-infected cells were maintained for 72 h in culture medium either with or without PFA (200 µg ml⁻¹). No HHV-7 gO was detected in the cells treated with PFA, although the U27 protein was detected. Moreover, pp85 was not detected. These results indicate that the gO proteins are late class proteins in HHV-7 infection.

Expression of HHV-7 gO in HHV-7-infected SupT-1 cells

To examine the cellular localization of gO, an IFA was performed with HHV-7-infected SupT-1 cells at 7 days post-infection (Fig. 5). There was a significant overlap of signals when the infected cells were double-labelled with the anti-gO mAb 7gO-A and HPL–FITC conjugates. HPL–FITC is a fluor-labelled lectin, which binds to N-acetyl-D-galactosaminyl residues and is used as a cis-Golgi marker.

Fig. 3. Immunoblotting of HHV-7-infected SupT-1 cells and partially purified virions with several antibodies under reducing conditions. The lysates were resolved by SDS-PAGE under reducing conditions and electrotransferred to PVDF membranes. The blots were reacted with mAbs for IE1, pp85 and gO, and polyclonal antibody for gB. Numbers show molecular masses. Two forms of envelope gB were identified in infected cells, a precursor form of 112 kDa and a cleaved form of 51 kDa. In virions, gB was only detected as the 51 kDa cleaved form. The tegument protein pp85 was detected in both infected cells and virions. gO was identified in both infected cells and virions, as for the envelope glycoprotein gB and the virion tegument protein pp85.

Fig. 4. Time course of HHV-7 gO synthesis in the absence and presence of PFA. SupT-1 cells were infected with HHV-7 by using the centrifugal method and the cells were cultured without (a) or with (b) PFA and collected at the indicated time point. The cells were lysed with SDS-PAGE sample buffer, resolved by SDS-PAGE under reducing conditions and electrotransferred to PVDF membranes. The blots were reacted with mAbs for IE1 (a) and pp85, gO and U27 (a and b). As controls, the membranes were subsequently stripped and analysed with anti-α-tubulin antibody. h.p.i., Hours post-infection.
This observation provides evidence that gO accumulates in the cis-Golgi apparatus and suggests that gO is glycosylated there.

**gO associates with gH**

The HCMV and HHV-6 gO proteins are reported to form a tripartite complex with gH and gL. To investigate whether HHV-7 gO also forms a complex, immunoprecipitates of HHV-7-infected cells obtained with the anti-gO mAb were immunoblotted with an anti-gH mAb that recognizes 80 and 90 kDa proteins (Mukai et al., 1997). In the HHV-7-infected cells, the anti-gH mAb recognized the gH proteins as 80 and 90 kDa bands and, in the virions, the anti-gH mAb mostly detected the 90 kDa band (Fig. 6a). gH, but not gB or pp85, was co-immunoprecipitated by 7gO-A and the gH appeared as an 80 kDa protein in the immunoprecipitate (Fig. 6a–c).

We also performed immunoprecipitation with anti-gH and anti-gO followed by Western blotting with anti-gO mAb. However, because the molecular mass of gO proteins was 49–51 kDa and that of the immunoglobulin heavy chain was also around 50 kDa, the bands of the heavy chain overlapped with those of gO by immunoprecipitation–Western blotting. Therefore, we performed co-immunoprecipitation by using a ProFound Co-Immunoprecipitation kit for the detection of gO proteins masked with the antibody heavy chain. An amine-reactive gel was mixed with the primary antibody (anti-gH or anti-gO mAb) and direct covalent immobilization of the primary antibody was attained by using sodium cyanoborohydride, as described in Methods. As shown in Fig. 7, gO protein was co-precipitated with gH protein, although neither pp85 nor gB protein was co-precipitated with gH proteins. These findings indicate that gO interacted with gH specifically, and the association between these glycoproteins was stable, even in the presence of 0.1% SDS.

**DISCUSSION**

There have been several reports of HHV-7-encoded glycoproteins being expressed in infected cells (Gompels et al., 1988; Hata et al., 1996; Hudson et al., 2001; Mukai et al., 1997; Nicholas, 1996; Secchiero et al., 1997).

Here, to further investigate the roles of HHV-7 glycoproteins expressed in virions, we focused on the product of the HHV-7 U47 gene, a positional homologue of HCMV UL74 and HHV-6 U47, which encode gO.

Sequence analysis has shown that the U47 gene product has N-terminal hydrophobic sequences that may serve as a cleavable signal sequence, 11 potential N-linked glycosylation sites and six cysteine residues, and consists of 313 aa, with a predicted molecular mass of approximately 37 kDa (Huber & Compton, 1998; Megaw et al., 1998; Nicholas, 1996).

Using a mAb for the HHV-7 U47 gene product, we detected 49 and 51 kDa bands in lysates from HHV-7-infected cells and the bands were shifted to approximately 35 kDa after Endo H treatment and to 34 kDa after PNGase F treatment, as shown in Fig. 2(a). These results indicate that the HHV-7 U47 gene products were glycoproteins modified with N-linked oligosaccharides. Therefore, we termed the U47 gene products gO, as in HCMV and HHV-6. The HHV-7 gO protein was also detected in partially purified virions (Fig. 2b), indicating that the gO protein is expressed in virions and may play an important role in the virus entry process.

Furthermore, we found that HHV-7 gO associates with gH in HHV-7-infected cells, similar to the gO of HCMV or HHV-6, and consistent with the previous findings that HCMV gO associates with the gH–gL complex (Huber & Compton, 1998) and that HHV-6 gO forms a tripartite complex with gH–gL (Mori et al., 2004).

To eliminate non-specific interactions of gH and gO, we performed immunoprecipitation with an mAb for gO followed by Western blotting with an mAb for gB, which is an envelope glycoprotein that binds to cell-surface heparan sulfate proteoglycans (Secchiero et al., 1997), or an mAb for...
U14, which is tegument protein pp85 (Stefan et al., 1997; Takeda et al., 2000). The mAb for gO precipitated gH, but not gB or pp85, in HHV-7-infected cell lysates (Fig. 6).

Therefore, we conclude that the mAb for gO co-precipitated gH specifically, and did not merely trap it non-specifically in a protein–antibody complex.

Fig. 6. Detection of the gH–gO complex in HHV-7-infected SupT-1 cells. (a) HHV-7- or mock-infected SupT-1 cell lysates or virion lysates were immunoprecipitated (IP) with the anti-gH mAb 7gH-2 or anti-gO mAb 7gO-A and subjected to SDS-PAGE under reducing conditions. The gel was electrotransferred to a PVDF membrane and probed with anti-gH mAb. (b) HHV-7- or mock-infected SupT-1 cell lysates or virion lysates were immunoprecipitated with the anti-pp85 mAb 24G7 or anti-gO mAb 7gO-A and subjected to SDS-PAGE under reducing conditions. The gel was electrotransferred to a PVDF membrane and probed with the anti-pp85 mAb, 24G7. (c) HHV-7- or mock-infected SupT-1 cell lysates or virion lysates were immunoprecipitated with the anti-gB mAb 33A7 or anti-gO mAb 7gO-A and subjected to SDS-PAGE under reducing conditions. The gel was electrotransferred to a PVDF membrane and probed with anti-rabbit antibody. HC, Immunoglobulin heavy chain.

Fig. 7. Co-immunoprecipitation (IP) of gH–gO complex with the primary antibody (anti-gH or anti-gO mAb) covalently immobilized to the amine-reactive gel. Immunocomplexes precipitated with anti-gH mAb 7gH-2 or anti-gO mAb 7gO-A were subjected to SDS-PAGE under reducing conditions, and were immunoblotted with anti-gH (7gH-2), anti-gO (7gO-A) or anti-pp85 (24G7) mAbs, or anti-gB rabbit antibody.
Because gH is found in a heterodimer of gH–gL in HHV-7 (Mukai et al., 1997), gL might be expected to exist in a complex with gH and gO. Therefore, we generated polyclonal antibodies against gL and used them in IFAs of HHV-7-infected SupT-1 cells and to probe Western blots of the cell lysates. However, we could not detect gL proteins with the antibodies at any time during infection (data not shown). To confirm that the antibodies for gL recognized HHV-7 gL, we cloned the full-length gL gene into a eukaryotic expression vector, pCAGGS, to make pCAGGS/gL. When gL was transiently expressed in 293T cells, it was clearly detected with the anti-gL antibodies (data not shown), suggesting that gL proteins may be expressed in HHV-7-infected SupT-1 cells at a very low level or that the antibodies may not recognize the gL in gH–gL–gO or gH–gL complexes in HHV-7-infected cells. Mukai et al. (1997) also reported that sera against the HHV-7 gL protein had high nonspecific signals, and they showed an interaction between gH and gL by using radiolabelled immunoprecipitation with anti-gH sera. However, the bands of gL that co-immunoprecipitated with the anti-gH sera were very faint (Mukai et al., 1997). For further studies of the HHV-7 gO–gH–gL complex, new antibodies against HHV-7 gL are being made in our laboratory.

The mAb for HHV-7 gH, named 7gH-2, recognized 80 and 90 kDa proteins in HHV-7-infected cells, but only the 90 kDa band was detected in virions by immunoprecipitation followed by Western blotting. Thus, although the mAb for gH immunoprecipitated both the 80 and 90 kDa forms of gH in HHV-7-infected cell lysates, it precipitated only the 90 kDa form from virions, as shown in Fig. 6, indicating that the 80 kDa form may be a precursor and that the 90 kDa protein may be a mature form of gH that is incorporated into virions. The mAb for gO, named 7gO-A, co-immunoprecipitated mainly the 80 kDa form of gH in HHV-7-infected cells (Fig. 6), and did not co-precipitate gH in virions, indicating that our mAb, 7gO-A, may recognize a precursor form of gO in HHV-7-infected cells but not the mature form that is incorporated into virions. We propose that the mAb 7gO-A may recognize a natural form of gO, but only a precursor form, and the gO epitope recognized by the mAb may be linear, because we purified the recombinant HHV-7 gO protein under denaturing conditions for immunization in mice, and the mAb could be used for Western blotting. Next, to confirm the interaction of gH and gO, we also performed immunoprecipitation with anti-gH or anti-gO mAbs followed by Western blotting with anti-gO mAb. As shown in Fig. 7, anti-gH mAb co-immunoprecipitated gO protein, confirming that gO associates with gH. However, the amount of gO protein co-immunoprecipitated with anti-gH mAb was at a lower level than that of the gO protein co-immunoprecipitated with anti-gO mAb. In addition, we have pretreated HHV-7-infected cell lysates with anti-gH mAb; however, the mAb did not clear gO protein completely (data not shown), suggesting that gO associates with gH but that the amount of gO expressed alone may be higher than that of the gH–gO complex in HHV-7-infected cells, and therefore it may be difficult to clear gO protein completely by using the gH mAb.

In conclusion, we have shown that the HHV-7 U47 gene encodes a glycoprotein (gO) that forms a complex with gH in infected cells. Further studies of the HHV-7 gO and the gH–gO complex are required to elucidate the functional roles of the gO protein and the complex in HHV-7-infected cells and the virus entry process.

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