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Intriguing interplay between feline infectious peritonitis virus and its receptors during entry in primary feline monocytes

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ARTICLE INFO

Article history:
Received 13 January 2011
Received in revised form 24 April 2011
Accepted 29 April 2011
Available online 12 May 2011

Keywords:
FIPV
Entry
Monocytes
Aminopeptidase N
DC-SIGN

ABSTRACT

Two potential receptors have been described for the feline infectious peritonitis virus (FIPV): feline aminopeptidase N (fAPN) and feline dendritic cell-specific intercellular adhesion molecule grabbing non-integrin (fDC-SIGN). In cell lines, fAPN serves as a receptor for serotype II, but not for serotype I FIPV. The role of fAPN in infection of in vivo target cells, monocytes, is not yet confirmed. Both serotype I and II FIPVs use fDC-SIGN for infection of monocyte-derived cells but how is not known. In this study, the role of fAPN and fDC-SIGN was studied at different stages in FIPV infection of monocytes. First, the effects of blocking the potential receptor(s) were studied for the processes of attachment and infection. Secondly, the level of co-localization of FIPV and the receptors was determined. It was found that FIPV I binding and infection were not affected by blocking fAPN while blocking fDC-SIGN reduced FIPV I binding to 36% and practically completely inhibited infection. Accordingly, 66% of bound FIPV I particles co-localized with fDC-SIGN. Blocking fAPN reduced FIPV II binding by 53% and infection by 80%. Further, 60% of bound FIPV II co-localized with fAPN. fDC-SIGN was not involved in FIPV II binding but infection was reduced with 64% when fDC-SIGN was blocked. In conclusion, FIPV I infection of monocytes depends on fDC-SIGN. Most FIPV I particles already interact with fDC-SIGN at the plasma membrane. For FIPV II, both fAPN and fDC-SIGN are involved in infection with only fAPN playing a receptor role at the plasma membrane.

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1. Introduction

Feline coronaviruses (FCoVs) belong to coronavirus subgroup 1 and two pathotypes are described: the often clinically unapparent enteric feline coronavirus (FECV) and the deadly feline infectious peritonitis virus (FIPV). Each pathotype belongs to either serotype I or II. Serotype I causes most natural infections, whereas serotype II infections are rare. Serotype II is mostly used for research purposes because it grows better in culture (Pedersen et al., 1984).

The process of viral entry is an attractive target for the development of new therapeutic agents. Therefore, a lot of research has been focussing on entry processes for a range of viruses (Cooley and Lewin, 2003; Timpe and McKeating, 2008). This has led to the development of a number of promising agents, for example in the treatment of HIV-1 (Cooley and Lewin, 2003). The knowledge on the entry of feline coronaviruses in host cells has expanded. After binding to the receptor(s), FIPV 79-1146 is internalized in monocytes through endocytosis, more specifically via a clathrin- and caveolae-independent pathway using dynamin (Van Hamme et al., 2007, 2008). According to Regan et al. (2008), subsequent escape from endosomes is mediated by cathepsin B for FIPV strains 79-1146 and DF2, while for the enteric strain 79-1683 low pH in endocytic compartments and cathepsin L need to assist cathepsin B. In contrast, de Haan et al. (2008) observed that infection with FIPV 79-1146 appears to be insensitive to cathepsin inhibitors.

Two potential receptors have been described for the feline coronaviruses. The first one is aminopeptidase N (APN), also designated CD13, a ubiquitous and multifunctional glycoprotein of approximately 110 kDa and 967 amino acids (Luan and Xu, 2007). It is a type II metalloprotease that contains seven domains (Sjöström et al., 2000). Domains V–VII can interact to form non-covalently linked homodimers (Sjöström et al., 2000). Feline APN (fAPN) serves as a receptor for feline, canine, porcine and human coronaviruses in coronavirus subgroup 1 (Tresnan et al., 1996). However, only serotype II and not serotype I FCoV strains are able to recognize fAPN (Hohdatsu et al., 1998; Dye et al., 2007; Tekes et al., 2010). Binding of serotype II strains to fAPN from cell lines can be blocked completely by the monoclonal antibody R-G-4 that binds to a region on fAPN between aa 251 and aa 582, i.e., in domains V or VI (Hohdatsu et al., 1998; Tusell et al., 2007). The interaction between FIPV and fAPN was mainly studied on cell lines and by means of a fAPN cDNA clone originating from the FCWF-4 cell line. Secondly, it has been described that serotype II FCoVs use dendritic cell (DC)-specific
Recently, these data were extended to monocytes, the competitor of DC-SIGN binding. Further, infection of feline monocytes induced an increase of infection that was blocked by mannan, a carbohydrate-recognition domain ligand. Many viruses, such as HIV, Ebola and hepatitis C, use DC-SIGN or the homologue L-SIGN, expressed in liver and lymph nodes, to augment infection (Geijtenbeek et al., 2000; Alvarez et al., 2002; Lozach et al., 2003; Pohllmann et al., 2003). Some coronaviruses also interact with these lectins. For SARS-CoV, DC-SIGN and L-SIGN can enhance infection of cells that co-express the major SARS receptor, ACE2 (Jeffers et al., 2004; Marzi et al., 2004; Yang et al., 2004). DC-SIGN, but not L-SIGN, can similarly augment infection with human coronavirus (HCoV) NL63, that also relies on ACE2 for infectious entry (Hofmann et al., 2006). Further, L-SIGN expressed in non-susceptible cells can bind HCoV-229E (Jeffers et al., 2006).

For serotype II FCoVs, expression of human DC-SIGN in CrFK cells induced an increase of infection that was blocked by mannan, a competitor of DC-SIGN binding. Further, infection of feline monocytes, the in vivo target cell, was strongly reduced by mannan (Regan and Whittaker, 2008). Recently, these data were extended and it was shown that both type I and type II FCoVs can use feline DC-SIGN for infection of monocyte-derived dendritic cells (Regan et al., 2010).

Clearly, previous research focused on the interaction between FCoVs and cell lines. It is not known if these data can be extrapolated to the in vivo target cells, monocytes. This knowledge is required if we want to target the entry process with antivirals. Therefore, the role of the candidate receptors was determined in the multi-step entry process in blood monocytes. The effects of blocking fAPN and fDC-SIGN were studied for the processes of attachment and infection by FIPV strains Black (serotype I) and 79-1146 (serotype II). In addition, co-localization studies were performed between FIPV and these potential receptors. The aim of this study was to understand how FIPV interacts with its receptors on the primary FIPV target cells in vivo, blood monocytes.

2. Materials and methods

2.1. Cells and virus

Feline blood monocytes were isolated from blood collected from a feline coronavirus, feline leukaemia virus and feline immunodeficiency virus-negative cat and cultured as described before (Dewerchin et al., 2005). The kinetics of attachment and internalization in monocytes of this cat are described by Van Hamme et al. (2007), this cat is referred to as ‘cat 2’. CrFK cells were purchased from the ATCC. CHO control cells and CHO transfectants stably expressing wild-type human DC-SIGN (De Witte et al., 2006), were a gift from Geijtenbeek (Department of Molecular Cell Biology and Immunology, VU University Medical Centre Amsterdam, Amsterdam, The Netherlands). FIPV serotype I strain Black (FIPV I) was passaged on FCWF cells and serotype II strain WSU 79-1146 (FIPV II) on CrFK cells (Black, 1980). Both were a kind gift from Dr. Egberink (Department of Infectious Diseases and Immunology, Utrecht University, Utrecht, The Netherlands).

2.2. Antibodies

The monoclonal antibody R-G-4 (mAb R-G-4) directed against feline aminopeptidase N (fAPN) (Hohdatsu et al., 1998) was a kind gift from Dr. Hohdatsu (Department of Veterinary Infectious Diseases, Towada, Japan). The monoclonal antibody 25-2B against fAPN was purchased from Veterinary Medical Research and Development (VMRD, Pullman, USA). A polyclonal mouse antibody raised against full-length human DC-SIGN, also designated CD209, was purchased from Abnova (Taipei, Taiwan). mAb DH59B (VMRD) was used to stain CD172a in the plasma membrane of monocytes. This antibody can be used to stain a random membrane protein on the surface of monocytes. Immunoglobulin G1 13D12 against pseudorabies virus gD was produced in the laboratory (Nauwynck and Pensaert, 1995) and was used as an irrelevant isotype-matched control antibody. Polyclonal anti-FIPV antibodies against FIPV serotype I strains were isolated from ascites from cats with FIP. Polyclonal anti-FIPV antibodies against FIPV serotype II strain WSU 79-1146 were a kind gift of Dr. Rottier (Department of Infectious Diseases and Immunology, Utrecht, The Netherlands). FITC-labelled, polyclonal antibodies against FIPV were purchased from VMRD.

2.3. Inhibition assays

The experimental design to study attachment separately and the time points used to evaluate the potency to inhibit these processes, were determined based on data obtained earlier on the kinetics of attachment and internalization of FIPV (Van Hamme et al., 2007).

2.3.1. Attachment inhibition assay

Monocytes (and CrFK cells only for experiments with FIPV II) were washed at 68 h post-seeding and chilled at 4 °C for 20 min before pre-incubation at 4 °C for 60 min with mAb R-G-4 (25 mg/ml) and/or mannan (50 mg/ml), or an irrelevant isotype-matched mAb. After pre-treatment, FIPV was added to the cells at a multiplicity of infection (moi) of 0.05 for FIPV I and moi 1 for FIPV II (resulting concentrations: 8 mg/ml antibody and/or 16 mg/ml mannan). Cells and virus were incubated further at 4 °C for 1.5 h (monocytes) or 3 h (CrFK and CHO cells). Then, cells were washed with ice-cold RPMI 1640 and fixed with paraformaldehyde (1%). Bound particles were stained with anti-FIPV-biotin, followed by streptavidin-FITC (Molecular Probes-Invitrogen, Merelbeke, Belgium). After mounting of the coverslips, attachment was quantified per cell by counting the number of bound particles for at least 20 cells.

2.3.2. Infection inhibition assay

At 56 h post-seeding, cells were washed with RPMI 1640 and pre-incubated for 1 h at 37 °C with mAb R-G-4 and/or mannan, or an irrelevant isotype-matched mAb. After pre-treatment, FIPV was added to the cells at a moi of 0.05 for FIPV I and moi 1 for FIPV II. Then, after 1 h the inoculum was replaced by medium supplemented with the antibodies or mannan, at the same concentrations as for pre-treatment. The cells were incubated for another 11 h at 37 °C. Finally, cells were washed, fixed and permeabilized with Triton X-100 (0.1%) for 2 min at room temperature. Permeabilization was followed by 1 h of incubation at 37 °C with anti-FIPV-FITC and 10 min with Hoechst 33342 (Molecular Probes). Coverslips were mounted onto microscope slides and analyzed by fluorescence microscopy. Cells with cytoplasmic expression of viral proteins were scored as infected cells. All cells on the coverslips were evaluated.

2.3.3. Ligand internalization inhibition assay

At 56 h post-seeding, cells were washed with RPMI 1640 and pre-incubated for 1 h at 37 °C with mannan. After pre-treatment, FITC-labelled albumin or transferrin was added to the cells. Then, after 1 h the cells were washed with ice-cold RPMI 1640 and fixed with paraformaldehyde (1% in phosphate buffered saline, pH 7.2). Cortical actin was stained with phalloidin-Texas Red (Molecular...
2.4. Co-localization assays

Monocytes, CrFK cells and CHO cells were washed at 68 h post-seeding and chilled at 4 °C for 20 min. Then, cells were inoculated with FIPV at a moi of 0.05 for FIPV I and a moi of 1 for FIPV II. Cells and virus were incubated further at 4 °C for 1.5 h. Then, cells were washed with ice-cold RPMI 1640 and fixed with paraformaldehyde (1%). Bound particles were stained with anti-FIPV-biotin, followed by streptavidin-FITC (Molecular Probes-Invitrogen). Slides were incubated with mAb 25-2B to stain fAPN, or with mouse pAb anti-DC-SIGN antibodies to stain DC-SIGN. The mAb DH59B was used to visualize CD172a (VMRD). As a conjugate, Texas Red-labelled goat anti-mouse antibodies were used (Molecular Probes). Coverslips were mounted onto microscope slides and analyzed by confocal microscopy.

3. Results

3.1. Expression of the potential receptors fAPN and fDC-SIGN on monocytes

fAPN was present on all monocytes and it was expressed in the plasma membrane as well as in the cytosol. This was assessed by stainings with mAb 25-2B before and after permeabilization (Fig. 1). It was, however, remarkable that the R-G-4 epitope appeared to be only abundantly present extracellularly on approximately 10% of the monocytes. After permeabilization, the R-G-4 epitope could be detected in all cells (Fig. 1). In contrast, on CrFK cells, the R-G-4 epitope was extracellularly present on all cells (data not shown). This suggests that the expression pattern and/or the conformation of APN are cell type dependent. Furthermore, it was shown that the extracellular expression of the R-G-4 epitope on monocytes increased over time, from no cells with extracellular R-G-4 epitope expression on day 0, up to 16% of cells with extracellular expression at day 5 post seeding (data not shown). For DC-SIGN, practically all monocytes expressed a substantial amount of DC-SIGN in their plasma membrane as well as intracellularly (Fig. 1).

3.2. Evaluation of fAPN and fDC-SIGN as receptors for FIPV I

The role of fAPN as an entry mediator was evaluated by inhibition studies with mAb R-G-4 and co-localization studies between FIPV and fAPN. To assess the involvement of fDC-SIGN, inhibition studies with mannan were performed and co-localization between FIPV and fDC-SIGN. To assess the involvement of fDC-SIGN, inhibition studies with mAb 25-2B to stain fAPN, or with mouse pAb anti-DC-SIGN antibodies to stain DC-SIGN. The mAb DH59B was used to visualize CD172a (VMRD). As a conjugate, Texas Red-labelled goat anti-mouse antibodies were used (Molecular Probes). Coverslips were mounted onto microscope slides and analyzed by confocal microscopy.

3.2.2. Role of fDC-SIGN in entry of FIPV I in target cells

(Pre-)incubation of monocytes with mannan to block fDC-SIGN, reduced virus binding significantly (to 36.2 ± 12.8% of binding observed in control cells; Fig. 2A). When both fAPN and fDC-SIGN were blocked with respectively R-G-4 and mannan, virus binding was reduced to 53.2 ± 11.3% of binding observed in control cells (Fig. 2). It is clear that the epitope of APN recognized by R-G-4 is not involved in the interaction between FIPV and DC-SIGN. On the contrary, the reduction of virus binding was slightly smaller compared to the reduction caused by mannan alone. Possibly the presence of the mAbs impair binding of mannan. The co-localization of 65.5 ± 6.8% of bound FIP virons with fDC-SIGN confirms its role in virus binding (Fig. 3). Further, infection is reduced in mannan-treated cells to 1.5 ± 3.7% of infection in control cells. This implies that binding of FIPV I to DC-SIGN results in infection. The reduction of infection is higher than reductions of virus binding, therefore it is possible that DC-SIGN is also involved in processes downstream virus binding.

3.3. Evaluation of fAPN and fDC-SIGN as receptors for FIPV II

The same approach was used as described above for FIPV I. Using this approach we could confirm that fAPN is the major receptor for FIPV II for infectious entry in CrFK cells. Treatment with mAb R-G-4 completely blocked binding of FIPV II and bound particles co-localized completely with fAPN. Most likely fAPN is also involved in the subsequent internalization of the virus in CrFK cells as FIPV was found to co-localize with fAPN inside these cells (data not shown). MAb R-G-4 also blocked infection (Fig. 3), therefore internalization after binding to fAPN leads to infection and fAPN is a necessary receptor for FIPV II infection in the CrFK cell line.
3.3.1. **faPN is a receptor for infectious entry of FIPV II in monocytes**

After incubation of cells with mAb R-G-4, attachment of FIPV II was significantly reduced to 46.6% of attachment on control cells (Fig. 2A). Inhibition was not complete like observed in CrFK cells. Infection was also significantly reduced (to 19.6% of the control) after treating cells with mAb R-G-4, which implies that particles internalized after binding to faPN productively infect the monocyte. Co-localization studies showed that 59.9 ± 16.2% of the FIPV II particles bound to monocytes, co-localize with faPN (Fig. 2B). This amount of co-localization was significantly higher than what was expected based on coincidence (27.8 ± 5.2%), as shown by the co-localization staining between FIPV II and CD172a, an irrelevant surface protein. This confirms the involvement of faPN in virus binding to monocytes. However, a fraction of binding (and infection) with FIPV II is still unaccounted for, indicating that faPN is a...
receptor for FIPV II but possibly not the sole receptor. Moreover, these results show that the entry events in CrFK cells do not reflect what occurs in monocytes.

3.3.2. Role of fDC-SIGN in entry of FIPV II in target cells

The role of fDC-SIGN in binding and internalization of FIPV II in monocytes was evaluated. Fig. 2A shows that blocking fDC-SIGN with mannan had no significant effect on virus binding. This was confirmed by the fact that combining mannan and R-G-4 did not significantly increase the inhibition of attachment caused by R-G-4. The results of the co-localization study between FIPV II and fDC-SIGN on monocytes supported this conclusion as the observed co-localization of 28.9 ± 4.5% did not significantly exceed the level of 'background' co-localization (27.8 ± 5.2%; Fig. 2B). For infection, unlike for attachment, a reduction to 36.2% of infection in untreated cells was observed when mannan was added. This suggests that fDC-SIGN is involved in infection of primary cells. When both mAb R-G-4 and mannan were added to the cells, infection was reduced significantly to 11.1% of infection in control cells (compared to 19.6% when only APN is blocked). Based on these results, it appears that fDC-SIGN does seem to play a role in the infection process albeit not in initial binding. The underlying mechanism remains elusive thus far.

3.4. Role of fDC-SIGN in entry of albumin and transferrin in target cells

Besides its role in FCoV infection of monocytes, DC-SIGN interacts with numerous viruses like HIV, Ebola, hepatitis C and many others (Geijtenbeek et al., 2000; Alvarez et al., 2002; Lozach et al., 2003; Pöhlmann et al., 2003). Therefore, one might question the specificity of the interaction. To make sure that the effects of mannan are specific, we evaluated the influence of mannan on internalization of cellular components (albumin and transferrin). Mannan did not affect these internalization processes, thus the effect of mannan on entry and infection determined in previous assays is virus-dependent (data not shown).
4. Discussion

In this study we show that FIPV I infection of monocytes depends on fDC-SIGN. Most FIPV I particles already interact with fDC-SIGN at the plasma membrane. For FIPV II, both fAPN and fDC-SIGN are involved in infection with only fAPN playing a receptor role at the plasma membrane. Studying FIPV entry processes in the \textit{in vivo} target cells, monocytes, provides important information that was not obtained when studying cell lines only.

The experimental data indicate that fDC-SIGN is an important virus binding receptor for FIPV I, while fAPN is not. However, probably another receptor besides fDC-SIGN is involved. Further, it cannot be excluded that fAPN interacts inefficiently with FIPV I through an epitope different from the R-G-4-recognized epitope, as suggested by Tekes et al. (2010). This interaction would not be inhibited by R-G-4 and the co-localization assays only reveal high levels of co-localization (‘background’ due to co-incidence is 27.8%). In contrast, fDC-SIGN is not a receptor for FIPV II, while fAPN is responsible for the majority of FIPV II binding. However, fAPN is not the only virus binding receptor for FIPV II on monocytes like on CrFK cells. Because blocking fAPN did not completely prevent infection, it remains possible that internalization through the other receptor also leads to infection independently from APN. Although not involved in virus binding, DC-SIGN is important for FIPV II infection, most likely in a step during or after internalization. SARS-CoV infection was also reduced without affecting virus binding by compounds targeting high-mannose oligosaccharides (O’Keefe et al., 2010). It was suggested that the high-mannose oligosaccharides are important for entry, possibly fusion. Our results suggest a similar role for high-mannoses on FIPV in the entry process through an interaction with DC-SIGN.

In this paper we show that DC-SIGN plays a different and more pronounced role in FIPV I infection than in FIPV II infection. This is also illustrated by the susceptibility of CHO cells stably expressing hDC-SIGN to infection (Engering et al., 2002). FIPV I replicates well in these cells while FIPV II is not able to infect these cells \textit{in vitro}. None of the serotypes can infect untransduced CHO cells (data not shown).

Having listed the results from this study, a comparison can be made with the results obtained by Regan and Whittaker (2008) and Regan et al. (2010). In these studies only limited data describe what happens on the target cell and conclusions about entry factors are solely based on infection assays. For FIPV I, Regan et al. (2010) report almost complete reduction of infection of feline monocyte-derived dendritic cells (DCs), which is in accordance with our findings in monocytes. For type II, a strong but incomplete reduction of infection was reported in both monocytes and monocyte-derived dendritic cells. The reduction of infection in monocytes was comparable to our findings. Apparently, mannan has a stronger effect on type I infectivity than on type II infectivity in both monocytes and monocyte-derived DCs.

Experiments with FIPV I were performed at a lower moi than those with FIPV II (moi 0.05 vs. 1). The amount of virus added to
the cells might influence receptor utilization. For several viruses it has been described that the effect of blocking DC-SIGN was higher at low moi or low receptor availability (De Parseval et al., 2004). Accordingly, the effect of blocking DC-SIGN was more pronounced for FIPV I, the strain used at lower moi. Concerning the in vivo relevance of these results, it seems likely that for FIPV I (most prevalent in the field) DC-SIGN will play a role in capturing virus particles in the first stages of infection (low number of virus particles present – comparable to low moi in vitro). Possibly, in the periphery of a pyogranuloma at later stages in infection (high numbers of virus particles present – comparable to high moi in vitro), IDC-SIGN might be less important at the level of virus binding.

The data obtained in this study lead to the hypothetical model for FIPV entry in monocytes depicted in Fig. 4. Type I virus can bind to DC-SIGN which results in infection. The virus can also bind to another unknown receptor (receptor X in Fig. 4). Following binding to the unidentified receptor, these virus particles might be unable to induce infection or infection might be mediated through a cascade of events in which DC-SIGN plays a role. Type II virus can bind to IAPN and will be internalized into the cell via this receptor. A particle internalized via this pathway leads to infection of the cell. A second, unknown receptor also binds FIPV II (receptor Y in Fig. 4). This pathway might also lead to infection. IDC-SIGN is not the unknown receptor, but fulfills a role in infection in a step after virus binding. Hypothetically, IDC-SIGN might be involved in genome release of virus that enters cells via IAPN and/or the unknown receptor.

Possibly, the proposed pathway for type II using the unknown receptor with DC-SIGN might also be used by type I FIPV (then receptor X and receptor Y are the same). Upon the recombination event with canine CoV FIPV II might have lost its ability to efficiently infect through the unknown receptor (with DC-SIGN, like FIPV I) but gained the efficient interaction with APN.

Taken together, in this study, the role of aminopeptidase N and DC-SIGN as receptors for FIPV were analyzed for the first time in the in vivo target cell, the monocyte. If a protein was shown to be important for FIPV infection, it was checked whether it was necessary for virus binding at the plasma membrane or downstream the internalization pathway. This specific information was not available until now. According to this development of antiviral drugs that cannot be based on data obtained in cell lines. Besides elucidating some aspects about FIPV entry in monocytes, these new insights reveal how much is unknown about FIPV entry. Further, this study is again a reminder that results of studies obtained in cell culture should be analyzed with care, knowing that viruses can use different receptors and a variety of cellular proteins to gain entry into different cells.

Acknowledgements

We thank Dr. Geijtenbeek for providing the CHO cell lines. We are grateful to Dr. Rotter and Dr. Egberink for supplying the polyclonal antibodies and the virus strain, and Dr. Hofhauts for the repeated gifts of mAb R-G-4. We thank Nele Dennequen and Chantal Vanmaercke for excellent technical assistance. Evelyne Van Hamme was supported by a doctoral grant from the Special Research Fund of Ghent University (01D20005) and Hannah L. Dewerchin by the Institute for the Promotion of Innovation through Science and Technology in Flanders (IWV Vlaanderen).

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