Biochemical and Biophysical Research Communications 389 (2009) 84–89

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Differential suppressive effect of promyelocytic leukemia protein on the replication of different subtypes/strains of influenza A virus

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ARTICLE INFO

Article history:
Received 12 August 2009
Available online 22 August 2009

Keywords:
Promyelocytic leukemia protein
Influenza A virus
Replication

ABSTRACT

Promyelocytic leukemia protein (PML) plays an important role in the defense against a number of viruses, including influenza A virus. However, the sensitivity of influenza A virus subtypes/strains to PML is unknown. We investigated the role of PML in the replication of different influenza A virus subtypes/strains using pan-PML knock-down A549 cells and PML-VI-overexpressed MDCK cells. We found that (i) depletion of pan-PML by siRNA rendered A549 cells more susceptible to influenza A virus strains PR8(H1N1) and ST364(H3N2), but not to strains ST1233(H1N1), Qa199(H9N2) and Ph2246(H9N2); (ii) overexpression of PML-VI in MDCK cells conferred potent resistance to PR8(H1N1) infection, while lacked inhibitory activity to ST1233(H1N1), ST364(H3N2), Qa199(H9N2) and Ph2246(H9N2). Our results suggest that the antiviral effect of PML on influenza A viruses is viral subtype/strain specific.

Introduction

Influenza A virus is a highly contagious, causative agent of seasonal epidemic or pandemic human influenza. Each influenza pandemic is associated with the emergence of a novel influenza A virus subtype or strain. H1N1 and H3N2 subtypes are responsible for the majority of influenza cases in humans [1]. H9N2 subtype, on the other hand, has become panzootic during the past two decades and has been isolated from terrestrial poultry and aquatic birds worldwide [2]. Occasionally this subtype is transmitted to other mammals, including humans [3], and continues to pose a potential threat to public health.

Influenza A virus has been shown to be inhibited by numerous interferon (IFN)-induced host factors, including promyelocytic leukemia protein (PML) [4,5]. PML is present in almost all mammalian cell types reported so far in the form of discrete speckle-like structures in the nucleus, known as PML nuclear bodies (PML NBs) [6]. It is also present in the cytoplasm and shuttles dynamically between the cytoplasm and nucleus. It has been implicated in many diverse cellular processes such as transcriptional regulation, DNA repair, apoptosis and the stress response [7,8]. Human PML protein comprises seven PML isoforms (PML-I to PML-VII), all sharing a common N-terminus but different C-termini [9]. Depending on the alternative splicing pattern of exons 4, 5 and 6, PML isoform can be further classified into a, b and c variants [9]. PML-VII and b, c variants of other isoforms localize in the cytoplasm, because they lack the nuclear localization signal (NLS) within exon 6 [10].

Influenza A virus has numerous subtypes/strains due to frequent gene mutations and rearrangements. Subtypes/strains of influenza A virus differ in their sensitivity to innate and adaptive immune responses. For example, different strains of influenza A virus exhibit apparent diversity in their sensitivity to the antiviral action of Mx-GTPase [11]. It is not known whether the same phenomenon exists with respect to PML.

In this study, we examined five strains of influenza A virus from three subtypes (H1N1, H3N2 and H9N2) for their infectivity and replicability in pan-PML knock-down and PML-VI-overexpression experiments. Our results revealed the differential suppressive effect of human PML against these subtypes/strains of influenza A virus.

Materials and methods

Cell lines, viruses, plasmids and reagents. Madin-Darby canine kidney (MDCK) cells and a human lung carcinoma cell line (A549) were routinely cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum and antibiotics (100 U penicillin and 100 μg/ml streptomycin) at 37 °C in 5% CO_2.

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doi:10.1016/j.bbrc.2009.08.091

Influenza A virus strains A/PR/8/34(H1N1), A/ST/1233/2006 (H1N1), A/ST/364/2005(H3N2), A/Qa/ST/199/2006(H9N2) and A/Ph/ST/2246/2006(H9N2), abbreviated herein to PR8, ST1233, ST364, Qa199 and Ph2246, respectively, were used in this study.

PML RNAi plasmid (siPML2), with a pSIREN-RetroQ vector backbone, was a generous gift from Dr. Thomas Stamminger (Institute for Clinical and Molecular Virology, University Hospital Erlangen, Germany). HA-PML/pcDNA3 plasmid, encoding full-length PML-VI, was kindly provided by Dr. Toshihiro Nakajima (Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan). RNAi negative control plasmid (si-NC), which carries an siRNA sequence non-homologous to mammalian genes, was constructed by inserting the annealed product of sense oligonucleotides (5′-GATCCGTGCGTTGCTAGTACCAACTTCAAGAGAGTTG GTACTAGCAACGCACTTTTTTG-3′) and antisense oligonucleotides (5′-AATTCAAAAAAGTGCGTTGCTAGTACCAACTCTCTTGAAGTTGGTA CTAGCAACGCACG-3′) into pSIREN-RetroQ vector digested with BamHI and EcoRI. The construct was verified by DNA sequencing.

Mouse monoclonal anti-PML antibody (PG-M3) was purchased from Santa Cruz (CA, USA), mouse anti-β-actin antibody and peroxidase-conjugated goat anti-mouse antibody from Sigma (St. Louis, MO, USA), Cy3-labeled goat anti-mouse antibody from Beyotime Biotechnology (Jiangsu, China), Lipofectamine 2000 from Invitrogen (Carlsbad, CA, USA) and puromycin from Amresco (Solon, OH, USA).

Establishment of a PML knock-down cell line. The PML knock-down A549 cell line and negative control cells were generated by stable transfection. Briefly, A549 cells were transfected with siPML2 or si-NC plasmid using Lipofectamine 2000. Cells were subcultured at a 1:10 dilution, 24 h after transfection, and maintained for 24 h in the absence of puromycin. Stably transfected cells were selected by the addition of puromycin (1 μg/ml) and cultured at 37 °C for 2–4 weeks. Knock-down effect was confirmed by semi-quantitative reverse transcription PCR, Western blotting and indirect immunostaining, as described below.

Semi-quantitative reverse transcription PCR. Total RNA was isolated from stably-transfected A549 cells using Trizol (Invitrogen). First strand synthesis was performed using AMV reverse transcriptase (Takara, Dalian, China). PCRs were carried out using the following specific primer sets: 5′-ACCAGTCGGTGCGTGAGTT-3′ and 5′-TGGATCTCTGCGCTGATGTC-3′ for PML; 5′-CCAAGGCCAACCGC GAGAAGATGAC-3′ and 5′-AGGGTACATGGTGGTGCCGCCAGAC-3′ for β-actin. Amplified products were visualized on 1.2% agarose gels.

Western blotting. Cell monolayers were washed once with PBS and lysed with Laemmli sample buffer for 5 min in boiling water. The lysate was sonicated briefly. Protein concentration was determined using an RC-DC kit (Bio-Rad, Hercules, CA, USA). Twenty micrograms of protein per lane was used in 10% SDS–PAGE and transferred onto a nitrocellulose membrane. The membrane was blocked with Tris-buffered saline containing 0.1% Tween 20 (TBST) containing 10% non-fat milk for 2 h and incubated overnight at 4 °C with anti-PML (1/1000) or anti-β-actin (1/3000) antibodies. The membrane was rinsed extensively and incubated for 2 h with peroxidase-conjugated secondary antibody (1/3000). Immunoblots were developed using the Enhanced chemiluminescence (ECL) reagents (Pierce, Rockford, IL, USA).

Immunofluorescence microscopy. Cell cultures on the glass coverslips were washed twice with PBS, fixed for 10 min with 4% paraformaldehyde, permeabilized with 0.2% Triton X-100 for 7 min and incubated for 30 min in PBS containing 3% BSA. Cells were subsequently incubated at room temperature with anti-PML antibody (1/500) for 2 h and Cy3-labeled secondary antibody (1/300) for 1 h, followed by nuclear staining with Hoechst 33358 for 5 min. Images were captured with the Olympus IX70 system (Olympus, Tokyo, Japan).

Viral replication kinetics. Confluent A549 or MDCK cells were infected with influenza A virus at a multiplicity of infection (MOI) of 0.001 in serum-free DMEM containing 0.2 or 1 μg/ml TPCK-trypsin (Worthington, Freehold, NJ, USA), respectively, and incubated at 37 °C. An aliquot of the supernatant was harvested every 12 h and virus yield was titrated by plaque assay in MDCK cells.

Antiviral activity assays. MDCK cells were seeded onto six-well plates and transfected the next day with HA-PML/pcDNA3 plasmid or pcDNA3 empty vector. After 24 h of transfection, cells were infected with different influenza A viruses. After 1 h incubation, the medium was removed and the cells were overlaid with 1% low melting-point agarose gel containing serum-free medium plus 0.3% BSA and 1 μg/ml TPCK-trypsin. After 3 days of infection, the cells were fixed with 10% formalin for 2 h, and stained with 0.1% crystal violet for 1 h.

Results

Effect of viral infection on PML morphology in A549 cells

Indirect immunofluorescence was used to monitor endogenous PML after the cells were infected for 12 h with influenza A virus at an MOI of two. The majority of PML was present as characteristic discrete punctuate dots in uninfected cells (Fig. 1, mock), with diffusely distributed PML in the cytoplasm. Infection with PR8(H1N1), ST1233(H1N1) and ST364(H3N2), induced increasing numbers and size of PML NBs (Fig. 1, PML NBs). However, Qa199(H9N2) and Ph2246(H9N2) infection did not alter PML morphology compared with uninfected cells.

Establishment of the PML knock-down A549 cell line, A549(PML−)

To elucidate the role of PML in the replication of different influenza A viruses, a PML knock-down A549 cell line and negative control cell line were generated by RNAi technology. This involved using the siPML2 plasmid, that encodes the shRNA sequence targeting the conserved region (codons 394–400) of all PML isoforms (pan-PML), or the si-NC plasmid, respectively. After selection of puromycin-resistant single cell colonies, endogenous pan-PML expression was examined by semi-quantitative RT-PCR, Western blotting and indirect immunostaining. RT-PCR showed that a large proportion of PML mRNA had been silenced successfully (Fig. 2A). Western blot analysis demonstrated a striking reduction in PML expression in siPML2-transfected cells compared with control si-NC-transfected cells (Fig. 2B). Additionally, a significant decrease of PML NBs both in size and number was observed in siPML2-transfected cells by indirect immunostaining (Fig. 2C). The results of three different experiments thus confirmed that a pan-PML knock-down cell line, A549(PML−), had been established. The control cell line is referred to as A549(C).

Differential suppressive effect of pan-PML on replication kinetics of influenza A viruses

To investigate if the replication of influenza A viruses could be affected by the expression level of pan-PML, we examined viral titers in pan-PML knock-down A549(PML−) and control A549(C) cells. Cells were infected with relatively low doses of influenza A viruses (MOI = 0.001), and virus yield was determined by plaque assay in MDCK cells. The viral titer of strain PR8 increased up to 11-fold in A549(PML−) cells compared with control cells (Fig. 3). Similarly, ST364 titer was also about 4-fold elevated at the middle and late phases of infection, with only a slight increase at the early stage of infection in A549(PML−), implying that ST364 was less sensitive to pan-PML than PR8. Replication kinetics of viral strains

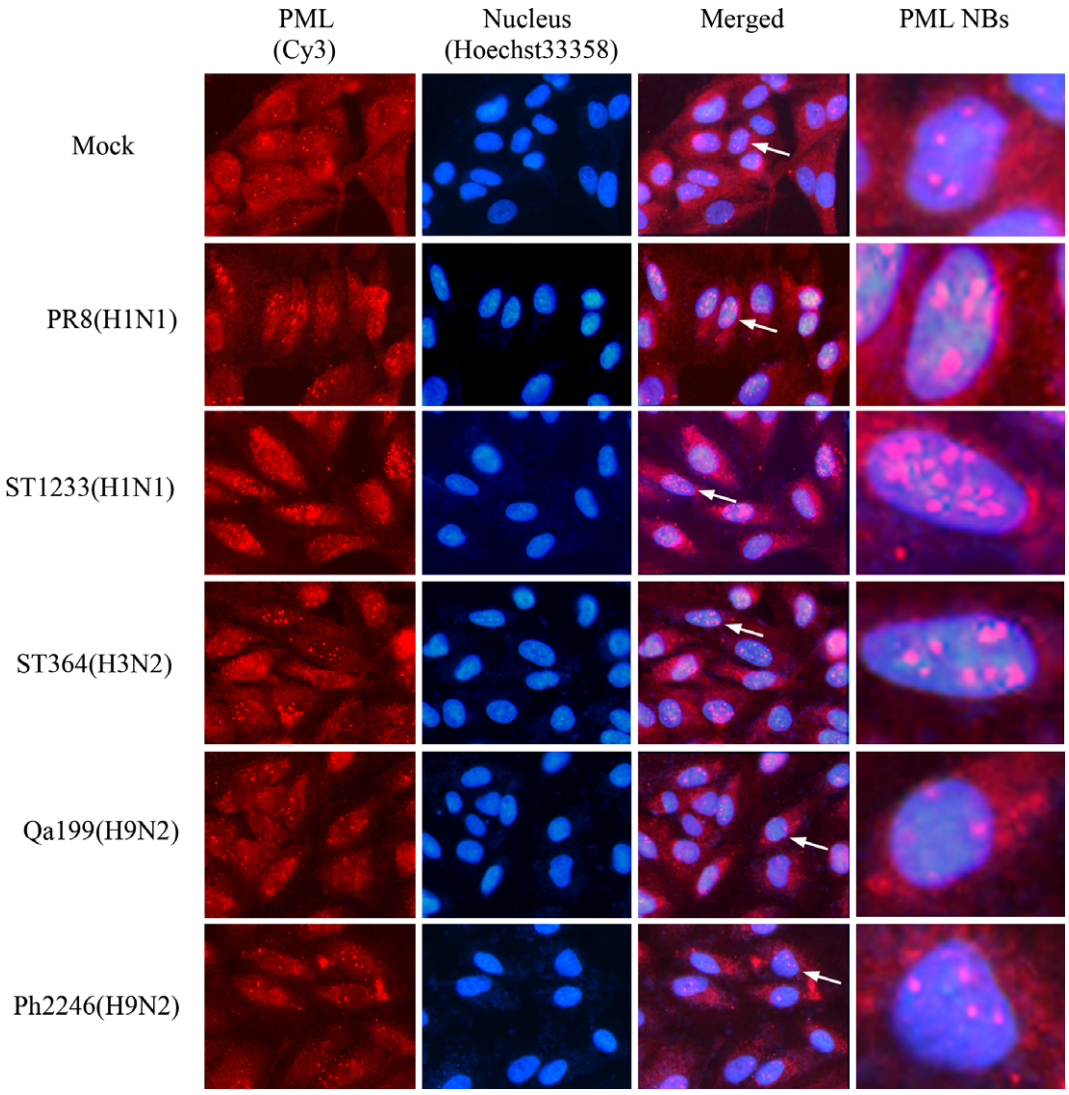

Fig. 1. Immunostaining of influenza A virus-infected and non-infected (mock) A549 cells. Virus-infected (MOI = 2) cells and mock cells cultured for 12 h were stained with anti-PML antibody and Cy3-labeled secondary antibody. Nuclei were counterstained with Hoechst 33358. Localization of endogenous PML (*red*), the nucleus (*blue*), overlaid images of PML and nuclei (merged) and magnified views of PML NBs are seen as punctuate dots in the nucleus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

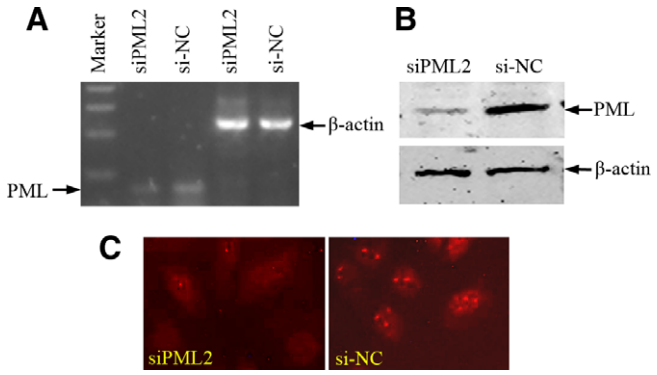

Fig. 2. Silencing of PML in stably-transfected A549 cells. An RNAi vector against all PML isoforms, siPML2, and an unrelated control plasmid, si-NC, were transfected into A549 cells. Single colonies growing in puromycin-containing DMEM were selected and examined for the transcriptional and translational expression of PML and β-actin in A549(siPML2) and A549(si-NC) cells by (A) RT-PCR, (B) Western blot analysis using anti-PML or anti-β-actin antibody and peroxidase-conjugated secondary antibody and (C) indirect immunostaining using anti-PML antibody and Cy3-labeled secondary antibody.

ST1233, Qa199 and Ph2246 in A549(PML−) cells did not differ from that in A549(C) cells. These results demonstrate the differential repressive effects of pan-PML on different influenza A virus strains.

Effect of exogenous PML-VI isoform on influenza A viruses

Having demonstrated that pan-PML causes differential repressive effects on influenza A viruses, we further examined this effect at the individual isoform level. Based on its recognized inhibitory effect on other influenza A virus strains [5], the PML-VI isoform was chosen and studied for its ability to mediate the antiviral response. PML-VI encoded by HA-PML/pcDNA3 was overexpressed in MDCK cells and the plaque formation assay was performed. As expected, overexpression of PML-VI do not have any effect on the size and number of plaques formed by influenza A virus strains ST1233, Qa199 and Ph2246 (Fig. 4A). Strain PR8 produced plaques with a mean diameter of around 1 mm in control MDCK cells after 3 days culture. In contrast, this viral strain formed pinpoint plaques of reduced size (about 0.3 mm) in PML-VI transiently trans-

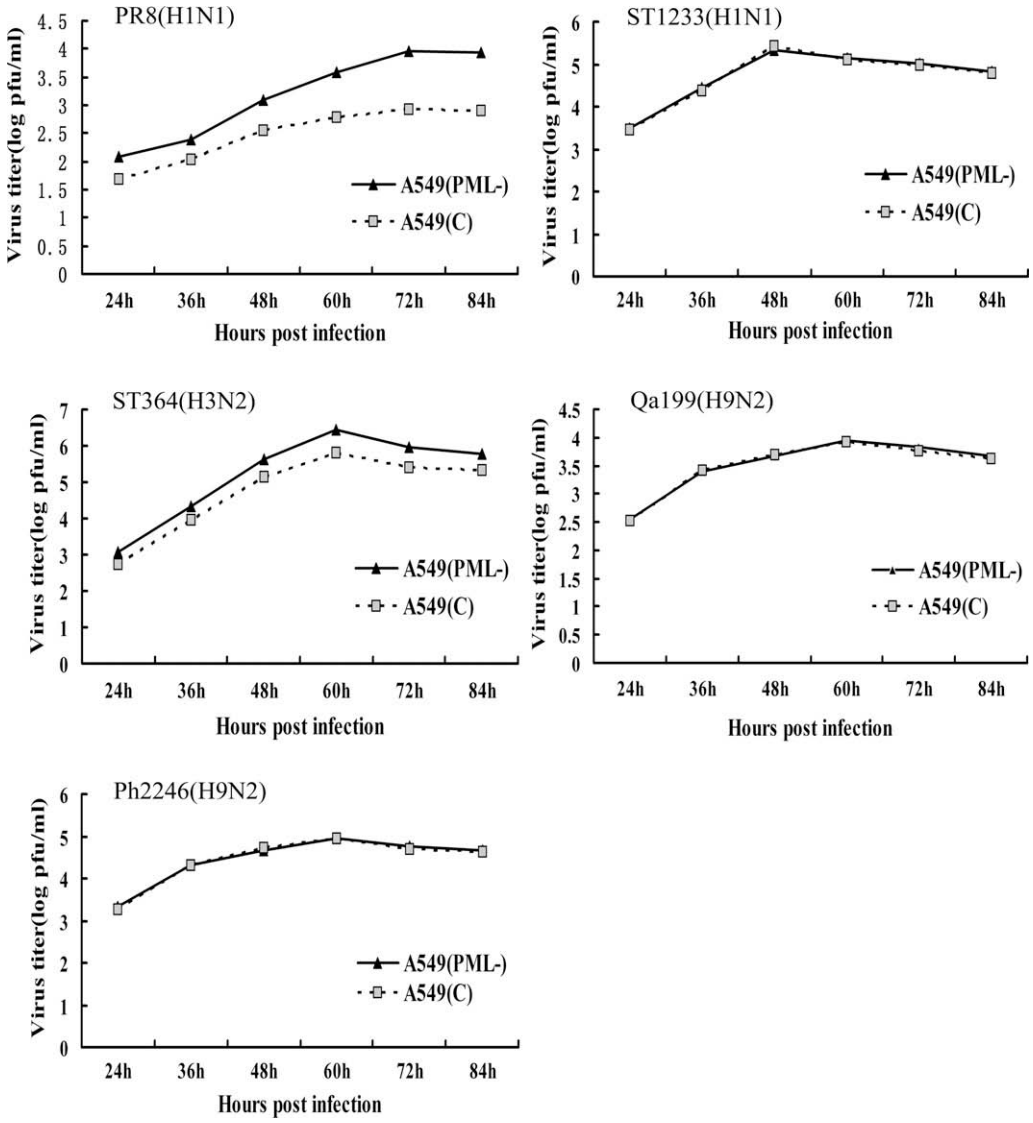

Fig. 3. Replication kinetics of influenza A viruses in PML knock-down A549(PML−) and control A549(C) cells. Cells were infected with influenza A viruses at an MOI of 0.001 and incubated with serum-free medium containing 0.2 μg/ml TPCK-trypsin. Yield of virus in the culture supernatant was titrated every 12 h, from 24 h post-infection by plaque assay in MDCK cells.

fected MDCK cells. Surprisingly, viral strain ST364 infected MDCK (control) cells presented almost the same plaque phenotypes as those with MDCK(PML-VI) cells, suggesting PML-VI failed to exert its antiviral function on this viral strain.

The role of PML-VI was further investigated by growth curve analysis in MDCK cells. As shown in Fig. 4B, at any time point tested, PR8 viral titers in normal MDCK cells remained about 1–1.5 log units above those in PML-VI overexpressing cells. This finding is in agreement with the role of PML-VI in the suppression of PR8 virus as measured in plaque formation assays. Conversely, PML-VI exhibited an intrinsic defect in blocking the replication of other influenza A viruses tested (ST1233, ST364, Qa199 and Ph2246), regardless of its expression level in MDCK cells.

Discussion

In this study, we investigated the role of PML in innate defense against five viral strains from three different subtypes of influenza A virus. PR8(H1N1) is a well-established laboratory-adapted strain with low pathogenicity to humans. The other viral strains used in this study were isolated in Shantou, southern China in recent years, and represent the major strains circulating in humans [ST1233(H1N1), ST364(H3N2)] or domestic poultry [Qa199(H9N2), Ph2246(H9N2)] in this region.

In normal A549 cells, endogenous PML distribution was diffuse in the cytoplasm but localized in the nucleus in 3–4 concentrated spots. Whereas, in A549 cells infected with PR8(H1N1), ST1233(H1N1) or ST364(H3N2), an increased number of enlarged PML NBs were observed. Infection with two H9N2 strains of bird origin, Qa199 and Ph2246, however, had no effect on PML morphology, indicating strain-specific PML morphological changes. The expression level of PML correlates with a variety of factors, especially the IFN and its downstream signaling molecules [12]. Different subtypes/strains of influenza A virus differ much in their abilities to induce IFN [13]. In addition, some downstream molecules of IFN pathway, including JAK1 and STAT1, were dramatically reduced or inhibited in influenza A virus-infected cells [14]. Differential expression of STAT1 and IRF9 caused by different influenza A virus strains has also been observed [15]. Therefore, the inconsistent change of PML NBs may be derived from the complicated

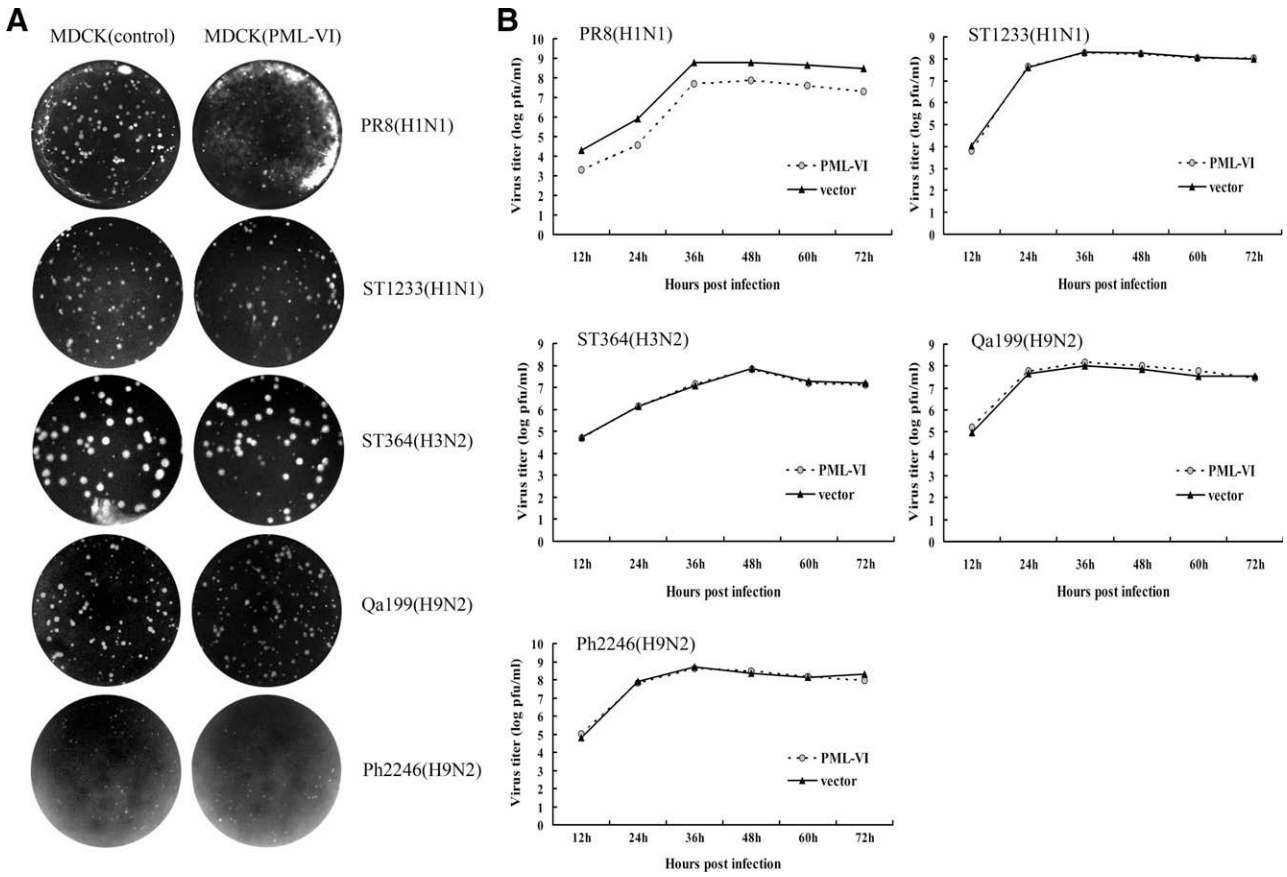

Fig. 4. Differential suppressive effect of overexpressed PML-VI on influenza A viruses. (A) Plaque formation assay in control and PML-VI-overexpressing MDCK cells. Cells were transfected with HA-PML/pcDNA3 or pcDNA3 plasmid for 24 h, followed by infection with different influenza A viruses. Three days later, plaque formation was assessed by fixation in 10% formalin and staining with 0.1% crystal violet. (B) Replication kinetics of influenza A viruses in MDCK cells with overexpressed PML-VI or control vector. Confluent cells were infected individually with five different influenza A viruses (MOI = 0.001) in the presence of 1 μg/ml TPCK-trypsin. The virus titers in the supernatant medium were measured by plaque assays at the indicated times after infection.

interaction between various influenza A virus strains and the host cells.

Depletion of pan-PML by siRNA, rendered A549 cells more susceptible to some influenza A virus strains (PR8 and ST364) but not to others (ST1233, Qa199 and Ph2246) (Fig. 3). As different PML isoforms have distinct localization patterns, interacting partners and biological functions [16], the suppressive effects of pan-PML on influenza A viruses observed in this study could not simply be attributed to a general feature of all isoforms. The high level expression of exogenous PML-VI can greatly inhibit the replication of many viruses including human cytomegalovirus (HCMV) [17], adenovirus [18] and other influenza A virus strains [5], we therefore examined the antiviral effect of this isoform by plaque assay and growth curve analysis in MDCK cells. Both experiments resulted in similar findings. Strain PR8 displayed an impaired growth phenotype in PML-VI overexpressing MDCK cells, whereas other influenza A virus strains apparently overcame the antiviral effect of exogenous PML-VI.

Taken together, our results lead to the following conclusions: pan-PML inhibited the replication of PR8(H1N1) and ST364(H3N2) at different degrees, but failed to suppress ST1233(H1N1), Qa199(H9N2) and Ph2246(H9N2); PML-VI significantly decreased the viral yield of PR8(H1N1), whereas had no repressive activity on ST1233(H1N1), ST364(H3N2), Qa199(H9N2) and Ph2246 (H9N2).

It is evident from our finding that the antiviral effect of PML on influenza A virus is affected by the virus subtypes/strains. In agreement with our finding, previous studies have described the apparent inhibition of WSN33(H1N1) by PML-III [4], A/Hokkaido/92/99(H3 subtype) by PML-IV and PML-VI [5]. In addition, other result has also been reported, in which FPV-B, a mammalian cell-adapted influenza A virus variant of A/FPV/Dobson/34(H7N7), displayed similar growth kinetics both in PML knock-out mouse embryo fibroblasts (MEF cells) and wild-type MEF cells [19].

It also can be seen that, even for the same viral strain, different PML isoforms may exert differential suppressive effects. Results shown in Figs. 3 and 4 suggested that ST364(H3N2) can be inhibited by other PML isoforms but not by PML-VI. In fact, a similar situation is common in other viruses. For instance, overexpression of PML-III does not reduce the yield of rabies virus [20] and lymphocytic choriomeningitis virus (LCMV) [21], but the multiplication of these viruses is significantly higher in $PML^{-/-}$ MEF cells than $PML^{+/+}$ cells [20,22]. Also in the case of poliovirus, multiplication of the virus was not influenced by exogenous expression of PML-III, but viral titer increased significantly when pan-PML was knocked-down by siRNA [23]. Moreover, high level expression of nuclear PML isoforms (III, IV and VI) alone fail to exert antiviral action against herpes simplex virus 1 (HSV-1) [24–26], while a cytoplasmic PML isoform (PML-Ib) can mediate strong resistance against HSV-1 [27].

The reason for the inability of PML to repress viral strains ST1233, Qa199 and Ph2246 is unclear. A possible explanation is that these strains have evolved some way to counteract the action of PML. It is known that P protein of rabies virus [20] and Z protein of LCMV [28] can delocalize PML from NBs to the cytoplasm. Additionally, IE1 protein of HCMV [17], and BZLF protein of Epstein–Barr virus (EBV) [29] have been implicated in the dispersal

of PML NBs. However, infection of ST1233, Qa199 and Ph2246, neither influenced the location of PML NBs nor disrupted them. With strain ST1233, infection even dramatically enhanced the expression of PML (Fig. 1). Therefore, there must be some other mechanisms responsible for compromising PML during infection of the above strains.

In conclusion, this is the first report of the variable susceptibility of influenza A virus subtypes/strains to human PML proteins. The exact mechanism behind PML-mediated intracellular defense against influenza A virus, and the strategy by which influenza A virus evades this defense mechanism, requires further study.

Acknowledgments

We are grateful to Dr. William Ba-Thein for critical discussion and manuscript editing. We thank Drs. Thomas Stamminger and Toshihiro Nakajima for providing siPML2 and HA-PML/pcDNA3 plasmids, respectively. This work is supported by the National Natural Science Foundation of China (30571674, 30771988), Guangdong Natural Science Foundation (05008347, 8151503 102000022), Outstanding Young Scientists Foundation of Guangdong Province Education Department (LYM08056).

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