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Research paper

HA of H1N1 enhanced the expression of ICAM-1 and IL-6 in HUVECs and pathological injury in the lungs in mice

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ABSTRACT

Objective: Both COVID-19 and influenza are viral respiratory tract infections and the epidemics of viral respiratory tract infections remain highly prevalent with lethal consequences in susceptible individuals. Expression of ICAM-1 on vascular endothelium recruits leukocytes which initiates inflammation. IL-6 induces ICAM-1. Both ICAM-1 and IL-6 can be enhanced in influenza virus infection and COVID-19 patients. Besides initiation of virus entry host cells, whether HA alone, instead of whole virus, of influenza has the effects on expression of ICAM-1 and IL-6 in vascular endothelium with injury in the lungs, remains to be demonstrated.

Methods: RT-qPCR and Western blot as well as histopathologic examination were used to examine mRNA and protein of ICAM-1 and IL-6 as well as pathological injury in the lung tissues, respectively.

Results: After incubation of the Human Umbilical Vein Endothelial Cells (HUVECs) with HA of H1N1 for 24 h, the mRNA and protein of ICAM-1 and IL-6 in HUVECs were increased in group of 5 μg/ml concentration with statistical significance ($p < 0.05$). Pathological injury in lung tissues of the mice was shown 12 h after tail intravenous injection with 100 μl of HA (50 μg/ml and 100 μg/ml in normal saline), including widened alveolar spaces with angiotelectasis in alveolar wall, alveolar luminal and interstitial inflammatory infiltrates, alveolar luminal erythrocyte effusion.

Conclusions: HA alone, instead of whole H1N1 virus, induced more expression of ICAM-1 and IL-6, two molecules involving in pathological and inflammatory responses, in HUVECs and pathological injury in lung tissues of the mice. This knowledge provides a new HA-targeted potential direction for prevention and treatment of disease related to H1N1 infection.

1. Introduction

Pandemic of COVID-19, one of the viral respiratory tract infections, caused by the novel coronavirus SARS-CoV-2 (Li et al., 2020), with a major impact on health and life of the people, as well as severe disturbance on economy, throughout the world, has not stoped. COVID-19 Vaccine facilitates the control of COVID-19. Variants of SARS-CoV-2, however, are becoming a new challenge (Kirby, 2021). Although major efforts have been put in public health, besides the recently emerged COVID-19 (Paules et al., 2020), epidemics of viral respiratory tract infections, such as common cold and influenza, remain highly prevalent with lethal consequences in susceptible individuals (Moriyama et al., 2020). It has been estimated that the yearly costs in the United States are $40 billion for the common cold (Fendrick et al., 2003) and over $87 billion for influenza (Molinari et al., 2007).

Inflammation, which involved in many infections (Dai et al., 2020; Hu et al., 2020; Zhao et al., 2019; Chen et al., 2021; Gémez-Mata et al., 2021; Sun et al., 2017); plays an important role in patients with COVID-19 and influenza as well as many other viral respiratory tract infections. Recruitment of leukocytes such as monocytes and neutrophils into damaged or infected tissues is essential for the initiation of inflammation (Shi and Pamer, 2011; Hussain et al., 2019). Expression of specific cell surface molecules, adhesive for ligands on circulating leukocytes, such as intercellular adhesion molecule 1 (ICAM-1), on vascular endothelium contributes to recruitment of leukocytes in inflammation, (Munro, 1993). ICAM-1 can be induced by IL-6, a multifunctional cytokine with

Abbreviations: HA, Hemagglutinin; ICAM-1, Intercellular Adhesion Molecule 1; HE, Hemagglutinin-Esterase; HEF, Hemagglutinin-Esterase-Fusion; HUVEC, Human Umbilical Vein Endothelial Cells.

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an important role in immunity (Wung et al., 2005; Duits et al., 1992). There are many parallels of clinical and epidemiological features between COVID-19 and influenza (Chotpitayasunondh et al., 2020). Higher tissue expression of ICAM-1, as well as IL-6, was found in COVID-19 patients compared to H1N1 and control group (Malaquias et al., 2020). The enhanced expression of ICAM-1 and production of IL-6 can be found in influenza virus infection as well (Othumpangat et al., 2016; Yu et al., 2011; Liu et al., 2019).

The glycoproteins in SARS-CoV-2 and Influenza virus play important roles in the infection and pathogenesis and one of the glycoproteins in Influenza virus is hemagglutinin (HA). It was known that HA on the surface of Influenza virus binds to sialic acid residues at the host cell surface which ensure further virus internalization into host cells (Ustinov et al., 2017). In SARS-CoV-2, besides other glycoproteins, Hemagglutinin-Esterase (HE) with the function to hemagglutinates and destroys receptors has been found (Kim, 2020), and the role of Hemagglutinin-Esterase-Fusion (HEF) protein, which combines the functions of both HA and NA in influenza A and B (Herrler et al., 1988; Herrler and Klenk, 1991), likewise, recognizes and binds to a receptor on the cell surface to initiate virus entry into host cells has been reported in influenza C virus (Wang and Veit, 2016). A unique licensed drug targeting HA, arbidol (Zeng et al., 2017), as one of the candidate drugs against SARS-CoV-2 and COVID-19 (McKee et al., 2020), has shown promising results (Amawi et al., 2020). Therefore, it is considerable that the HA alone, instead of the whole virus, of influenza may have the effects on the expression of ICAM-1 and IL-6 in vascular endothelium with inflammation in the lungs, which remains to be demonstrated. The present study is designed to investigate these propositions with the Human Umbilical Vein Endothelial Cells (HUVEC) treated by the HA of H1N1 influenza virus.

2. Materials and methods

2.1. Culture and preparation of HUVECs

Human umbilical vein endothelial cells (HUVECs) (Beijing Beina Chuanglian Biotechnology Institute, Beijing, China) were maintained at 37 °C in a humidified atmosphere with 5% CO_2 in DMED medium containing 10% FBS. After overnight culture of the HUVECs (at a density of 1×10^6/well in 6 well culture plates) from 3 to 5 passages of the HUVECs used in this study, the cells were stimulated with Influenza A H1N1 HA (Sino Biologica, Beijing, China) at the concentration of 0 μg/ml, 2.5 μg/ml, and 5 μg/ml in DMEM containing 1% FBS for 24, then the ICAM-1 and IL-6, as well as their mRNA were detected (The Recombinant Hemaglutinin external envelope protein, Full-Length glycosylated H1N1 California/04/2009 with N-linked sugars, produced using baculovirus vectors in insect cells and its Mw is approximately 72 kDa). Three times of the experiments were individually performed.

2.2. Real-time RT-PCR

TRIzol reagent (Invitrogen, Carlsbad, USA) was applied under RNAase free condition to extract the total RNAs from the HUVECs after 24-h treatment with the HA according to manufacturer's instruction. The RNAs were reverse transcribed into cDNAs by a FastQuant RTkit (Tiangen Biotech Co., Ltd., Beijing, China) followed by Quantitative real-time PCR (qPCR) with the responsible primers using SuperReal PreMix Plus kit (Tiangen Biotech Co., Ltd., Beijing, China) on Roche Cobas z 480 Real-Time PCR Detection System (Roche, Basel, Switzerland). All the primers used for RT-qPCR were obtained from GeneCopoeia (GeneCopoeia Inc., Germantown, Maryland, USA). The expression of the mRNAs was normalized by expression of GAPDH mRNA as a control and calculated based on the $2^{-\Delta\Delta Ct}$ method.

2.3. Western blot

The total cellular proteins in the HA treated and untreated HUVECs grown in 6-well culture plates were extracted by lysis with radioimmunoprecipitation assay (RIPA) buffer (Beijing Solarbio Science & Technology Co., Ltd., Beijing, China) containing protease inhibitor. The proteins were quantified using the BCA Protein Assay Kit (Beijing Solarbio Science & Technology Co., Ltd., Beijing, China). The same amount of protein was separated by 10% (for ICAM-1) or 12% (for IL-6) sodium-dodecyl-sulfate–polyacrylamide-gel electrophoresis (SDS-PAGE) and electrotransferred onto polyvinylidene difluoride (PVDF) membranes. After 1 h incubation with TBST solution containing 5% skim milk at room temperature to block the nonspecific antibody, the protein on the membranes was cultured with primary antibodies at 4 °C overnight followed by incubation with secondary antibody (1: 5000; Proteintech) for 2 h at room temperature after three washes. The protein bands were visualize with enhanced chemiluminescence (ECL) and Image J software (US National Institutes of Health, Bethesda, ML, USA) was used for quantification with normalization by GAPDH in relative intensity manner compared with the control.

2.4. H&E Staining and histopathologic examination

The lung tissue specimens were taken from BABL/c mice (Beijing Vital River Laboratory Animal Technology Co. Ltd, Beijing, China) (All the mice were used for experiments at 8–10 weeks of age and with a body-weight of 20–22 g. The use of mice was approved by the Ethics Committee) 12 h after tail intravenous injection with 100 μl of HA (50 μg/ml and 100 μg/ml in normal saline to simulate 2.5 μg/ml and 5 μg/ml in vivo, respectively, because the total body fluid of a mouse is about 2 ml) and the normal saline as control. All lung tissues were fixed in 10% neutrally buffered formalin and embedded in paraffin. The 4 μm sections were prepared, deparaffinized and rehydrated through degraded ethanol. The slides with tissue section on them were stained for 8 min in Harris's hematoxylin reagent, destained in 0.5% acid-alcohol for 3 s and washed in running tap water. It was then counterstained with 0.5% eosin for 1 min. After dehydration with alcohol and xylene treatment, it was mounted with DPX mounting medium for histopathologic examination by a pathologist.

3. Results

3.1. Increase of the ICAM-1 in HUVECs by HA of H1N1

After incubation of the HUVECs with HA of H1N1 for 24 h, the relative levels of ICAM-1 mRNA in HUVECs were increased by HA of H1N1 in group of 5 μg/ml concentration compared with the control group with statistical significance ($p < 0.05$) (Fig. 1A), according to RT-qPCR assay. The levels of ICAM-1 protein in group of 5 μg/ml concentration of H1N1 HA were increased as well compared with the control group with statistical significance, after incubation of the HUVECs with HA of H1N1 for 24 h ($p < 0.05$) (Fig. 1B), according to Western blot assay.

3.2. Increase of the IL-6 in HUVECs by HA of H1N1

ICAM-1 can be induced by IL-6. After incubation of the HUVECs with HA of H1N1 for 24 h, the relative levels of IL-6 mRNA in HUVECs were increased by HA of H1N1 in group of 5 μg/ml concentration compared with the control group with statistical significance ($p < 0.05$) (Fig. 2A), according to RT-qPCR assay. The levels of IL-6 protein in group of 5 μg/ml concentration of H1N1 HA were increased as well compared with the control group with statistical significance, after incubation of the HUVECs with HA of H1N1 for 24 h ($p < 0.05$) (Fig. 2B), according to Western blot assay.

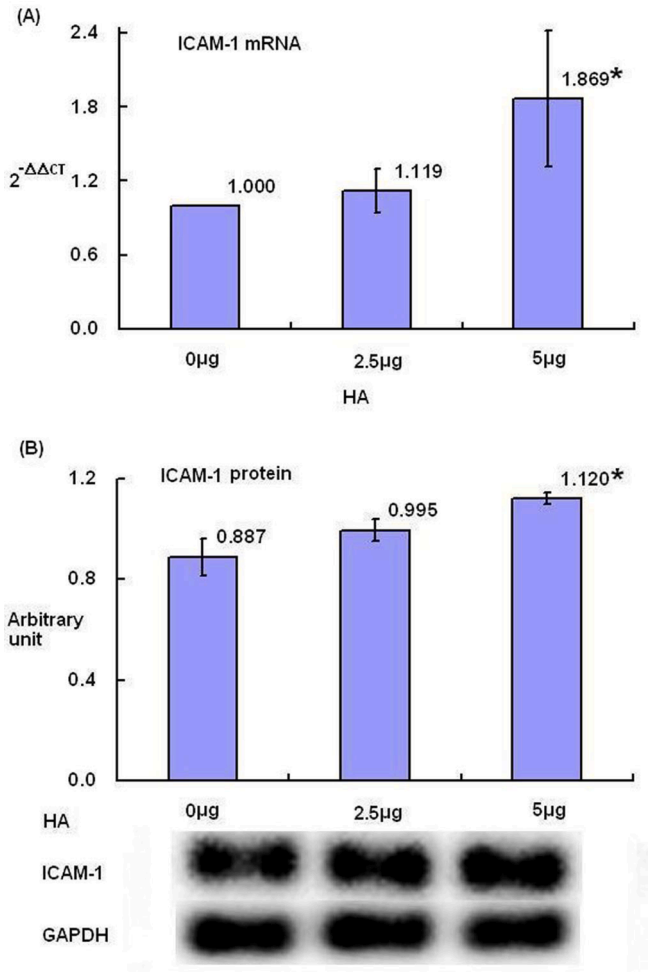

Fig. 1. The expression of ICAM-1 mRNA and protein in HUVECs. After 24 h treatment of HUVECs with HA of H1N1, the expression of ICAM-1 mRNA and protein were detected by RT-qPCR (A) and Western blot (B), respectively. Error bars indicate standard deviation of the means. Asterisks indicate LSD p-values < 0.05, compared with the control after one-way anova.

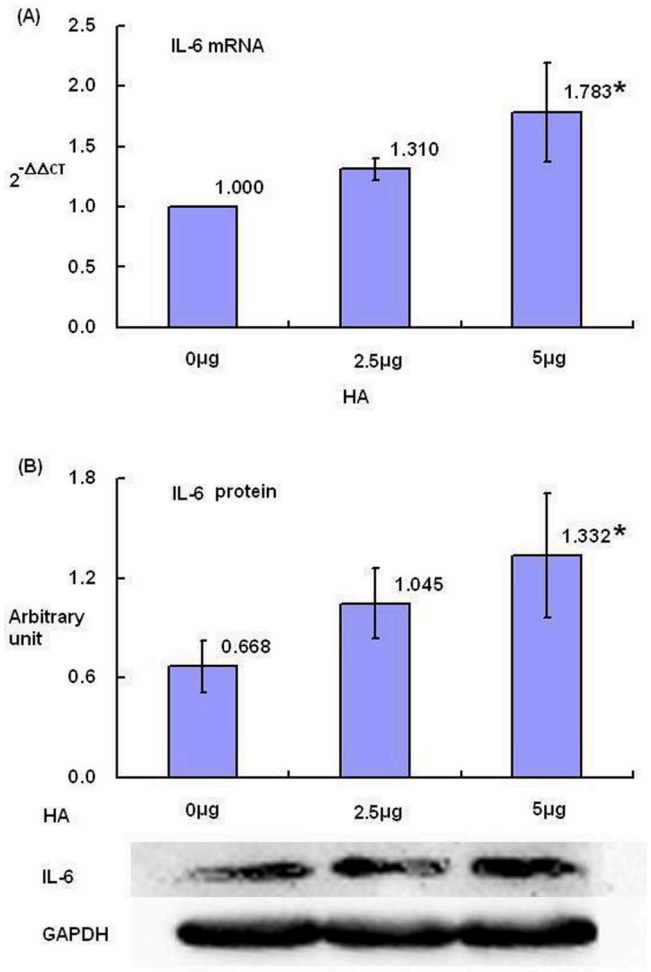

Fig. 2. The expression of IL-6 mRNA and protein in HUVECs. After 24 h treatment of HUVECs with HA of H1N1, the expression of IL-6 mRNA and protein were detected by RT-qPCR (A) and Western blot (B), respectively. Error bars indicate standard deviation of the means. Asterisks indicate LSD p-values < 0.05, compared with the control after one-way anova.

3.3. Histopathological changes of the lungs in mice treated with HA of H1N1 in vivo

Twelve hours after tail intravenous injection with HA of H1N1, it was shown by H&E Staining and histopathologic examination that, in the tissues of the lungs, the alveoli were uniform in size with relative integrity without interstitial angiotelectasis in control group, but the alveolar spaces widened with angiotelectasis in alveolar wall, a little alveolar luminal and interstitial inflammatory infiltrates, more alveolar luminal erythrocyte effusion, and focal pathological injury in the lung tissue of the 2.5 μg/ml group, and the alveolar spaces obvious widened with angiotelectasis in alveolar wall, a lot of alveolar luminal and interstitial inflammatory infiltrates, severe alveolar luminal erythrocyte effusion, and diffuse pathological injury in the lung tissue of 5 μg/ml group (Fig. 3).

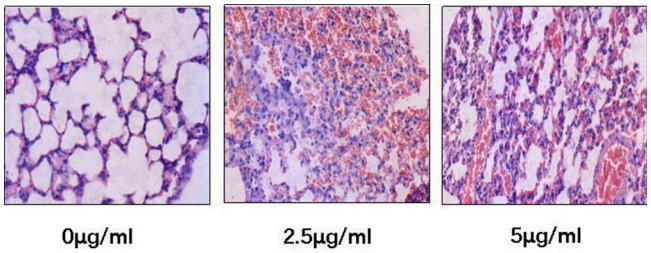

Fig. 3. Histopathologic examination on the lungs of the mice. After12 h of tail intravenous injection with 100 μl of HA (50 μg/ml and 100 μg/ml in normal saline to simulate 2.5 μg/ml and 5 μg/ml in vivo, repectively, because the total body fluid of a mouse is about 2 ml) with the normal saline as control, it was shown by H&E Staining and histopathologic examination that, in the tissues of the lungs, the alveoli were uniform in size with relative integrity without interstitial angiotelectasis in control group, but the alveolar spaces widened with angiotelectasis in alveolar wall, a little alveolar luminal and interstitial inflammatory infiltrates, more alveolar luminal erythrocyte effusion, and focal pathological injury in the lung tissue of the 2.5 μg/ml group, and the alveolar spaces obvious widened with angiotelectasis in alveolar wall, a lot of alveolar luminal and interstitial inflammatory infiltrates, severe alveolar luminal erythrocyte effusion, and diffuse pathological injury in the lung tissue of 5 μg/ml group.

4. Discussion

Both COVID-19 and influenza are viral respiratory tract infections in which Inflammation play an important role. Expression of ICAM-1 on vascular endothelium contributes to recruitment of leukocytes which is essential for the initiation of inflammation. IL-6 induces the expression of ICAM-1. It has been demonstrated that the expression of ICAM-1 and production of IL-6 was enhanced in influenza virus infection as well as

COVID-19 patients. Besides initiation of virus entry into host cells, the role of HA, a constitutional protein in influenza A and B virus, instead of the whole virus, in the expression of ICAM-1 and production of IL-6 in HUVEC in vitro and inflammation in the lungs of the mice in vivo was invastigated using HA of H1N1 in this study with affirmative results.

Influenza viruses is an enveloped negative-sense RNA virus, possessing 8 segmented RNA genomes that code for 11 protein and low proof-reading RNA polymerase, and the segment 4 codes for HA, a major envelope protein (Zeng et al., 2017). In HA, the receptor binding sites in the globular membrane distal head domains of the trimer and the fusion machinery resides in the stem region play an important role in entry of the virus into host cells mediated by functions of the HA binding to cellular receptors and facilitating fusion of the virion membrane with the endosomal membrane (Byrd-Leotis et al., 2017). Additionally, it was shown in this study that the HA of H1N1 plays its roles in elevation of the expression of ICAM-1 and IL-6 in HUVEC in vitro with inflammation in the lungs of the mice in vivo.

ICAM-1 is a type I transmembrane glycoprotein (with a molecular weight of 80–114 kDa depending on its level of glycosylation and unglycosylated ICAM-1 has a molecular weight of 60 kDa) (van de Stolpe and van der Saag, 1996). The ICAM-1 consists of three regions including an extracellular region with 453 mainly hydrophobic amino acid residues forming five immunoglobulin (Ig)-like domains, a single hydrophobic transmembrane region with 24 residues and a short cytoplasmic tail with 28 residues (Lawson and Wolf, 2009). Instead of classical signaling motifs, the cytoplasmic tail has one tyrosine residue, which may be important for signaling (Staunton et al., 1990; Tsakadze et al., 2004). As a biosensor, after ligand engagement of the extracellular domain, ICAM-1 transduces outside-in-signaling via association of its cytoplasmic domain with the actin cytoskeleton to play its role as a master regulator of many essential cellular functions both at the onset and at the resolution of pathologic conditions (Bui et al., 2020). The best known role of ICAM-1 as an adhesion receptor is to regulate leukocyte recruitment from circulation to sites of inflammation (Bui et al., 2020). It is demonstrated in this study that the HA of H1N1 elevated the expression of ICAM-1 in HUVEC, which may contribute to induction of the inflammation during H1N1 infections.

ICAM-1 can be induced by IL-6, which consists of 212 amino acids in human, including a 28-amino-acid signal peptide, with molecular weight of about 20 kDa for the core protein, and glycosylation accounts for the size of 21–26 kDa of natural IL-6 (Tanaka et al., 2014). IL-6 is a prototypical cytokine with the function of maintaining homeostasis, and homeostasis disruption, caused by infections or tissue injuries, may immediately induce the production of IL-6 which contributes to host defense against such emergent stress with the activation of acute-phase and immune responses, but dysregulated excessive and persistent synthesis of IL-6 has a pathological effect on, respectively, acute systemic inflammatory response syndrome and chronic immune-mediated diseases (Tanaka et al., 2018). It is demonstrated in this study that the HA of H1N1 elevated the expression of IL-6 in HUVEC, which may contribute to induction of the expression of ICAM-1 with inflammation during H1N1 infections.

In non-fatal cases of influenza viral infections, the upper respiratory tract and trachea are predominantly involved, but in fatal cases of influenza, evidence of pneumonia is usually shown. Autopsies of influenza with classic histopathologic studies showed the characteristics of severe influenza viral pneumonia, including capillary and small vessel thromboses, interstitial edema and inflammatory infiltrates, the formation of hyaline membranes in alveoli and alveolar ducts, varying degrees of acute intra-alveolar edema and/or hemorrhage, and diffuse alveolar damage in addition to necrotizing bronchitis and bronchiolitis (Taubenberger and Morens, 2008). It is histopathologically demonstrated in this study that pathological injury involving inflammation, such as widened alveolar spaces with angiotelectasis in alveolar wall, alveolar luminal and interstitial inflammatory infiltrates, alveolar luminal erythrocyte effusion, had been induced by the administration of the HA of H1N1 in the lung tissues of the mice in vivo, suggesting the role of the HA of H1N1 alone in the pathogenesis of H1N1 infection.

In this study, the enhancement of ICAM-1 and IL-6 expression in HUVECs and pathological injury in lung tissues of the mice caused by HA of H1N1 were demonstrated, it can also do with Covid 19 since both COVID-19 and influenza are viral respiratory tract infections with some similar characteristics. No experiment, however, was performed in this study to prove the meaning for COVID-19. Therefore, further experiments are required to demonstrate the meaning for COVID-19 in the future.

In conclusion, more expression of ICAM-1 and IL-6, two molecules involving in pathological and inflammatory responses, in HUVECs and pathological injury in lung tissues of the mice were induced by HA alone, instead of whole H1N1 virus, besides its role in initiation of virus entry into host cells. This knowledge suggests that HA-targeted agents may be potential anti-influenza drugs, encouraging development of HA-based vaccines and antiviral inhibitors [40] such as arbidol, monoclonal antibodies, small molecule inhibitors such as nitazoxanide, natural compounds such as stachyflin and pentacyclic triterpenes for prevention and treatment of disease related to H1N1 infection.

CRediT authorship contribution statement

Ming-Zhen Zhao: Conceptualization, Writing - original draft. **Xiang Guo:** Investigation. **Bo Sun:** Visualization. **Xiao-Fang Sun:** Methodology. **Gui-Fen Pang:** Project administration. **Lin-Ying Yang:** Resources. **Xing Zhao:** Formal analysis. **Li-Xin Sun:** Writing - review & editing. **Qing Zhang:** Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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