Human Antibody Neutralizes Severe Fever with Thrombocytopenia Syndrome Virus, an Emerging Hemorrhagic Fever Virus

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Severe fever with thrombocytopenia syndrome virus (SFTSV), a newly discovered member of the Bunyaviridae family, is the causative agent of an emerging hemorrhagic fever, SFTS, in China. Currently, there are no vaccines or effective therapies against SFTS. In this study, a combinatorial human antibody library was constructed from the peripheral lymphocytes of 5 patients who had recovered from SFTS. The library was screened against purified virions for the production of single-chain variable-region fragments (ScFvs). Of the 6 positive clones, one clone (monoclonal antibody [MAb] 4-5) showed neutralizing activity against SFTSV infection in Vero cells. MAB 4-5 was found to effectively neutralize all of the clinical isolates of SFTSV tested, which were isolated from patients in China from 2010 to 2012. MAB 4-5 was found to bind a linear epitope in the ectodomain of glycoprotein Gn. Its neutralizing activity is attributed to blockage of the interactions between the Gn protein and the cellular receptor, indicating that inhibition of virus-cell attachment is its main mechanism. These data suggest that MAB 4-5 can be used as a promising candidate molecule for immunotherapy against SFTSV infection.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging fatal hemorrhagic fever with fatality of up to 30% of all cases (1). The disease is caused by a newly identified bunyavirus, SFTS virus (SFTSV) (1), and it is characterized by sudden onset of fever, respiratory or gastrointestinal symptoms, and a decrease in whole white blood cell and platelet counts that gradually progresses into hemorrhage and multiorgan failure at the end stage (2). This disease has been reported across a broad geographic area in eastern and central China, including Jiangsu, Anhui, Shandong, Henan, Hubei, and Liaoning Provinces (1). Heightened surveillance of acute febrile illness has led researchers to add Zhejiang, a southeastern province, to the list of regions where SFTSV is endemic (3). This indicates that this disease is continuing to spread in China. Recently, a bunyavirus named Heartland virus (HLV) has been isolated from patients from Missouri in the United States. HLV has 70% homology to the Chinese virus based on amino acid sequences (4). The clinical symptoms of HLV infection are similar to those caused by SFTSV. One case of human SFTS outside China has been reported (5). This demonstrates that SFTS or a virus similar to SFTSV probably has worldwide distribution.

Although most human SFTS cases in China are sporadic, and the patients tend to have histories of arthropod bites, person-to-person transmissions through blood contact have been reported (2, 6, 7, 8). Despite the medical importance of this disease, no clinical treatment for SFTSV infection other than supportive care has been developed. Prophylactic and therapeutic measures, including therapeutic antibodies and vaccines that would protect susceptible individuals and those at high risk of complications of infection, are urgently needed.

SFTSV is a member of the Phlebovirus genus in the Bunyaviridae family (1). Like all bunyaviruses, SFTSV has a trisegmented, single-stranded RNA genome with negative (L and M segments) or ambisense (S segment) polarity, and it encodes seven proteins (9). The two glycoproteins, Gn and Gc, which are produced by cleavage of a precursor encoded by the M segment, are highly antigenic envelope proteins. They are responsible for receptor binding and membrane fusion (10). For this reason, viral surface glycoproteins may be targets for neutralizing antibody responses.

Antibody has played a critical role in the treatment of a wide variety of viral diseases, such as those caused by Hantaan virus, cytomegalovirus, rabies virus, and respiratory syncytial virus infection (11–14). The mechanisms of antibody protection include neutralization, complement activation, antibody-dependent cellular cytotoxicity, and opsonization (15). Patients infected with SFTSV, like those infected with other systemic arboviruses, can remain viremic for up to 12 days (unpublished data). The administration of neutralizing antibodies can conceivably reduce viral load, prevent viral dissemination into other systems, and likely reduce the risk of severe outcome of the disease. They could also be used for prophylactics in high-risk persons, such as hospital personnel and family members of patients, who are at risk for person-to-person transmission, and immunocompromised patients, who might not respond well to vaccines.

In this study, we developed a human monoclonal antibody (MAb), called MAb 4-5, isolated from a phage antibody library...
using whole SFTSV virions. Its binding and neutralizing properties were investigated. MAb 4-5 was found to bind a linear epitope in the ectodomain of Gn. This unidentified epitope was found to be conserved among disparate geographic virus isolates within China, since MAB 4-5 shows a cross-neutralizing activity. The mode of inhibition was also characterized, indicating that MAB 4-5 mediates neutralization by blocking the binding of Gn to the cellular receptor. These data suggest that MAB 4-5 could be developed into a therapeutic agent in passive immunotherapy.

**MATERIALS AND METHODS**

**Virus strains and virion preparation.** The SFTSVs used in this study are listed in Table 1. They were propagated at 37°C in Vero cells at a multiplicity of infection (MOI) of 1.0 and cultivated for 10 days. Supernatants containing viral particles were harvested, aliquoted, and stored at -70°C until use. Fifty-percent tissue culture infective doses (TCID50) of working stocks of each strain were titrated on Vero cells. For virion purification, culture supernatant of the JS-2010-003 virus was successively treated with β-propiolactone inactivation, removal of cell debris, ultracentrifugation, and gel filtration chromatography as described previously (16). The purified virions were analyzed by SDS-PAGE to confirm purity. All operations involving SFTSV were performed under biosafety level 2 containment conditions.

**Construction, panning, and screening of the human single-chain variable-region fragment (ScFv) antibody library.** Human lymphocytes were collected from 5 convalescent SFTS patients in Jiangsu Province. The research protocol was approved by the Human Bioethics Committee of Jiangsu Center for Disease Prevention and Control (Jiangsu CDC), and all participants provided written informed consent. Total RNA was extracted from lymphocytes using an RNA purification kit (Qiagen, Valencia, CA). First-strand cDNA was synthesized from total RNA by using a first-strand cDNA synthesis kit (Invitrogen, Carlsbad, CA) with oligo(dT). The variable-region genes of heavy (VH) and light (VL) chains were amplified by using specific primers and cloned into pAc-K-CH3 baculovirus DNA (BD, San Jose, CA) for expression by cotransfection with a recombinant IgG1 plasmid and linearized AcNPV baculovirus DNA (BD, San Jose, CA) into SF9 insect cells according to the manufacturer’s instructions. The supernatant containing recombinant human IgG1 was purified through protein G columns (GE Healthcare, Uppsala, Sweden) and kept at -20°C until use.

**Neutralization assays.** First, 50 μl of SFTSV-specific ScFv (100 μg/ml) was mixed with an equal volume of suspension of 100 TCID50 of SFTSV strain JS-2010-003 and incubated at 37°C for 1 h. The virus-antibody mixture was then transferred onto monolayers of Vero cells in 96-well plates and incubated at 37°C for 1 h. After being washed with minimal essential medium (MEM), a maintenance medium, the samples were incubated at 37°C in a 5% CO2 incubator. Cytotoxic effects (CPE) were observed every 24 h for 6 days. Each antibody was considered to have neutralizing activity if it could inhibit ≥90% of viral CPE. For the positive clone, here designated MAB 4-5, ScFv was reformatted into full-length IgG1. This molecule was used to further characterize its neutralizing potency and cross-binding activity, as described above. Individual measurements were performed in triplicate, and the relative neutralization was calculated in the presence of patient convalescent-phase sera and an irrelevant human IgG1 (or its ScFv format, enterovirus 71 specific) as positive and negative controls, respectively.

**Western blot analysis.** To determine the binding target of the selected MAB 4-5 IgG1, purified SFTSV strain JS-2010-003 virions were lysed with sample buffer and proteins were fractionated by 10% SDS-PAGE. The separated proteins were electrotransferred to a nitrocellulose (NC) membrane and incubated consequently with MAB 4-5 IgG1 and horseradish peroxidase (HRP)-conjugated goat anti-human immunoglobulin (ZHGB-BIO, Beijing, China). The blots were visualized by 3,3’-diaminobenzidine (DAB) (Boster Bio, Wuhan, China) according to the manufacturer’s instructions.

**Immunofluorescence assay.** Reactivity between human MAB 4-5 IgG1 and SFTSV-infected cells was assessed using indirect immunofluorescence assay (IFA). The infected and noninfected (SFTSV, JS-2010-003) Vero cells were grown on an 8-well Millicell EZ slide (Millipore, Billerica, MA) for 36 h at 37°C, and cells were fixed by treatment with acetone for 10 min at -20°C. Human MAB 4-5 IgG1 or an irrelevant human IgG1 (described above) were incubated with the fixed cells for 30 min at 37°C. Bound antibodies were detected using fluorescein isothiocyanate (FITC)-conjugated anti-human antibodies (KPL, Gaithersburg, MD; diluted by phosphate-buffered saline PBS containing 0.01% [wt/vol] Evans blue) and observed under an immunofluorescence microscope.

**Electron microscopy.** Immunoelectron microscopy (immunoe-EM) of the SFTSV virion was performed essentially as described previously (20). SFTSV JS-2010-003 from the supernatant of infected Vero cells was adsorbed to copper grids coated with carbon and Pioloform. These were incubated with MAB 4-5 IgG1 by floating on droplets for 30 min at room temperature, and an irrelevant human IgG1 (described above) was used as a negative control. Bound monoclonal antibodies were detected by incubation on droplets of anti-human IgG gold 10-nm conjugates (Jieliy Bio-tech, Shanghai, China). The grids were negatively contrasted with 2% osmium tetroxide.
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RESULTS

Generation of MAbs against the SFTSV virion. The human ScFv library was panned against the purified inactivated SFTSV virion coated on plastic plates. After 3 rounds of panning, 90 randomly picked clones were screened, and 14 clones were found to recognize SFTSV by ELISA (data not shown). Sequence analysis of positive ScFv clones revealed the presence of 6 unique clones (Fig. 1). The selected ScFv clones were encoded by 6 different VH and VL sequences. The gene families were VH5 and VH1 for VH and VL domains. Protein transmembrane helices were predicted using TMHMM server, version 2.0 (http://www.cbs.dtu.dk/services/TMHMM/), for the prediction of protein transmembrane helices. One ectodomain was identified for Gn (amino acids [aa] 20 to 452) and Gc (aa 1 to 473). Their corresponding genes were generated by PCR and cloned into a pXJ40-HA expression vector. All sequences were confirmed by DNA sequencing. These functional domains were expressed in 293 cells by transient transfection, and the recombinant protein-antibody mixture was added to the Vero cell suspension, mixed, and incubated at room temperature for 2 h. The cells were washed and then lysed with sample buffer. Proteins were analyzed by Western blotting, with an anti-HA-HRP conjugate.

In vitro neutralizing activity of antibodies to SFTSV. The neutralizing activity of the purified soluble ScFv for SFTSV (JS-2010-003) was tested using Vero cells. Of the 6 ScFv clones tested, only clone 4-5 (VH5/VL1) was mixed with its superior avidity. The concentration required to obtain 50% neutralization of 100 TCID50 SFTSV was about 2.0 μg/ml, but the same activity was achieved by MAb 4-5 ScFv at a concentration of 25 μg/ml. The control antibody did not exhibit any neutralization activity against SFTSV. The neutralization breadth of MAb 4-5 IgG1 was investigated by using a panel of different SFTSV isolates obtained from regions where SFTSV is endemic, including Jiangsu, Anhui, Shandong, Henan, and Zhejiang, between 2010 and 2012 (Table 1). MAb 4-5 IgG1 was separately titrated against the JS-2010-003 strain. As shown in Fig. 2B, MAb 4-5 IgG1 exhibited far more potent neutralization activity against SFTSV than its ScFv format. This was consistent with its superior avidity. The concentration required to obtain 50% neutralization of 100 TCID50 SFTSV was about 2.0 μg/ml, but the same activity was achieved by MAB 4-5 ScFv at a concentration of 25 μg/ml. The control antibody did not exhibit any neutralization activity against SFTSV. The neutralization breadth of MAB 4-5 IgG1 was investigated by using a panel of different SFTSV isolates obtained from regions where SFTSV is endemic, including Jiangsu, Anhui, Shandong, Henan, and Zhejiang, between 2010 and 2012 (Table 1). MAB 4-5 IgG1 was separately titrated in the presence of 100 TCID50 of SFTSV isolates for 1 h at 37°C before incubation with Vero cells. Complete protection from most SFTSV strains was achieved at a dose of 5 μg/ml MAB 4-5 IgG1. The two exceptions were both Jiangsu isolates, JS-2011-004 and JS-2012-020, for which MAB 4-5 IgG1 showed neutralization rates of 80% and 90%, respectively (Fig. 2C). This indicates that MAB 4-5 recognizes a conserved epitope within SFTSV structural proteins shared by disparate geographic virus isolates in China.

Characterization of MAB 4-5 binding specificity. Western blot showed that MAB 4-5 is immunoreactive with two bands with molecular masses of 72 kDa and 170 kDa, respectively, under reducing conditions (Fig. 3A). They probably represent the Gn glycoprotein and the homo- or hetero-oligomer of Gn or Gc from the observed molecular mass, compared to the purified virus SDS-PAGE profile (Fig. 3B), indicating that it recognizes a continuous linear epitope within Gn. To confirm the specificity of MAB 4-5 for the virus, immunofluorescence was performed on SFTSV-infected and uninfected Vero cells. The SFTSV-infected cells fixed to slides with acetone were moderately stained (Fig. 4A). When treated by MAB 4-5 IgG1, the localization of the gold label to the outer peplomer region of the SFTSV JS-2010-003 strain, but a control human IgG1 did not stain either infected (Fig. 4B) or uninfected (Fig. 4D) cells. The control human IgG1 didn’t stain either infected (Fig. 4B) or uninfected (Fig. 4D) cells. Immune-EM was used to investigate the binding of MAB 4-5 to glycoproteins in whole virions. Incubation with MAB 4-5 caused labeling of the outer peplomer region of the SFTSV virion, indicating that the control human IgG1 did not induce any labeling (Fig. 5A and B).
Inhibition of binding of the Gn1 domain to cellular receptor by MAb 4-5. As shown in Fig. 7, when Vero cells were incubated with the recombinant Gn ectodomain in the presence of MAb 4-5 ScFv and analyzed by Western blotting, MAb 4-5 ScFv completely inhibited the binding of Gn to Vero cells, but the nonneutralizing antibody A5 did not inhibit binding under the same conditions. This demonstrated that the mechanism of the neutralizing activity of MAb 4-5 involves blocking binding of Gn to its cellular receptor.

**DISCUSSION**

In China, SFTS is a severe emerging hemorrhagic fever that causes thousands of people to be hospitalized each year, with an average case fatality of 12% and up to 30% (8). Vaccination is the most

![Image of Western blot](https://example.com/image1)

**FIG 3** Western blot. Purified SFTSV JS-2010-003 strain virions were electrophoresed on a 10% SDS-PAGE gel and transferred on an NC membrane. MAb 4-5 IgG1 binds two bands with molecular masses of 72 kDa and 170 kDa under reducing conditions (Fig. 3A). They probably represent Gn glycoprotein and homo- or hetero-oligomer of Gn or Gn/Gc compared to the purified virion SDS-PAGE profile (Fig. 3B).
effective countermeasure against viral disease (21, 22). However, the low incidence (0.8 to 0.94%) (23, 24) and sporadic nature (9) of SFTSV infection makes it difficult to target the human population most in need of vaccination and to access the vaccine’s economic feasibility. This severely influences vaccine development. An antibody-mediated therapeutic may be a useful contributor to treat and prevent SFTS. It can be used in susceptible individuals and those at high risk of complication of infection. In this study, a human antibody against SFTSV was described. The actual breadth of the neutralizing spectrum, functional activity, and binding target were also investigated.

The viral envelope glycoproteins of SFTSV, such as Gn and Gc, mediate receptor attachment and the fusion of viral and cellular membranes, giving the viral genome access to the host cell’s cytoplasm. Antibodies can inhibit viral infection through two distinct mechanisms that occur in parallel with the stages of viral entry into the cells. They can directly block viral attachment to target cells by interfering with virus-receptor interactions. These include antibodies against the S1 protein of severe acute respiratory syndrome coronavirus (SARS-CoV) (25) and antibodies against the envelope protein of West Nile virus (26). Antibodies can also target viral receptors, as exemplified by treatment of arenavirus infection with an anti-human transferring receptor antibody (27).

During viral entry via endocytosis, antibodies may block the conformational changes in envelope protein required for fusion between viral and endosomal membranes. For example, some anti-hemagglutinin MAbs neutralize the infectivity of the influenza virus by interfering with the low pH-induced structural rearrangements in the HA2 domain, inhibiting of fusion during viral replication (21, 28). In this study, consistent with the first mechanism described above, MAb 4-5 generated from the memory B cell repertoire of SFTS convalescent patients was found to neutralize SFTSV infectivity by interfering with the interactions between the

FIG 4 Characterization of MAb 4-5 IgG1 in IFA. Infected (A, B) and noninfected (SFTSV, JS-2010-003) (C, D) Vero cells were fixed on slides and incubated with MAb 4-5 IgG1 (A, C) or an irrelevant human IgG1 (B, D). Bound antibodies were detected by using FITC-conjugated anti-human antibody with PBS dilution buffer (pH 7.4) containing 0.01% (wt/vol) Evans blue counterstain.

FIG 5 Analysis of glycoprotein binding by immune-EM. Gold immunolabeling of glycoproteins in SFTSV viral peplomers with MAb 4-5 IgG1 (A) or a negative control IgG1 (B) was carried out. This was followed by incubation with anti-human IgG gold 10-nm conjugates. The bar indicates 100 nm.

FIG 6 Identification of an MAb 4-5 binding target in SFTSV glycoproteins. (A) Of the 2 predicted ectodomains expressed in 293 cells, MAb 4-5 reacted only with the Gn domain 50 kDa in size. (B) The recombinant Gn and Gc ectodomains were hybridized by an anti-HA-HRP conjugate.
Conformational one (Fig. 3A). This may facilitate rational vaccine binding that takes place during viral transmission. MAb 4-5 may host immune pressure and plays a critical role in the receptor details of this process. This uncharacterized epitope can resist the genetic evolution of SFTSV may have accrued in terms of mutation and reassortment (33). However, very little is known about the netic evolution of SFTSV may have accrued in terms of mutation and reassortment (33). However, very little is known about the

class of SFTSV strains. It has a single-stranded RNA genome, so the gene-
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