A Newly Discovered Severe Fever with Thrombocytopenia Syndrome Virus and its Mechanisms in Evading Host Innate Immunity

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Abstract

Severe fever with thrombocytopenia syndrome virus (SFTSV) is a newly found virus that causes severe fever and thrombocytopenia. There is no specific treatment for SFTSV infection, although researches have been focusing on the pathogenic mechanisms of SFTSV. It has been shown that TBK1/IKKε plays an important role in IFN induction. Interestingly, the S segment of SFTSV genome encodes nonstructural protein (NSs) that can induce inclusion bodies (IBs) formation to isolate the kinases from mitochondrial platform to evade host innate immunity. As a result, interactions between NSs of SFTSV and TBK1/IKKε pathway become a hot topic to pursue new antiviral drugs against this virus. Furthermore, glycoprotein Gn/Gc encoded by the M segment could mediate virus entry into host cells, which may become a target for neutralizing antibody.

Keywords: SFTSV IBs; TBK1/IKKε; NSs; Gc/Gn; Innate immunity

Introduction

SFTSV is a newly discovered virus that was first reported in 2009 in China [1]. It was known as Huaiyangshan virus which is a new member of the Phlebovirus genus from the Bunyaviridae family [1]. Clinically, SFTSV can cause fever, gastrointestinal symptoms, myalgia, and regional lymphadenopathy [2]. The most significant manifestations of this disease are severe fever and thrombocytopenia [3]. The disease which could be transmitted via ticks has been found in many cities in China now, and the highest numbers of reported cases were in Henan (48% of the total), Hubei (22%), and Shandong (16%) [4]. Epidemiological study shows that 1.0%-3.8% of the examined population in hilly areas had SFTSV antibodies, which suggests that SFTSV has circulated widely in China, especially in rural areas [5]. SFTSV infection was also reported in other Asia countries such as Korea and Japan [6,7]. The mortality of SFTSV infection in China is about 2.5%-30% [8]. Most patients are farmers who come from rural areas. Many of them have reported tick bites 7-9 days before getting illness. The disease occurs mainly in April and May during the peaking season in Henan [9]. One study indicated that SFTSV could cause the asymptomatic infections via person-to-person contact with infected blood [6]. At present, there is no specific medication to treat this disease. Patients are often treated with Ribavirin, a traditional nonspecific antiviral drug, but its efficacy remains uncertain [10]. There is also report says that antibodies play an important role in curing the disease [11]. Neutralizing antibodies can reduce viral load, and prevent SFTSV spreading. A human monoclonal antibody, 4-5, has been shown to have neutralizing activity against SFTSV in vitro and it might be used for high risk people in the future [11]. For now, there is no effective vaccine to prevent SFTSV infection, so people living in rural areas should pay special attention to this virus, taking some preventive measures, for example protection against tick bites, avoidance of wooded and bushy areas where ticks are abundant, especially in April or May. Repellents, such as permethrin can also be applied [12,13]. SFTSV is susceptible to acid, heat, ether, sodium deoxycholate, other common disinfectants, and ultraviolet irradiation, and can be rapidly inactivated [14-19].

Genome Structure and Encoded Proteins

SFTSV is a single-stranded negative-sense RNA virus, with 3 genomic segments, L, M, and S [3]. The full-length of L segment consists of 6368 bp, M segment is 3378 bp and S segment is 1744 bp [20]. The L segment encodes viral RNA polymerase, while M segment encodes the 2 envelope glycoproteins Gn and Gc. The S segment contains 2 ORFs that encodes nucleoprotein (NP) and nonstructural protein (NSs), respectively [15]. RNA-dependent RNA polymerase (RdRp) encoded by the L segment plays an important role in the replication and transcription of the viral RNA [20]. The influenza-like endonuclease domain within its N-terminal is essential for viral cap-dependent transcription [21]. M segment encodes the Gn and Gc which mediate SFTSV entry into human and animal cell lines [16]. Most recently, it has been shown that the lectin dendritic-cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) facilitates certain Phleboviruses entry into dendritic cells via Gn/Gc mediation, and over-expression of DC-SIGN was sufficient for SFTSV Gn/Gc-mediated entry into otherwise non-susceptible cells [22]. Glycoproteins encoded by M segment are also excellent targets for neutralizing antibodies [17]. Monocytic cells (THP-1), HEP, and cervical carcinoma (Hela) cells were resistant to SFTSV Gn/Gc mediated entry, which indicating that these cells may lack the expression of appropriate receptors [16]. The S segment encoded NSs interfere with host interferon induction pathway through suppressing TBK1/IKKe-IRF 3 signaling. Further studies show that NSs mediate the formation of cytoplasmic inclusion bodies (IBs) which can efficiently capture TBK1/IKKe to the IBs leading to a spatial isolation of TBK1/IKKe from the mitochondrial antiviral platform, to inhibit antiviral signaling and IFN induction [18]. The spatial isolation of the kinases could not be reversed by SFTSV infection. The report also confirms

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that NSs strongly inhibits IFN-β induction mainly through suppressing ISRE (interferon stimulated response element) activation but slightly influence on NF-kB (nuclear factor kB) signaling [18]. Interestingly, both SFTSV NSs and NP might suppress the activation of NF-kB and IFN-β promoter activities [19]. Another study shows that NSs protein can form viroplasm-like structures (VLS). They found that the middle portion of NSs, especially the region NSs 66-205, was essential for the formation of VLS. Simultaneously, this study confirms that NSs and NP interact with each other, and NP was localized in VLSs [23].

Pathogenesis of SFTSV

Sun et al reported that non-muscle myosin heavy chain IIA (NMMHC-IIA), a cellular protein with surface expression in multiple cell types, may play an important role in SFTSV entry into host cells [24]. They further confirmed that Gn binds to NMMHC-IIA fused with an immunoglobulin Fc tag at its C terminus (Gn-Fc) bound to multiple cells susceptible to the infection of SFTSV and blocked viral infection of human umbilical vein endothelial cells (HUVECs). Small interfering RNA (siRNA) knockdown of NMMHC-IIA, but not the closely related NMMHC-IIB or NMMHC-IIIC, reduced SFTSV infection. So NMMHC-IIA may be a useful target for antiviral intervention against viral infection. There is also report says that NP is crucial for SFTSV replication. Zhou et al demonstrated that NP facilitates viral RNA encapsidation and is responsible for the formation of ribonucleoprotein complex [25]. This study shows that NP processes a ringshaped hexameric form to accomplish RNA encapsidation [25]. Sun and colleagues [26] analysed the immune function of patients with SFTS. They found that numbers of CD3-positive and CD4-positive T lymphocytes in SFTSV infected patients are significantly lower than normal control population although the number of natural killer cells is increased in the acute phase of SFTSV infection. Simultaneously, serum from patients with SFTS has almost no detectable interferon β. As discussed above, SFTSV-encoded proteins, including nucleoprotein and non-structural protein, inhibit the activation of interferon β promoter and nuclear factor kB signaling [19]. Inflammatory cytokines play an important role in the pathogenesis of many viral diseases. In patients with SFTSV infection, expression of interleukin-1 receptor antagonist interleukins 6 and 10, G-CSF, interferon-γ-inducible promoter and nuclear factor κB signaling [19]. Inflammatory cytokines and non-structural protein, inhibit the activation of interferon β promoter and nuclear factor kB signaling [19]. Interestingly, ISRE (interferon stimulated response element) activation but slightly influence on NF-kB (nuclear factor κB) signaling [18]. Another study shows that NSs protein can form viroplasm-like structures (VLS). They found that the middle portion of NSs, especially the region NSs 66-205, was essential for the formation of VLS. Simultaneously, this study confirms that NSs and NP interact with each other, and NP was localized in VLSs [23].

Discussion and Conclusions

SFTSV is newly discovered virus that was first reported in China dated back to 2009. The virus was also reported in some other countries, such as in Japan, Korea and USA. Until now, there is no effective vaccine to prevent this disease, and the efficacy of traditional antiviral treatment needs improving. As a result, many labs have been focusing on studying the molecular mechanisms of pathogenesis of SFTSV in order to find the targets for antiviral drug intervention and vaccine development. One example comes from NSs of SFTSV, due to the fact that it can mediate IBS information and IBS can irreversibly spatial isolateTBK1/IKKe from mitochondrial antiviral platform. But there is no report about TBK1/IKKe signaling at other subcellular sites which can be prevented by the spatial isolation of IBS as well. Many scientists now concentrate on the research of NSs inhibitors which may be a hot spot in the future. The M segment encoded glycoprotein Gn/Gc is also a target for research. The glycoprotein entry into the envelope of the virus, and combines the cell receptor, promotes virus entry into the host cells, and the C-type lectin DC-SIGN was found to serve as a receptor for SFTSV Gn/Gc-driven entry into cell lines and dendritic cells. But Monocytic (THP-1) cells, HFF, and cervical carcinoma (HeLa) cells were resistant to SFTSV Gn/Gc-driven entry, indicating that these cells lack expression of the appropriate receptor(s). So Gn/Gc could be a target for neutralizing antibodies on one way and it may also become a hot spot for the research of antiviral drugs on the other way. Under current condition, we should concentrate on the prevention of this disease; keep away from each route of transmission and more in depth study on the molecular mechanisms of viral pathogenesis for more effective antiviral drug intervention.

References