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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 studying 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 meditate 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 through 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 Shangdong (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), HEF, 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/IKKε-IRF 3 signaling. Further studies show that NSs mediate the formation of cytoplasmic inclusion bodies (IBs) which can efficiently capture TBK1/IKKε to the IBs leading to a spatial isolation of TBK1/IKKε 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-κB (nuclear factor κB) signaling [18]. Interestingly, both SFTSV NSs and NP might suppress the activation of NF-κB 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-IIC, 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 κB 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 protein, and monocyte chemotactic protein 1 is increased, interleukins 1β and 8, and macrophage inflammatory proteins 1α and 1β is increased only in fatal cases [26]. These cytokines play an important role in serum viral load and various clinical features. SFTSV can also adhere to platelets and be phagocytosed by splenic macrophages, causing thrombocytopenia [27]. A newly report indicates that SFTSV infects reticular cells but did not infect dendritic cells, megakarvocytes, monocytes/macrophages, neutrophils, or endothelium [28].

Model for SFTSV

Cong Jin et al. [27] reports that they used C57/BL6 mouse as model to study the pathogenesis of SFTSV, and they found that splenic macrophages were identified as target cells for SFTSV replication, and promote thrombocytopenia because of their responsibility of phagocytosing platelets. And they also found that In SFTSV-infected mice, the spleen was the principle target organ of SFTSV at the early infection stage, serving as a place for virus replication and showing marked pathological changes.

Treatment

There is no specific treatment at present [10], but interestingly, many scientists now focus on researching of antibodies of SFTSV. The M segment encoded glycoproteins can serve as the targets for neutralizing antibodies [17]. A newly report [29] confirms that NP can be a target for monoclonal antibodies (MAbs), and there were at least 4 distinct binding sites in N protein, represented by the MAbs of H2A12,M3E11, M1D8 and H2H9, and the epitope of MAbs. H2A12 was the major binding site of N protein for most human and mouse MAbs. Guo et al. [11] confirms that a human monoclonal antibody [6,7], has shown neutralizing activity against SFTSV in vitro and might be used for high risk people in the future. 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.

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 meditate IBs information and IBs can irreversibly spatial isolateTBK1/IKKε from mitochondrial antiviral platform. But there is no report about TBK1/IKKε 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

1. Lani R, Moghaddam E, Haghani A, Chang LY, AbuBakar S, et al. (2014) Tick-borne viruses: a review from the perspective of therapeutic approaches. Ticks Tick Borne Dis 5: 457-465.
2. Zhang X, Liu Y, Zhao L, Li B, Yu H, et al. (2013) An emerging hemorrhagic fever in China caused by a novel bunyavirus SFTSV. Sci China Life Sci 56: 697-700.
3. Li DX (2011) [Fever with thrombocytopenia associated with a novel bunyavirus in China]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 25: 81-84.
4. Liu Q, He B, Huang SY, Wei F, Zhu XQ (2014) Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. The Lancet Infectious Diseases 14: 763-772.
5. Wang LY, Cui N, Lu QB, Wo Y, Wang HY et al. (2014) Severe fever with thrombocytopenia syndrome in children: a case report. BMC infectious diseases 14: 366.
6. Hiraki T, Yoshimitsu M, Suzuki T, Goto Y, Higashi M, et al. (2014) Two autopsy cases of severe fever with thrombocytopenia syndrome (SFTS) in Japan: A pathognomonic histological feature and unique complication of SFTS[J]. Pathol Int 64: 569-575.

7. Park SW, Song BG, Shin EH, Yun SM, Han MG, et al. (2014) Prevalence of severe fever with thrombocytopenia syndrome virus in Haemaphysalis longicornis ticks in South Korea. Ticks and tick-borne diseases 5: 975-977.

8. Wang Y, Deng B, Zhang J, Cui W, Yao W, et al. (2014) Person-to-Person Asymptomatic Infection of Severe Fever with Thrombocytopenia Syndrome Virus through Blood Contact. Intern Med 53: 903-906.

9. Xu B, Liu L, Huang X, Ma H, Zhang Y, et al. (2011) Metagenomic analysis of fever, thrombocytopenia and leukopenia syndrome (FTLS) in Henan Province, China: discovery of a new bunyavirus. PLoS Pathog 7: e1002369.

10. Liu W, Lu QB, Cui N, Li H, Wang LY, et al. (2013) Case-fatality ratio and effectiveness of ribavirin therapy among hospitalized patients in china who had severe fever with thrombocytopenia syndrome. Clin Infect Dis 57: 1292-1299.

11. Guo X, Zhang L, Zhang W, Chi Y, Zeng X, et al. (2013) Human antibody neutralizes severe Fever with thrombocytopenia syndrome virus, an emerging hemorrhagic Fever virus. Clin Vaccine Immunol 20: 1426-1432.

12. Lv M, Sun Y, Pei L (2013) Advances in Severe Fever with Thrombocytopenia Syndrome Bunyavirus. Journal of Microbiology 2: 025.

13. Jiao Y, Zeng X, Guo X, Qi X, Zhang X, et al. (2012) Preparation and evaluation of recombinant severe fever with thrombocytopenia syndrome virus nucleocapsid protein for detection of total antibodies in human and animal sera by double-antigen sandwich enzyme-linked immunosorbent assay. J Clin Microbiol 50: 372-377.

14. Li D (2013) A highly pathogenic new bunyavirus emerged in China. Emerg Microbes Infect 2: e1.

15. Wu X, Qi X, Liang M, Li C, Cardona CJ, et al. (2014) Roles of viroplasm-like structures formed by nonstructural protein NSs in infection with severe fever with thrombocytopenia syndrome virus. FASEB J 28: 2504-2516.

16. Hofmann H1, Li X, Zhang X, Liu W, Kühl A, et al. (2013) Severe fever with thrombocytopenia virus glycoproteins are targeted by neutralizing antibodies and can use DC-SIGN as a receptor for pH-dependent entry into human and animal cell lines. J Virol 87: 4384-4394.

17. Lozach PY, Kühbacher A, Meier R, Mancini R, Bitto D, et al. (2011) DC-SIGN as a receptor for phleboviruses. Cell Host Microbe 10: 75-88.

18. Ning YJ, Wang M, Deng M, Shen S, Liu W, et al. (2014) Viral suppression of innate immunity via spatial isolation of TBK1/IKKÎµ from mitochondrial antiviral platform. J Mol Cell Biol 6: 324-337.

19. Qu B, Qi X, Wu X, Liang M, Li C, et al. (2012) Suppression of the interferon and NF-κB responses by severe fever with thrombocytopenia syndrome virus. J Virol 86: 8388-8401.

20. Walter CT, Barr JN (2011) Recent advances in the molecular and cellular biology of bunyaviruses. J Gen Virol 92: 2467-2484.

21. Reguera J, Weber F, Cusack S (2010) Bunyaviridae RNA polymerases (L-protein) have an N-terminal, influenza-like endonuclease domain, essential for viral cap-dependent transcription. PLoS Pathog 6: e1001101.

22. Hofmann H, Li X, Zhang X, Liu W, Kühl A, et al. (2013) Severe fever with thrombocytopenia virus glycoproteins are targeted by neutralizing antibodies and can use DC-SIGN as a receptor for pH-dependent entry into human and animal cell lines. J Virol 87: 4384-4394.

23. Wu X, Qi X, Liang M, Li C, Cardona CJ, et al. (2014) Roles of viroplasm-like structures formed by nonstructural protein NSs in infection with severe fever with thrombocytopenia syndrome virus. FASEB J 28: 2504-2516.

24. Sun Y, Qi Y, Liu C, Gao W, Chen P, et al. (2014) Nonmuscle myosin heavy chain IIA is a critical factor contributing to the efficiency of early infection of severe fever with thrombocytopenia syndrome virus. J Virol 88: 237-248.

25. Zhou H, Sun Y, Wang Y, Liu M, Liu C, et al. (2013) The nucleoprotein of severe fever with thrombocytopenia syndrome virus processes a stable hexameric ring to facilitate RNA encapsidation. Protein Cell 4: 445-455.

26. Sun Y, Jin C, Zhan F, Wang X, Liang M, et al. (2012) Host cytokine storm is associated with disease severity of severe fever with thrombocytopenia syndrome. J Infect Dis 206: 1085-1094.

27. Jin C, Liang M, Ning J, Gu W, Jiang H, et al. (2012) Pathogenesis of emerging severe fever with thrombocytopenia syndrome virus in C57/BL6 mouse model. Proc Natl Acad Sci U S A 109: 10053-10058.

28. Liu Y, Wu B, Paessler S, Walker DH, Tesh RB, et al. (2014) The pathogenesis of severe fever with thrombocytopenia syndrome virus infection in alpha/beta interferon knockout mice: insights into the pathologic mechanisms of a new viral hemorrhagic fever. J Virol 88: 1781-1786.

29. Yu L, Zhang L, Sun L, Lu J, Wu W, et al. (2012) Critical epitopes in the nucleocapsid protein of SFTS virus recognized by a panel of SFTS patients derived human monoclonal antibodies. PLoS One 7: e38291.