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Current Opinion in Virology

Current status of Severe Fever with Thrombocytopenia Syndrome vaccine development

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Severe Fever with Thrombocytopenia Syndrome (SFTS) is a new emerging tick-borne disease caused by the phlebovirus, SFTS virus (SFTSV). The virus was discovered in central China in 2009 and has since been identified in both Japan and South Korea. Significant progress has been made on the molecular biology of the virus, and this has been used to develop diagnostic assays and reagents. Less progress has been made on the epidemiology, maintenance and transmission, clinical manifestations, immunological responses, and treatment regimens. A number of animal models have been investigated but, to date, none recapitulate all the clinical manifestations seen in humans. Vaccine development is at an early discovery phase.

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Current Opinion in Virology 2018, **29**:72–78

This review comes from a themed issue on **Preventive and therapeutic vaccines**

Edited by **Marc van Regenmortel** and **Martin Friede**

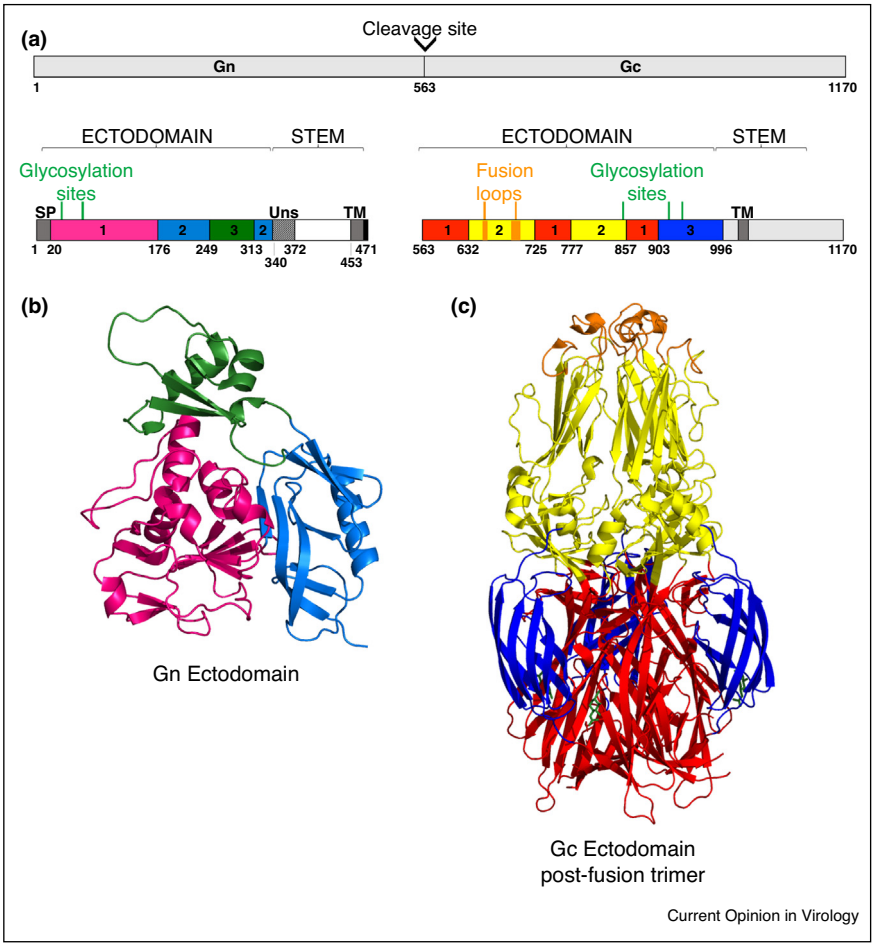
https://doi.org/10.1016/j.coviro.2018.03.005

SFTSV phylogenetics and virology

Severe Fever with Thrombocytopenia Syndrome (SFTS) is a disease caused by SFTS virus (SFTSV), a member of the order Bunyavirales, family *Phenuiviridae*, *Phlebovirus* genus. The phleboviruses are divided into two groups, the *Phlebotomus* fever and *Uukuneimi* virus (UUKV) groups that are transmitted by sandflies and ticks, respectively [1]. Upon phylogenetic analyses, it was determined that although SFTSV had been shown to infect ticks, it was distantly related to viruses from both the *Phlebotomus* fever and UUKV groups, indicating that it was part of a new group of phleboviruses [2,3•,4,5,6•,7–9]. There are at least five SFTSV genotypes, but there may be more as different papers are not consistent in nomenclature [6•,10–12,13•,14]. The virus is enveloped, approximately 80–100 nm diameter, and has glycoprotein (GP) spikes 5–10 nm long [4,6•,15,16]. The SFTSV genome is composed of 3 segments of negative-sense RNA: L — 6368 nucleotides (nts), M — 3378 nts, and S — 1744 nts. The L segment encodes the RNA-dependent RNA polymerase (RdRp); the M segment encodes two GPs: Gc and Gn, which likely form a complex on the surface of virions with Gc thought to lie at the membrane interface of the complex; and the S segment that encodes the nucleoprotein (NP) and the nonstructural protein (NSs) [6•,10,17–19]. NP participates in ribonucleoprotein (RNP) packaging [20], whereas NSs participates in inclusion body formation responsible for interfering with host interferon signaling [21,22].

Gn and Gc are derived by cleavage of a polyprotein precursor and both proteins are post-translationally modified to become glycosylated. Recently, there has been great progress in understanding the structure–function of phlebovirus glycoproteins. The structure of Rift Valley fever virus (RVFV) Gn and Gc (pre- and post-fusion structures), SFTSV Gn and post fusion Gc, and Heartland virus post-fusion Gc have been determined [23–27]. Both glycoproteins have multiple N-linked glycans that are likely involved in virus attachment and tissue tropism. For SFTSV, Gn corresponds to residues 1–562 and Gc to residues 563–1170 in the M segment polyprotein. Gn has three subdomains (I, II and III) with N-linked glycans at residues 33 and 63 in subdomain I, and is a target for neutralizing (NT) antibodies. Gc is a class II fusion protein that undergoes pH-dependent conformational rearrangements from a prefusion dimer form in free virions to a post-fusion trimer following the fusion of SFTSV with host membranes (Figure 1). The overall structure of Gc is similar to that of the E1 and E envelope proteins of *Togaviridae* and

Figure 1



SFTSV M-segment organization and structure. **(a)** The glycoproteins, Gn and Gc, are generated following cleavage of the M-segment at amino acid 563. Gn is organized into ectodomain and stem regions. The Gn signal peptide (SP), three discontinuous domains, unstructured region (Uns), and transmembrane (TM) region are depicted in the protein cartoon. Glycosylations at N33 and N63 are depicted by green lines. Gc contains an ectodomain of three discontinuous domains, with the fusion loops (orange lines) in domain II and glycosylation sites (green) in domains II and III, followed by a transmembrane (TM) region in the stem. **(b)** Rendering of the Gn head domain structure (pdb 5Y10) shows the three discontinuous domains: I (1, pink), II (2, marine blue), and III (3, forest green). **(c)** Gc exists as a dimer prior to fusion with the host cell, but a post-fusion conformational change leads to a trimer formation (rendering of pdb 5G47) with the discontinuous domains I (1, red), II (2), and III (3, blue) rearranging to expose the fusion loops (orange) located in domain II. Predicted glycosylation sites are depicted in green.

Flaviviridae, respectively. The SFTSV Gc ectodomain (N-terminal residues 563–996 with N-linked glycans at residues 853, 914 and 936) consists of three domains (EDI, EDII, and EDIII). Although the EDIII domain of flaviviruses is one of the critical neutralization antigenic sites on flaviviruses, no neutralizing antibodies against SFTSV have yet been mapped to the EDIII of Gc which may be linked to the fact that SFTSV EDIII is glycosylated at residues 914 and 936 while the flavivirus EDIII is not glycosylated.

SFTS epidemiology, clinical symptoms and diagnostics

The transmission cycle of SFTSV is poorly understood. *Haemaphysalis longicornis* is considered the primary vector [6•,28], but other tick species can transmit the virus. Vertebrate reservoir(s) have yet to be identified. Person-to-person transmission has also been reported, via direct contact with blood from infected individuals [9,29,30,31•]. The virus was discovered in central China in 2009 and has also been identified in both Japan and South Korea. Seroprevalence studies indicated approximately 4.3% of the Chinese population in endemic areas has been infected with SFTSV [6•,29,32–35]. From 2011–2016, ~1000–2500 Chinese SFTS cases were reported annually with a case fatality rate (CFR) of 5.3%. Peak outbreak months in China are May–July and farmers in endemic areas of hilly wooded environments are at greatest risk (87.6% of confirmed cases) of infection [6•]. Since