Crimean-Congo Hemorrhagic Fever Virus (CCHFV)

Subjects: Microbiology

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Crimean-Congo hemorrhagic fever virus (CCHFV) is an emerging TBV of the Nairoviridae family that causes serious disease that can be fatal in humans.

Keywords: CCHF ; epidemiology ; tick ; host ; outbreak

1. Introduction

Crimean-Congo hemorrhagic fever virus (CCHFV) is a tick-borne virus that causes moderate to severe hemorrhagic disease (Crimean-Congo hemorrhagic fever, CCHF) in humans with high case fatality ratios (up to 40%). The name is derived from the regions, where it was first reported (Crimea, 1945, and Congo, 1956). In terms of antigenicity, virus isolates from the two regions were indistinguishable [1]. CCHFV is transmitted to humans by bites of infected ticks (mainly species of genus *Hyalomma*) [2], but may also be transmitted to humans through contact with blood or tissue of infected animals, including human-to-human transmission in nosocomial settings [3]. The various vector species and the virus are widespread throughout the world, and endemic foci are absent only from North America, South America, and Australia. The transmission activity and distribution are dynamic, and both the virus and vector species have been introduced into new regions in recent years.

2. Etiological Agent and Biology

CCHFV is a member of the *Orthonairovirus* genus, family *Nairoviridae*, and order *Bunyavirales*. The 41 species of the genus are classified into seven serogroups based on antigenic relationships [4]. The CCHFV serogroup contains CCHFV, Hazara virus from Pakistan, and Khasan virus from eastern Russia. In addition to CCHFV, Nairobi sheep disease virus (NSDV) and Dugbe virus are the only members of the genus known to be pathogenic for humans. NSDV, a tick-borne virus (TBV) of sheep and goats that causes intermittent benign illness in humans in East Africa, is thought to be similar to Ganjam virus in India [5]. Dugbe virus is a TBV that is generally associated with mild infection in cattle and sheep in West Africa and causes benign human disease on rare occasion [6]. The nairoviruses were originally classified based on their antigenic relatedness; however, the groupings have later been substantiated through the demonstration of morphological and molecular affinities between the viruses [7] and through comprehensive full-length sequence analysis [8]. Namely, CCHFV, NSDV, Hazara virus, Dugbe virus, and Kupe virus likely form a genogroup, yet formerly were divided into two serogroups (CCHFV serogroup and NSDV serogroup) [8]. CCHFV appears spherical under an electron microscope, with a dense core (capsid) surrounded by a lipid envelope and protruding spikes, and a diameter of around 100 nm [4].

3. CCHFV Genome

The viral genome is trisegmented and is comprised of single-stranded negative sense RNA. The three genomic segments of CCHFV have conserved 3′ end sequences of 3′AGAG (A/U) UUCU and a complementary 5′ end sequence, allowing the vRNA to form a looped structure. The small (S) segment (approximately 1.6 kb) has a single open reading frame encoding the nucleocapsid (N) protein. The medium (M) segment (approximately 5.4 kb) encodes a large glycoprotein precursor (GPC), which is processed into the two transmembrane surface glycoproteins (Gn and Gc) and several non-structural proteins. The large (L) segment (~12.1 kb) encodes a single L protein of approximately 460 kDa—the viral RNA-dependent RNA polymerase. Virus invasion of cells is most likely accomplished by clathrin-mediated endocytosis mechanism, followed by fusion of the viral envelope with endosomal membranes. Since monoclonal antibodies targeting Gc can neutralize CCHFV infection in mammalian cells, Bertolotti-Ciarlet et al. suggested that Gc is responsible for binding to cellular receptors [9]. All stages of viral replication happen in the cell cytoplasm, although little is known of this mechanism. Similar to many enveloped viruses, CCHFV surface glycoproteins are highly N-glycosylated, and glycosylation is important for several protein functions, such as folding, cellular transport and virus infectivity [10].

As CCHFV is a negative-sense RNA virus, the first step in replication is the transcription of the viral genomic RNA (vRNA) into positive-sense complementary RNA (cRNA). Viral messenger RNA (mRNA) is formed from cRNA by cap-snatching from host mRNAs, and the positive-sense cRNA also functions as a template for genomic vRNA. Virion assembly occurs in the Golgi complex [11]. Genetic reassortment might occur in CCHFV, especially in endemic areas where several CCHFV variants are circulating at the same time [12]. Further, there is evidence of genetic recombination in the CCHFV genome, which increases the diversity of the CCHFV genome [13][14].

The three ribonucleoprotein segments, with RdRP attached, acquire their outer viral glycoprotein-rich envelope by budding into the Golgi lumen. The virions are then transferred to the cell membrane and released from the infected cell by exocytosis [15]. The environmental stability of CCHFV is unknown, but the enveloped virions are susceptible to lipid solvents, and infectivity is destroyed by low concentrations of formalin and beta-propiolactone. Although the virus is labile in infected human tissues after death, analysis of human patient specimens tends to show that infectivity is maintained for at least a few days in separated serum at room temperature. Autoclaving destroys infectivity, however the virus remains stable at temperatures below 60 °C [16].

CCHFV replicates in various cell lines, such as Vero, CER, SW13 and BHK21, but does not usually yield high titers [17]. The virus is poorly cytopathic in cell culture, so titers may be demonstrated by indirect immunofluorescence in infected cells [18]. Historically, CCHFV has been isolated and titers have been determined most frequently by intracerebral inoculation of suckling mice [19].

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