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Recent advances in research on Crimean-Congo hemorrhagic fever

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ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF) is an expanding tick-borne hemorrhagic disease with increasing human and animal health impact. Immense knowledge was gained over the past 10 years mainly due to advances in molecular biology, but also driven by an increased global interest in CCHFV as an emerging/re-emerging zoonotic pathogen. In the present article, we discuss the advances in research with focus on CCHF ecology, epidemiology, pathogenesis, diagnostics, prophylaxis and treatment. Despite tremendous achievements, future activities have to concentrate on the development of vaccines and antivirals/therapeutics to combat CCHF. Vector studies need to continue for better public and animal health preparedness and response. We conclude with a roadmap for future research priorities.

1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is characterized by fever and hemorrhagic manifestations with fatality up to 30% [1]. It is endemic in focal areas in Asia, Europe and Africa, with geographic distribution following that of *Hyalomma* ticks, the main vectors of CCHF virus (CCHFV). Apart from the bite of an infected tick (Fig. 1), the virus can be transmitted to humans by direct contact with blood or tissues of viremic patients or animals. Nosocomial and intra-family transmission have been reported [2,3,4].

The disease typically presents with an incubation phase (1–9 days), prehemorrhagic and hemorrhagic phases (in severe cases), and convalescence [5]. The hemorrhagic manifestations range from petechiae and epistaxis to extended ecchymosis and bleeding from various systems (Fig. 2).

CCHFV (genus *Nairovirus*, family *Bunyaviridae*) is an enveloped single-stranded negative sense RNA virus with a tri-segmented genome consisting of a small, medium and large RNA segments, encoding for the nucleocapsid protein (N), the glycoproteins Gn and Gc and the RNA-dependent RNA polymerase, respectively. CCHFV is characterized by a great genetic variability with complex evolutionary patterns [6]. Due to its high pathogenicity and the lack of approved vaccines and specific intervention strategies, CCHFV must be handled under biosafety level 4 (BSL-4) containment. The recent emergence of CCHFV causing either sporadic human infections [7,8] or epidemics in previously unaffected areas [9,10], has raised animal and public health concerns. As a result, great progress has been made in CCHF pathogenesis, diagnostics and epidemiology/ecology, while efforts are underway to design effective vaccines and treatment strategies including antiviral and immunotherapeutic compounds. This article summarizes and discusses the progress in the field over the past decade and identifies knowledge gaps and future research perspectives.

2. Advances in eco-epidemiology

CCHFV is maintained in nature by ixodid ticks mainly of the genus *Hyalomma* [11,12]. Additional tick species from the genera *Dermacentor*, *Boophilus*, *Amblyomma*, *Rhipicephalus*, and *Haemaphysalis*, have been implicated in harboring CCHFV in the field or were shown to be experimentally infected, but there is little evidence for a role of these species in natural transmission or maintenance of CCHFV [13]. Thus, it appears that *Hyalomma* ticks are necessary for the maintenance of active CCHFV foci even during

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periods of enzootic or silent activity. Studies on the vectorial abilities of soft ticks (family *Argasidae*) confirmed that these ticks cannot transmit the virus despite getting infected while feeding on viremic hosts and detectable virus in blood remnants [14]. Thus, reports on the vectorial capacity of other ticks are unreliable and less convincing [15–17]. Detection of CCHFV RNA in those tick species is likely the result of virus uptake while feeding on viremic hosts.

In addition to the fundamental role played by the presence and abundance of the most prominent tick vectors, an adequate density of reservoir hosts seems to be necessary in order to reach a critical transmission rate of CCHFV [12,18]. For other tick-borne diseases, such as tick-borne encephalitis or Lyme disease, it has been speculated that changes in host abundance, social habitats, economic fluctuations, environmental conditions, and to a lesser extent climate, have increased the disease incidence rate [19–22]. Climate change, however, has been frequently linked to CCHF outbreaks. The development of a process-driven model for *H. marginatum*, the main vector in the Mediterranean region [23], has provided an adequate framework to study the impact of climate features on virus spread by the tick vector in an endemic area [24] and to evaluate the effect of host abundance on viral transmission [25]. It has been proposed that such study should precede the active surveillance of the tick vectors [26]. Results from modeling approaches indicated that the Balkans are the area in the Mediterranean basin where climate trends might have a larger impact on the spread of *H. marginatum* [24]. The modeling study provided evidence that the most important factor for increased transmission of CCHFV might be the increased abundance of large hosts (e.g. wild and domestic ungulates), on which adult ticks feed, thus, allowing further amplification through transovarial transmission [24]. Further field surveys investigating the infestation and infection rates of different wild animals (mammals and birds) would enable a better understanding of the virus transmission cycle.

In the past years, the importance of habitat fragmentation and its consequences in the maintenance of active CCHFV foci have been discussed. There is evidence that a fragmented landscape with multiple smaller patches of vegetation within a matrix of unsuitable tick habitat, may lead to isolated populations of both ticks and hosts producing an amplification cycle with ticks feeding on infected hosts [27]. Due to the isolation of these host populations, the local movements of hosts are limited, and, therefore, new naive animals carrying uninfected ticks do not dilute the prevalence rate in the isolated patch [27]. For CCHFV eco-epidemiology, the degree of habitat patchiness contributes to the increased contact rate among reservoir hosts, humans, and ticks.

3. Advances in basic virology

Humans are the only known host that develops disease after CCHFV infection. The major pathological abnormalities of CCHF are related to vascular dysfunction resulting in hemorrhagic manifestations largely driven by erythrocyte and plasma leakage into the tissues [28]. Endothelial damage can contribute to coagulopathy by deregulated stimulation of platelet aggregation, which in turn activates the intrinsic coagulation cascade, ultimately leading to clotting factor deficiency and hemorrhages. Vascular leakage may be caused either by destruction of endothelial cells or by a disruption of the endothelial cell junctions. It is still unknown whether vascular dysfunction is due to a direct effect of virus on the endothelial cells or a consequence of a cytokine storm. In fact, for other hemorrhagic fever viruses, such as Ebola and Dengue viruses, there is a correlation among the level of the pro-inflammatory response, vascular leakage, and disease severity [29–33]. Key players in disease progression are interleukin (IL)-10, IL-1, IL-6 and tumor necrosis factor-a (TNF-a) [32]. *In vitro* studies showed that CCHFV replicates in human dendritic cells and macrophages resulting in the release of TNF-a, IL-6 and IL-8, which then can activate endothelial cells *in vitro* [34,35]. In contrast to milder CCHF cases, elevated levels of pro-inflammatory mediators (such as TNF-, IL-6, IL-10) and serum markers of vascular activation (sICAM-1 and sVCAM-1) have been detected in fatal CCHF cases [36–38]. These clinical observations are mirrored in an *in vitro* experiment, in which it was demonstrated that CCHFV infected endothelial cells can up-regulate ICAM-1 and VCAM-I [39]. It was shown that CCHFV induces apoptosis *in vitro* late post infection in human target cell lines [40,41]. This suggests that CCHFV may induce plasma leakage from the vessels and cause loss of lymphocytes by apoptosis. However, it remains unclear whether induction of apoptosis is due to direct effects of virus replication or to indirect effects induced by certain pro-inflammatory mediators known to induce apoptosis.

An efficient and rapid host response against virus invasion is the production of type I interferons (IFN-a/b). Besides their role as antiviral messengers, IFNs posses a wide range of biological activities including inhibition of cell proliferation, regulation of

Fig. 1. Tick on the back of a patient.

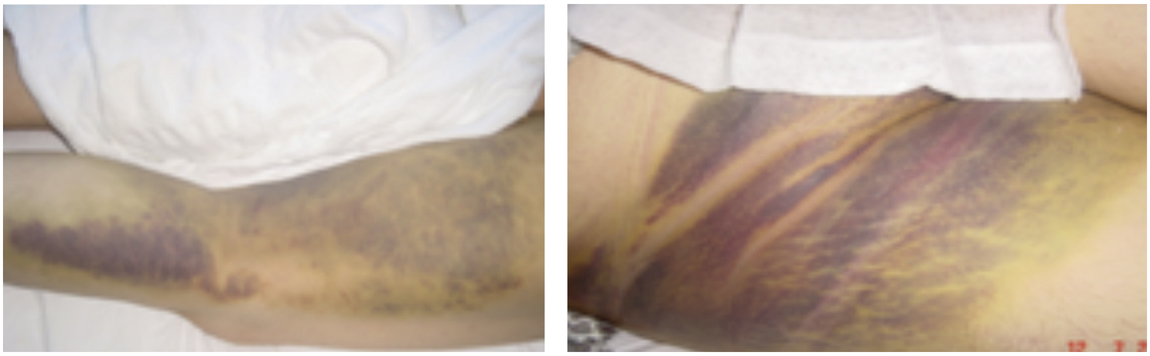

Fig. 2. A patient with Crimean-Congo hemorrhagic fever presenting ecchymosis on the right lower extremity and the pelvic area.

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