Zoonoses and Emerging Viruses

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Isolation and characterization of a cowpox virus derived from its supposed natural rodent reservoir host

Julia Schluckebier[1], Donata Kalthoff[1], Rainer Ulrich[1], Maria Jenckel[1], Bernd Hoffmann[1], Martin Beer[1]

[1]Friedrich-Loeffler-Institut - Insel Riems

Poxviruses have plagued human mankind for more than ten thousand years and claimed the lives of millions. Although the WHO declared smallpox, the deadliest poxvirus, eradicated in 1980, infections with closely related *orthopoxviruses* are still reported. Notably, cowpox virus infections saw a steep rise in recent years. Cowpox virus (CPXV) enters the human population mostly via direct contact to companion animals, especially cats and pet rats. Serological findings, however, have pointed to wild rodents as the main virus reservoir. Yet the actual isolation of CPXV from this source has hardly ever been achieved. As further proof for the reservoir hypothesis we present here a CPXV strain isolated from the liver of a feral common vole (*Microtus arvalis*).

First, we used next generation sequencing to obtain the full-length DNA sequence of this CPXV strain and compared it with a reference CPXV isolated from a 2009 pet rat/human outbreak in Germany that showed high virulence in the affected animals. We then characterized the pathogenicity of the vole strain in its natural host as well as in Wistar rats. Both the common voles and the Wistar rats were experimentally inoculated with high and low titers of the wild vole isolate. Another group of voles was also infected with the 2009 CPXV rat strain. The vole strain caused no to only mild clinical symptoms in its natural host, while all Wistar rats developed respiratory symptoms followed by rashes. Common voles infected with a high titer of the rat strain virus showed severe signs of respiratory disease but no skin lesions, whereas infection with the low titer lead to excretion of virus but with reduced clinical signs.

This study reveals the susceptibility of the common vole to different CPXV strains - ranging from a well-adapted virus, which causes only slight clinical symptoms in the host organism, to a highly virulent strain. The low pathogenicity of the vole isolate in its eponymous host also provides evidence for the common vole actually being a reservoir for CPXV. Combined with full genome data and the Wistar rat model, virulence studies in the common vole will facilitate future research on the correlation of genotype and pathotype of CPXV infections as well as the epidemiological role of the rodent reservoir and the zoonotic risk that emanates from these viruses.

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Detection of Bas-Congo virus-specific antibodies in individuals from the Republic of the Congo

Imke Steffen[1], William M. Switzer[2], Sentob Saragosti[3], Charles Y. Chiu[4], Graham Simmons[1]

[1]Blood Systems Research Institute; Department of Laboratory Medicine, University of California San Francisco; [2]Centers for Disease Control and Prevention; [3]Inserm U941; Université Paris Diderot; [4]Department of Laboratory Medicine, University of California San Francisco; Ucsf/Abbott Viral Diagnostics and Discovery Center

Using next-generation sequencing, the novel rhabdovirus Bas-Congo virus (BASV) was identified in a serum sample from a patient with hemorrhagic fever in the Democratic Republic of the Congo (DRC). However, attempts to culture the virus from the serum sample failed. Neutralizing antibodies specific for the BASV glycoprotein and antibodies against the BASV matrix (M) and nucleoproteins (N) could be detected in convalescent sera of the patient and one asymptomatic contact. To elucidate the penetration of this likely zoonotic viral infection into the human population in Africa, as well as the probable rate of asymptomatic or mild infections we are performing the first extensive serosurvey for this new, and potentially important, rhabdovirus. We developed a pseudotype neutralization assay based on glycoprotein-deficient vesicular stomatitis virus (VSV) and adapted it for high-throughput serology screening. The glycoproteins of the related rhabdoviruses VSV and Kotonkan virus serve as negative controls for pseudotype neutralization. As a confirmatory assay we generated recombinant BASV M and N proteins with a vaccinia/T7 driven mammalian expression system and used the purified proteins in an indirect enzyme-linked immunosorbent assay (ELISA) for the detection of BASV M or N specific antibodies. To date more than 600 human serum samples from the Central African countries of Ghana, Cameroon, Republic of the Congo, DRC and Uganda have been screened for the presence of BASV-specific antibodies. We identified six samples with pseudotype neutralization activity in a cohort from Nkayi, Republic of the Congo and four of the six samples were confirmed to be reactive against BASV N protein by ELISA. This is the first report of an apparent exposure to BASV outside the DRC and could indicate a broader geographic range of the virus. Our large and widespread serological survey will determine the importance of BASV as a human virus in Central Africa. It is possible that BASV or related viruses could be partially responsible for the high incidence of hemorrhagic fever with unknown etiology in the area.