

The Contribution of Autoimmunity to Long-Term Sequelae in Viral Hemorrhagic Fever Survivors

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Introduction

There is a wide variety of genetically distinct viruses able to induce viral hemorrhagic fever (VHF) in infected individuals. These viruses, including Ebola (EBOV), Lassa (LASV), Dengue (DENV) and Crimean-Congo hemorrhagic fever (CCHF) virus, are all feared for their ease of acquisition in relation to the small doses required to initiate disease and the symptoms associated with lethal infections. As a result, emphasis has been on the prevention and treatment of these diseases [1]. However, a large proportion of individuals surviving these infections faces long-term, sometimes permanent, sequelae. Unfortunately, the breath and underlying causes of these long-term symptoms are often poorly understood. For example, CCHF survivors take up to a year to fully recover following viral clearance [2]. To our knowledge, there are no published follow up studies on the spectrum of symptoms afflicting CCHF survivors. In contrast, hearing loss in LASV virus survivors, as well as various illness such as myalgia, arthralgia, mental confusion and ocular diseases in EBOV and DENV survivors has been well documented [3-9]. However, the causes of these persistence illnesses in survivors remain unknown.

Although no definitive proof is available, some observations from clinical and experimental evaluations suggest that autoimmunity may contribute to the long-term symptoms observed in many EBOV and DENV survivors. Elevated level of inflammatory markers such as C-reactive protein and immune complex have been described in more than 40% of survivors after symptomatic DENV infection [9]. Furthermore, autoantibodies were also detected in humans surviving DENV or EBOV infection. The level of these antibodies rise within days after symptoms onset. However, elevated autoantibody titers in peripheral blood are transient. Autoantibody levels decrease 1-3 weeks after the acute phase and drop close to background level within months [10-13]. Various mechanisms can trigger the production of these autoantibodies in EBOV and DENV survivors. Antigen mimicry between DENV virus envelop (E), non-structural (NS1) or precursor membrane (prM) proteins and various self-antigens is responsible for autoantibodies production in infected individuals [14]. Toll like receptor (TLR) stimulation of B cells by

cell-free DNA and released of sequestered antigens from dying cells is thought to drive autoantibodies induction in EBOV survivors [13]. Liver damage and to a lesser extent spleen and kidney necrosis are common features of severe VHF infections suggesting that autoantibodies induction is not restricted to EBOV or DENV survivors [15-19]. Additional studies are needed to determine whether disease severity correlates with autoantibody induction in VHF survivors. Research on DENV survivors indicate that autoantibody production is restricted to symptomatic infections [9].

Autoantibodies against various autoantigens including heat shock protein (HSP) 60 and double stranded (ds) DNA in EBOV survivors as well as endothelial cells, platelets and blood clotting molecules in DENV survivors have been described [13,14,20]. As not all autoantibodies are pathogenic [21], autoantibodies contribution to long-term sequelae in VHF survivors largely remains to be demonstrated. Indeed, research on DENV-induced autoantibodies has primarily focused on their pathogenic role during acute infection including liver damage and coagulopathy rather than long-term sequelae [20,22,23]. Correlation between level of autoimmune mediators and severity of long-term symptoms must first be established in VHF survivors prior to any clinical intervention. To do so, sera from survivor cohorts representing the full spectrum of these long-term sequelae are needed. Due to the contraction of the humoral response, samples collected within weeks following viral clearance would be needed for autoantibodies measurement. Unfortunately, such biobanks for VHF survivors do not currently exist. Since the 2014-2016 EBOV outbreak, African experts and international partners have been tackling the legal hurdles and infrastructure gaps needed to generate well curated biobanks of EBOV and LASV survivor samples [24]. Once generated, these biobanks containing survivor samples annotated with the severity of post VHF sequelae will be crucial in determining the contributions of autoimmunity in post VHF long-term symptoms.

In addition to autoantibodies, auto-reactive T cells may also contribute to long-term sequelae in VHF survivors. Unfortunately, measuring auto-reactive T cells frequency in peripheral blood can be challenging especially if the target

antigens or epitopes have not been identified [25]. Alternatively, association between specific MHC alleles and severity of post VHF long term sequelae could be investigated to inform on the role of autoreactive T cells in long-term symptoms in VHF survivors [26].

Conclusion

VHF survivors suffer from a variety of long-term sequelae following viral clearance from the circulation. Various studies also indicate the presence of autoantibodies in EBOV and DENV survivors. Clinical studies are therefore required to demonstrate that autoantibodies induction is frequent post VHF infections and to confirm autoimmunity as a causative agent of the long-term clinical diseases observed in VHF survivors. Clinical follow up of VHF survivors as well as the creation of biobanks containing annotated samples from these survivors will be paramount in better defining long-term sequelae in VHF survivors and in understanding their origins.

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