HANTAVIRUS AND ITS ASSOCIATED IMMUNOPATHOGENESIS

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ABSTRACT:

Hantavirus is a zoonotic virus manifesting two vital clinical symptoms viz., hemorrhagic fever with renal syndrome and cardiopulmonary syndrome. With a sudden onset of fatigue, fever, and body aches, in extreme cases can lead to shortness of breath and had resulted in major outbreaks in past decades. Pro-inflammatory cytokine responses and reticulo endothelial systems take the lead role in establishing the immuno-pathogenesis of the hantavirus disease. The virus genome consists of these segments of negative stranded RNA, where the large (L) segment encodes the viral RNA polymerase, the medium (M) segment the glycoprotein precursor which is co-translationally cleaved into the envelope glycoproteins Gn and Gc, and the small (S) segment the nucleocapsid protein (N). Hantavirus are divided into Old world and New world hantavirus based on the geographic regions in which they occur. They are strictly associated with their reservoirs hosts which are rodents, but from recent researches reported, also insectivores. Both innate and cellular immune responses function effectively in evading the viral replication, however the mutations and the typical variations in the virus finally establishes a disease in humans. This review thus provides an overview on hanta virus and its associated immune-pathogenesis.

KEYWORDS: Hantavirus , Immunopathogenesis, Viral replication, hosts, UUV , rodents - reservoirs .

INTRODUCTION:

Hantavirus are negative sense RNA viruses belonging to the Bunyaviridae family (Krüger, Schönrich, and Klempa 2011). The virus genome consists of these segments of negative stranded RNA, where the large (L) segment encodes the viral RNA polymerase, the medium (M) segment the glycoprotein precursor which is co-translationally cleaved into the envelope glycoproteins Gn and Gc, and the small (S) segment the nucleocapsid protein (N) (Shahzan et al. 2019). Hantavirus are divided into Old world and New world hantavirus based on the geographic regions in which they occur (Terajima et al. 2007). Phylogenetic trees based on the genomic RNA sequences form 3 main groups - Hantaan virus like viruses, Puumala virus like viruses and the Sin Nombre virus (SNV) like viruses (Vijayashree Priyadharsini, Smiline Girija, and Paramasivam 2018). (Priyadharsini et al. 2018). They are strictly associated with their reservoirs hosts which are rodents, but from recent researches reported, also insectivores (Terajima et al. 2007). These are emerging viruses hosted by small mammals. When transmitted to the humans, they cause 2 main clinical symptoms - hemorrhagic fever with renal syndrome or hantavirus cardiopulmonary syndrome (Lee and van der Groen 1989, Paramasivam, Vijayashree Priyadharsini, and Raghunandhakumar 2020).

The Old world hantaviruses, including Hantaan, Seoul , Dobrava and Puumala viruses which are seen throughout Europe and Asian countries, which causes a human disease known as hemorrhagic fever with

renal syndrome (HFRS) with more than 100,000 cases diagnosed annually (Smiline, Vijayashree, and Paramasivam 2018). HFRS are generally characterised by non specific Flu-like symptoms followed by thrombocytopenia and a capillary leak syndrome with hemoconcentration (Schmaljohn and Hjelle 1997). The New world hantavirus includes SNV and Andes virus, and are seen in the North, central and South America spectrum of hantavirus infection hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (Peters, Simpson, and Levy 1999). The pathology seen with Old world hantavirus focuses on the kidney, but the major target organ for the New world hantaviruses is the lung (Cheung, Shuk-ling, and Cheung n.d., Girija, Jayaseelan, and Arumugam 2018, Girija et al. 2019). Beta 3 integrin is a cellular receptor for human pathogenic hantaviruses (Gavrilovskaya et al. 2002). Hantaviruses infection did inhibit beta 3 integrin directed migration of endothelial cells, which might contribute to hantavirus pathogenesis (Gavrilovskaya et al. 1998). Infected monocytes / macrophages also contribute to immunopathogenesis by TNF-alpha production (Niikura et al. 2004). Until recent decades, not much studies were available with a vivid picture on the immuno-pathogenic mechanism of hanta virus and its associated viruses(Ashwin and Muralidharan 2015). This review thus highlights the same to provide an intimate knowledge on various immunological mechanisms related to hanta viral disease.

Immunopathogenesis of hantavirus

Clinical findings in in vitro experiments were increased capillary permeability of both Hantavirus cardiopulmonary syndrome (HCPs) and Hemorrhagic fever with renal syndrome (HFRS) caused by hantavirus-specific cytotoxic T cells that target endothelial cells with viral surface benefits (Niikura et al. 2004). In HPSand HFRS patients, the down-regulating mechanism for CD8 + T Cell activation and cytolysis for endothelial cell protection may be overwhelmed by the excess amount of activated CD8 + T cells, which appears to occur in HPS (Kilpatrick et al. 2004). Due to endothelial cell infection the protective mechanisms may not function properly (Bhargava, Shashikala, and Bhargava 2015). The down-regulating mechanism for CD8 + T Cell activation and cytolysis for endothelial cell defense in HPSand HFRS patients may be overwhelmed by the excess amount of activated CD8 + T cells that appears to occur in HPS (Spiropoulou et al. 2007). The protective mechanisms may not function properly, due to endothelial cell infection (P.S.Karthikeyan et al. 2017). Delayed production of antiviral responses in hynas may help to replicate pathogenic hantaviruses more effectively than non pathogenic hantaviruses (Kraus et al. 2004). Despite delayed Type 1 IFN induction, human cells mount antiviral intake responses that may also contribute to viral clearanceIn rat lungs with high amounts of vitus (Pratha, Ashwatha Pratha, and Geetha 2017), pattern recognition receptor expression is reduced or remains unchanged during SEOV infection, indicating that viral recognition inhibition can contribute to persistent infection (Hannah, Bajic, and Klein 2008). In contrast, a peripheral immune organ that supports low levels of virus in spleen increases the production and synthesis of proinflammatory and antiviral factors during acute SEOV infection, and is then restored to baseline (Klein, Glass, and Bird 2001, Ludert, Pujol, and Arbiza 2017). Mices as well as natural hantavirus rodent reservoirs do not develop any HPS or HFRS-like disease, which suggests that these specific T cells are positive, not immunopathogenic in mice (Meurant 2001, Rasmuson et al. 2011).

Hantavirus as a human pathogen and rodents as reservoirs:

Hantaviruses are emerging zoonotic viruses in Africa, America, Asia, and Europe (Hammerbeck, Wahl-Jensen, and Hooper 2009) that caused human disease. Fatigue, fever and body aches in extreme conditions contribute to shortness of breath, coughing, etc (Mertz et al. 2006) are the most common symptoms. Transmission of this virus from the most common reservoirs-rodents to humans occurs through aerosolized urine, saliva, and feces inhalation (Marickar, Geetha, and Neelakantan 2014). This mode of transmission is assumed to predominate between host animals reservoirs as well as for accidentally infected humans. Hantavirus are known to replicate in endothelial cells of the human umbilical vein and

can produce both pathogenic and non-pathogenic strains (Ferrés et al. 2007). HFRS-related hantaviruses cause cerebral hemorrhage and kidney failure-havetaviruses associated with HPS cause acute pulmonary edema (Castillo et al. 2004). Hantaviruses have spread more than 150,000 causes of HFRS and HPS worldwide which are reported annually (Terajima and Ennis 2011). Human beings are usually regarded as dead end ghosts that do not further transmit the virus; ANDV is the only hantavirus that has been documented for transmission of persons (Chaparro 1998).

As a result of the increased wildlife research, the variety of wild animals contaminated with hantaviruses has only recently come into view(*Website* n.d.). More than 80 known reservoirs belong to 51 rodent species, 7 bats and 20 shrews and moles(de Oliveira et al. 2014, *Website* n.d.). Within the genus of hantavirus, more than 80 genetically-related viruses have been identified, 25 recognized as human pathogens responsible for the broad range of diseases in the Old World and New WorldIn Brazil, where the diversity of mammals and particularly rodents is considered one of the largest genotypes in the world, 12 rodent species belonging to the genus Akondon, colornys, Holochilus, oligoryzomys, Oxymycterus, Necromys and Rattus have been described (de Oliveira et al. 2014). Following characterization of the Hantaan Virus prototype in human samples and the Apodemus agrarius rodent reservoir, other species linked to HFRS were identified in Eurasia, such as puumala Seoul and Dobrava-Belgrade. The species Dobrava-Belgrade is believed to be responsible for the bulk of Old World hantavirus deaths (Brummer-Korvenkontio et al. 1980). Hantavirus in the rodents Microtus Pennsylvanicus and Rattus norvegicus has been known to circulate in the Americas since the 1980s (Lee et al. 1985). Rodents possess an impaired immune mechanism against hantaviruses making them to survive as a reservoir and can transmit the virus to humans due to any spillover from its habitat(Smiline, Vijayashree, and Paramasivam 2018).

Puumala and other hantavirus infections

The Puumala virus is a borne rodent-a disease spread by bank voles(Girija et al. 2020). In humans with renal syndrome (HFRS) (24), PUUV infection triggers epidemic nephropathy, a moderate type of hemorrhagic fever(Vaishali and Geetha 2018). Puumala virus is classified as the Arvicolinae-related Phylogroup of 4 Hantaviruses, and the natural host of PUUV is bank vole (1). Puumala virus is the most prevalent hantavirus in Germany which causes an outbreak of nephropathy (NE); bank voles are the main reservoir. Many NEW cases reported from German occurred in the southwestern state of Baden Wurttemberg during the period 2001-2007 (24). PUUV 's primary rodent source is the bank vole, which extends in southern Europe from Scandinavia to Italy and Spain (25). Factors considered in favor of bank vole habitat were collected from the Baden-Württemberg Forest Research Institute prior to research assessing the percentage of land cover for 5 covariates suggested as preferred habitat for bank voles in Europe-beech trees, seedlings, bilberries, dwarf shrubs and black berries (26). Outdoor activities can also lead to making PUUV vulnerable to human peri-domestics((*Website* n.d., Shahana and Muralidharan 2016). A case-control analysis conducted in Baden Wurttemberg in 2007 found that, when visiting or dreaming human shelters in the forest, the risk of disease acquisition increased (27) among other factors.

Major epidemics and pandemics caused by Hantavirus with its impact

Two major disease outbreaks in the past century led to the discovery of hantaviruses in both the Old and New Worlds(Selvakumar and Np 2017). The first epidemic occurred during the Korean War (1950 to 1953), in which more than 3,000 United Nations soldiers became ill with Korean hemorrhagic fever, generally referred to as Renal Syndrome Hemorrhagic Fever (RSHF) (Jonsson, Figueiredo, and Vapalahti 2010). In 1993, the second outbreak of disease occurred in the United States' Four Corners area and was originally referred to as Four Corners disease, now called hantavirus pulmonary syndrome (HPS), or hantavirus cardiopulmonary syndrome (HCPS). These viruses can cause serious human diseases and in

some outbreaks have reached death rates of 12 percent (HFRS) and 60 percent (HPS). In 1978, almost 25 years after HFRS was identified, Lee et al reported the etiologic agent for this disease, Hantaan virus (HTNV), and its reservoir, the striped field mouse (Apodemus agrarius) (Lee, Lee, and Johnson 1978). It was discovered in the 1980s that urban cases of HFRS were caused by rat-borne Seoul virus (SEOV) in Asia, and in Europe, nephropathy epidemic (NE), a milder form of HFRS described in the 1930s, was found to be caused by another hantavirus, Puumala virus (PUUV), harbored by bank vole, Myodes glareolus (formerly known as Clethrionomys glareolus) (Kim et al. 1995, Hansen 2018). The discovery of these hantaviruses has led to the understanding that there could be as many as 150,000 HFRS cases per year worldwide, with more than half occurring in China (Lee 1996), (Mulic and Ropac 2003). Reporting an infection with hantavirus to health authorities in Germany has been compulsory since 2001. Fewer than 450 cases per year were registered during these years, with the exception of outbreaks in 2007 and 2010, with 1688 cases and 2017 cases, respectively. The number of infections began to rise as of October 2011, and cases have accumulated rapidly since spring 2012. Males are over-represented, and make up about 70% of events. The majority-infected age group ranges from 40 to 49 years old (Krautkrämer, Kruger, and Zeier 2012)

CONCLUSION :

Conclusively, hantaviruses were known to cause a chronic infection with no apparent harm to their natural hosts that are the small mammals. They are strictly associated with their reservoirs hosts which are rodents and can transmit the infection to humans during spillovers. Hantaviruses being associated with major outbreaks in the past decades, a critical knowledge on its pathogenic mechanisms is necessary to prevent future pandemics or epidemics. In this concern, this review had highlighted an overview on hantaviruses and its associated immuno-pathogenic mechanisms. The review also urges the need for the discovery of novel drugs and vaccines against hantaviruses in the near future.

AUTHOR CONTRIBUTIONS:

Ananya.R

Execution of the work

1. Data collection
2. Drafting of manuscript

Smiline Girija AS

1. Concept and Design of the study
2. Validation of the Data collection
3. Revision and proof- reading of the review

Ezhilarasan

1. Validation of the Data collection
2. Revision and proof- reading of the review

CONFLICT OF INTEREST : None to Declare

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