



Orthohantavirus Pathogenesis and Cell Tropism

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Orthohantaviruses are zoonotic viruses that are naturally maintained by persistent infection in specific reservoir species. Although these viruses mainly circulate among rodents worldwide, spill-over infection to humans occurs. Orthohantavirus infection in humans can result in two distinct clinical outcomes: hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). While both syndromes develop following respiratory transmission and are associated with multi-organ failure and high mortality rates, little is known about the mechanisms that result in these distinct clinical outcomes. Therefore, it is important to identify which cell types and tissues play a role in the differential development of pathogenesis in humans. Here, we review current knowledge on cell tropism and its role in pathogenesis during orthohantavirus infection in humans and reservoir rodents. Orthohantaviruses predominantly infect microvascular endothelial cells (ECs) of a variety of organs (lungs, heart, kidney, liver, and spleen) in humans. However, in this review we demonstrate that other cell types (e.g., macrophages, dendritic cells, and tubular epithelium) are infected as well and may play a role in the early steps in pathogenesis. A key driver for pathogenesis is increased vascular permeability, which can be direct effect of viral infection in ECs or result of an imbalanced immune response in an attempt to clear the virus. Future studies should focus on the role of identifying how infection of organ-specific endothelial cells as well as other cell types contribute to pathogenesis.

Keywords: orthohantavirus, hantavirus, hemorrhagic fever with renal syndrome, hantavirus cardiopulmonary syndrome, tropism, endothelium, pathogenesis

INTRODUCTION

The genus of orthohantaviruses in the family of *Hantaviridae* comprises emerging zoonotic negative-sense RNA viruses belonging to the recently reclassified order of *Bunyvirales* (Abudurexiti et al., 2019). Orthohantavirus strains are closely associated with specific rodent species or insectivores, as their natural reservoir hosts (Plyusnin and Morzunov, 2001; Zhang, 2014). Orthohantaviruses generally cause asymptomatic persistent infections in their reservoirs, and transmission between reservoir species primarily occurs via aerosolized urine, although wounding may also play a role in rodent-to-rodent transmission due to the presence of infectious virus in saliva (Glass et al., 1988; Kariwa et al., 1998). Some orthohantaviruses are capable of causing disease in humans following inhalation of aerosolized excreta from infected rodents (Lee and Johnson, 1982). Humans are considered dead-end hosts as they generally do not spread infectious

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virus efficiently. Although limited person-to-person transmission has been reported for Andes orthohantavirus (ANDV) (Padula et al., 1998; Martinez-Valdebenito et al., 2014). According to estimations, more than 20,000 annual cases of orthohantavirus-related disease occur worldwide with case fatality rates up to 40% (Schmaljohn and Hjelle, 1997; Alonso et al., 2019). To date, no United States Food and Drug Administration (FDA)– or European Medicines Agency (EMA)—approved specific treatments or vaccination strategies exist.

Orthohantaviruses can be divided into Old- and New World viruses due to the geographic distribution of their reservoir species with the exception of the worldwide presence of an Old World rodent: the wild rat. Currently, over 50 species of orthohantaviruses are known of which at least 24 are able to cause disease in humans (Jonsson et al., 2010; Reusken and Heyman, 2013; de Oliveira et al., 2014; Jiang et al., 2017). Clinical outcomes and disease severity in human cases largely depend on the virus species. Following respiratory transmission, orthohantaviruses can cause two distinct clinical outcomes, depending on the virus strain: hemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HCPS) (Hjelle and Torres-Perez, 2010; Jonsson et al., 2010).

Orthohantavirus pathogenesis is complex and the exact pathological mechanisms remain unknown. In general, pathogenesis seems to be associated with dysregulation of hemostasis, immune responses, and vascular permeability during infection due to infection of endothelial cells (ECs) lining the walls of blood vessels (Jonsson et al., 2010; Mackow et al., 2014). Immunopathology likely plays an important role in the development of disease (Rasmuson et al., 2016). In rodent reservoir hosts pro-inflammatory and antiviral immune responses are locally suppressed (e.g., by regulatory T cell responses) to establish viral persistence, without developing disease (Easterbrook et al., 2007; Schountz et al., 2007; Easterbrook and Klein, 2008a), suggesting that a lack of such regulation in humans may result in disease.

Studies into the pathogenesis of orthohantaviruses in humans have been hampered by the limited availability of clinical samples. Patient samples from the acute phase are frequently unavailable as incubation periods can take up several weeks before patients display clinical symptoms and orthohantavirus infection is often underdiagnosed (Goeijenbier et al., 2014; Sane et al., 2014). Therefore, animal models to study experimental infections are crucial in understanding the early steps in the pathogenesis of HFRS and HCPS. Unfortunately, development of laboratory animal models which recapitulate the clinical presentation of human infections has proven to be challenging. There are a very limited number of animal models to study orthohantavirus-induced disease, as reviewed in Golden et al. (2015). To date, the best characterized experimental infection model of *nephropathia epidemica* (NE; a mild form of HFRS) is Puumala orthohantavirus (PUUV) infection in non-human primates (NHP) exhibiting renal symptoms including transient proteinuria and microhematuria together with viral antigen distribution similar to that seen in human cases (Groen et al., 1995), while experimental *in vivo* models for HFRS remain largely unsuccessful in recapitulating the disease seen in humans

(Golden et al., 2015). The best characterized HCPS disease models are ANDV infection in Syrian hamsters, and ANDV and Sin Nombre orthohantavirus (SNV) infection in NHP, which all recapitulate human disease (Hooper et al., 2001; Wahl-Jensen et al., 2007; Safronetz et al., 2011).

Multiple factors can determine outcome of orthohantavirus infection, such as the ability of pathogenic (i.e., associated with clinical symptoms in humans) orthohantaviruses to inhibit antiviral responses whereas non-pathogenic viruses elicit innate responses that limit viral replication in humans (Geimonen et al., 2002; Kraus et al., 2004). Additionally, differences in receptor usage are believed to be one of the crucial determinants of pathogenicity (Gavrilovskaya et al., 2002). Specific integrins ($\alpha_v\beta_3$) are widely reported as receptors through which both HFRS and HCPS orthohantaviruses can enter host cells *in vitro* (Gavrilovskaya et al., 1998, 1999; Larson et al., 2005; Bondu et al., 2017). Recently, additional proteins like protocadherin-1 (Janra et al., 2018), decay-accelerating factor/CD55 (Krautkramer and Zeier, 2008), and the receptor for the globular head domain of complement C1q/p32/p33 (Choi et al., 2008) have been described as (co-)receptors for cell entry *in vitro*. However, their cell and tissue distribution does not explain the differences in clinical outcome between HFRS and HCPS viruses (Avraamides et al., 2008; Gavrilovskaya et al., 2010; Teoh et al., 2016).

The aim of this review is to provide an updated overview of the cell and tissue tropism of pathogenic orthohantaviruses and discuss how infection of these cell types could lead to pathogenesis based on *in vivo* data and supplemented with *in vitro* data. In addition to the role of endothelium in pathogenesis, we also focus on other cells potentially targeted in five key organ systems that are most frequently studied in the context of orthohantavirus infection and pathogenesis, e.g., lung, heart, kidney, liver, and spleen. We hypothesize that cells other than ECs play an important role in the pathogenesis of orthohantaviruses and the development of distinct clinical syndromes. We review differences in cell tropism between viruses with different clinical outcomes (HFRS and HCPS), as well as differences between human and reservoir hosts to provide novel hypotheses on virus and host-specific pathways involved in disease in humans. This is crucial for identifying novel potential therapeutic targets.

DISTINCT CLINICAL OUTCOMES OF ORTHOHANTAVIRUS INFECTION

HFRS is typically characterized by fever, thrombocytopenia, and acute kidney injury. In severe cases internal hemorrhaging caused by increased vascular permeability can even occur (Schmaljohn and Hjelle, 1997; Jonsson et al., 2010; Vaheri et al., 2013). Hantaan (HTNV), Seoul (SEOV), and Dobrava-Belgrade (DOBV) orthohantaviruses are mainly associated with severe presentation of HFRS with mortality rates of 5–15% (Papa, 2012; Hepojoki et al., 2014). PUUV is the most prevalent orthohantavirus circulating in Europe and Russia causing NE with thousands of cases each year and a mortality rate of <0.1% (Krautkramer et al., 2013; Tkachenko et al., 2019). NE patients

suffer from less severe kidney complications and less often hypotension, thrombocytopenia, and hematuria compared to HFRS cases (Jonsson et al., 2010). Tula (TULV) orthohantavirus infections have only been described in patients with severe comorbidities often related to immune suppression (Zelena et al., 2013). HCPS is a severe acute disease which mainly affects the lungs. Early non-specific flu-like symptoms rapidly develop to pulmonary edema, hypotension, and shock (Hallin et al., 1996; Khan et al., 1996; Macneil et al., 2011). ANDV and SNV are responsible for causing the majority of HCPS cases with fatality case rates up to 40% (Jonsson et al., 2010). More recently, it is becoming increasingly clear that the clinical differences between HFRS and HCPS are less distinct, with more frequent detections of respiratory disease in HFRS patients (Clement et al., 1994, 2014; Schutt et al., 2004; Gizzi et al., 2013) and kidney involvement in HCPS patients (Passaro et al., 2001; Peters and Khan, 2002). Thrombocytopenia (Connolly-Andersen et al., 2015; Latus et al., 2015) and vascular leakage (Gorbunova et al., 2010; Connolly-Andersen et al., 2015) are direct indicators for disease severity in both HFRS and HCPS.

PATHOLOGICAL OUTCOMES FOLLOWING ENDOTHELIUM INFECTION

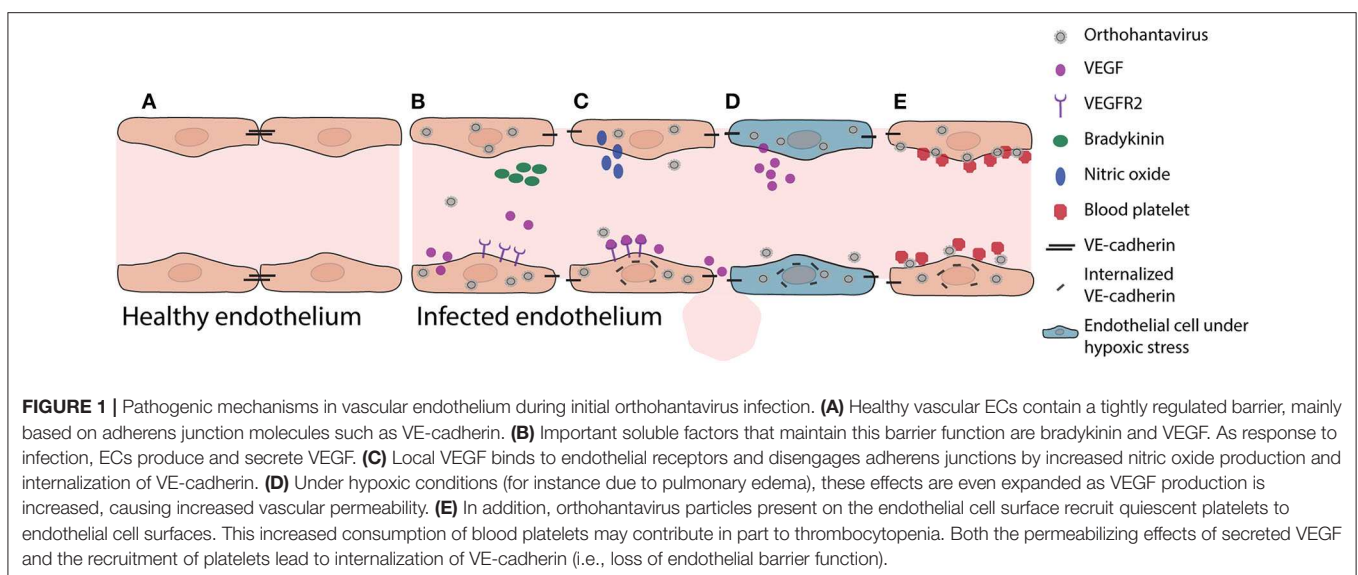
Infection of Human Endothelium

ECs are highly specialized cells which line the interior wall of blood and lymphatic vessels. ECs vary in phenotypical features and function, between different organs, including differences in expression of adhesion molecules and secretion products. ECs play an important role in vascular permeability, platelet activation, coagulation, and immune responses (Figure 1). Following entry via the respiratory tract through a yet unknown mechanism, orthohantaviruses infect ECs (primarily microvascular ECs) and subsequently spread to infect EC in almost all major organs in humans. Infection of ECs generally does not cause a cytopathic effect, but instead can lead to extensive impairment of EC functions, including barrier

integrity, adhesion factors, and fluid clearance from tissues by lymphatic vessels and capillary tone regulation (Dalrymple and Mackow, 2014; Mackow et al., 2014). As a result, infection of microvascular EC barrier functions can lead to capillary leakage, a key mechanism of pathogenesis during HFRS/NE and HCPS (Yanagihara and Silverman, 1990; Duchin et al., 1994; Zaki et al., 1995; Geimonen et al., 2002). Interestingly, while orthohantaviruses infect ECs in most major organs, organ dysfunction is only reported in specific organs and depends on the causative virus. HFRS viruses generally infect the microvasculature of the kidneys, specifically targeting glomerular and tubular ECs (Hung et al., 1992; Kim et al., 1993; Groen et al., 1996; Krautkramer et al., 2011, 2013). Pulmonary and splenic microvascular beds have also been reported as targets for infection (Hautala et al., 2002; Rasmuson et al., 2011; Clement et al., 2014; Sironen et al., 2017). HCPS viruses mainly target the pulmonary microvasculature (Zaki et al., 1995; Green et al., 1998; Toro et al., 1998). Additionally, these viruses can infect microvessels in the heart, kidneys, liver, and spleen (Nolte et al., 1995; Zaki et al., 1995; Green et al., 1998; Toro et al., 1998; Saggiaro et al., 2007). The mechanisms of distinct organ-specific dysfunction during HFRS and HCPS remain largely unknown. ECs from different large and microvascular vessels from different organs are considered phenotypically distinct with correspondingly characteristic gene expression profiles (Swerlick and Lawley, 1993; Chi et al., 2003). Furthermore, the microvessel wall has a more intimate association with the extracellular matrix compared to larger blood vessels, which might facilitate viral spread to other tissues.

Pathogenesis

Increased vascular permeability by infected microvasculature is a central feature of pathogenesis leading to HCPS and HFRS. For instance, during HCPS (and to a lesser extent HFRS) increased permeability can lead to pulmonary edema, which causes severe problems such as oxygenation and ventilation problems. Oxygenation problems, leading to hypoxia, modulates



actin cytoskeleton, and contractile proteins leading to further increased permeability (An et al., 2005). Hypoxic conditions also result in elevated vascular endothelial growth factor (VEGF) levels in pulmonary edema fluids (**Figure 1**) (Gavrilovskaya et al., 2012, 2013). Secreted VEGF binds to receptors (e.g., vascular endothelial growth factor receptor 2; VEGFR2) on ECs, acting locally to disassemble adherens junctions and induce elevated endothelial cell permeability (Dvorak, 2010; Gavard, 2014). The *in vitro* identified orthohantavirus entry receptor integrin $\alpha_v\beta_3$ is vital for regulating VEGF by forming complexes with VEGFR2, which are important for multiple cellular activities such as migration, survival, and angiogenesis (Robinson et al., 2004; Gavrilovskaya et al., 2008; Somanath et al., 2009; Dvorak, 2010). During initial orthohantavirus infection (**Figure 1**) localized increases of VEGF contribute to pathogenesis through enhanced endothelial permeability by causing higher production of nitric oxide (NO), internalization of VE-cadherin, and possibly redistribution of zonula occludens-1 (ZO-1) in renal cells (Groeneveld et al., 1995; Klingstrom et al., 2002; Gorbunova et al., 2011; Krautkramer et al., 2011; Dalrymple and Mackow, 2014). Sustained systemic elevations of VEGF may contribute to endothelial repair and convalescence later in infection. Different inhibitors involved in VEGF signaling are able to decrease orthohantavirus-induced permeability increases both *in vitro* and *in vivo* (Gorbunova et al., 2011; Bird et al., 2016). In addition to VEGF, bradykinin is an important mediator of vascular permeability (Liu et al., 2008; Kottke and Walters, 2016). Limited evidence suggests a role of bradykinin in orthohantavirus pathogenesis (Antonen et al., 2013; Taylor et al., 2013).

A second pathological event during early phase of infection is that orthohantavirus infection can result in coagulation abnormalities. Orthohantavirus particles cluster on the surface of ECs (e.g., pulmonary microvascular beds) (Goldsmith et al., 1995; Gavrilovskaya et al., 2010) and this accumulation recruits quiescent platelets to ECs (**Figure 1**) (Gavrilovskaya et al., 2010). This β_3 integrin-dependent platelet consumption may play a role in development of the observed acute thrombocytopenia, since it would result in wasting or loss of platelets adhered to infected ECs (Gavrilovskaya et al., 2010; Goeijenbier et al., 2015). This can also cause an increase of VEGFR2 phosphorylation and internalization of VE-cadherin from adherens junctions contributing to barrier function impairment and edema (Gavrilovskaya et al., 2002, 2010; Dehler et al., 2006; Bates, 2010; Gorbunova et al., 2011; Dalrymple and Mackow, 2014). In addition, disseminated intravascular coagulation without signs of hemorrhaging, major thrombosis or damage to the vascular ECs can be observed during the terminal stage of patients infected with SNV (Nolte et al., 1995; Zaki et al., 1995). These could also result in major decreases of clotting factors and platelet levels, promoting vascular leakage and hemorrhaging.

A third aspect of pathogenesis is not only described as virus-induced EC dysfunction but rather the result of immune-modulated effects (Temonen et al., 1996; Mori et al., 1999; Khaiboullina et al., 2017). There are two local immunopathological mechanisms that could contribute to the pathogenesis observed during HFRS and HCPS (Terajima and

Ennis, 2011). First, early antiviral and inflammatory responses aid in eliminating virus, thereby concurrently impairing EC function by secreting large amounts of cytokines, such as tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) (Mori et al., 1999; Maes et al., 2006). Second, if these responses are insufficient and virus clearance is delayed, prolonged inflammation can alter EC function and cause disruption of fluid barriers (Gavrilovskaya et al., 2008; Hammerbeck and Hooper, 2011).

Finally, damaged or detached ECs can be replaced by migration of adjacent ECs or mobilization of circulating endothelial progenitor cells (Sabatier et al., 2009). Recovery of symptoms due to orthohantavirus infection has been linked to appearance of high levels circulating endothelial progenitor cells (Krautkramer et al., 2014). However, whether circulating endothelial progenitor cells initiate disease recovery or are involved in the spread and pathogenesis requires further investigation.

Distinct Immune Responses to Infection in Non-diseased Reservoir

In reservoir rodents, orthohantaviruses are also primarily endotheliotropic (Netski et al., 1999; Maas et al., 2019). However, very little is known about the effect of orthohantavirus infection on the function and host responses by these cells. Instead, most studies have focused on the differential immunological responses that occur in reservoir rodents preventing them from developing disease. Studies on SEOV demonstrate that infection causes increases of immunoregulatory factors (e.g., expression of *Foxp3* and *Tgf β*) in pulmonary ECs and alveolar macrophages, respectively (Li and Klein, 2012). This contributes to a shift in CD4+T cell differentiation toward a more regulatory T cell phenotype during infection (Easterbrook and Klein, 2008a; Li and Klein, 2012). These data suggest that this local immunological shift may prevent complete viral clearance, hence causing persistence, as reviewed in Easterbrook and Klein (2008a). In addition, these data suggest that the pathogenesis of orthohantaviruses is at least in part the result of immunopathological responses that are controlled in reservoir species but not in humans.

HFRS/NE IN HUMANS AND DISEASE MODELS

Conducting Airways

While ECs are an important target for orthohantavirus infection, other cells likely play a role in entry and pathogenesis. Since cells of the conducting airways are the first to come into contact with orthohantavirus particles upon inhalation, identifying which cells are initially infected is of particular interest. To date, no data are available on the ability of HFRS-associated orthohantaviruses to target respiratory epithelial cells of the conducting airways.

Lungs

Nevertheless, pulmonary involvement during HFRS has been reported in PUUV-infected patients with NE, in which virus-infected cells can be detected in bronchoalveolar lavage fluids

(Rasmuson et al., 2016). Although pulmonary involvement during HFRS/NE is not considered a common clinical sign, post-mortem findings in severe NE cases have demonstrated extensive interstitial edema and mononuclear cell infiltrations with PUUV antigen presence in capillary vascular ECs and mononuclear cells in the lung (Rasmuson et al., 2011; Clement et al., 2014).

Heart

Cardiovascular disorders are identified as the leading cause of death during or shortly after PUUV infection (Connolly-Andersen et al., 2013). Although PUUV infection has a relatively low case fatality rate, cardiopulmonary complications can have implications on the recovery of a majority of patients (Rasmuson et al., 2013). Implications may consist of increased left ventricular stroke volume and myocardial contraction causing delayed functional hemodynamical recovery. During active NE, sinus bradycardia, T-wave inversion, and ST segment changes are described as common electrocardiographic (ECG) findings (Puljiz et al., 2005; Kitterer et al., 2016). However, these ECG abnormalities were transient in almost all of the patients and were not associated with negative cardiovascular outcome. Unfortunately, none of these studies specified viral antigen presence in cardiac cells. However, another case report specifically mentioned that heart tissue samples were negative for PUUV antigen (Hautala et al., 2002). Since there is no evidence of infection in the heart tissue, increased myocardial energy demand seems to be result of permeability increases of peripheral blood vessels.

Kidneys

While the exact mechanism of extrapulmonary spread remains unknown, once the virus reaches the vasculature there is a potential for rapid systemic dissemination. Following entry via the respiratory tract, the kidneys are considered the primary target for HFRS viruses. Renal function is dependent on the integrity of tubular epithelium and the glomeruli, which predominantly consist of fenestrated ECs, podocytes, and basement membrane. The disease severity of HFRS (including NE) ranges from reversible mild to severe acute kidney injury (Jonsson et al., 2010; Mustonen et al., 2017). In severe cases, oliguria, severe interstitial edema and hemorrhages are common clinical manifestations and hemodialysis may be required (Kim et al., 1993; Suh et al., 1995; Hautala et al., 2002; Jonsson et al., 2010). Patients can typically display acute interstitial inflammation, tubulointerstitial nephritis with focal interstitial hemorrhages (Collan et al., 1991; Kim et al., 1993; Groen et al., 1996; Temonen et al., 1996; Sironen et al., 2008; Meier et al., 2018). In addition to tubular and glomerular capillary ECs, HTNV and PUUV antigens have been detected in the tubular epithelial cells of HFRS patients (Hung et al., 1992; Kim et al., 1993; Groen et al., 1996; Krautkramer et al., 2011, 2013). Acute necrosis of antigen-positive tubular epithelium and the presence of tubular epithelial cells in urine (Kim et al., 1993; Hautala et al., 2002) suggest that—in addition to EC dysfunction—tubular damage contributes to kidney function impairment in HFRS (Hung et al., 1992). *In vitro* studies have demonstrated that orthohantavirus-induced interstitial

nephritis can be distinguished from non-orthohantavirus-induced interstitial nephritis due to signs of redistribution of tight junction proteins (e.g., ZO-1) in glomerular and tubular cells (Krautkramer et al., 2011). Decreased glomerular ZO-1 expression may also result in reduced function of the glomerulus as a molecular filter by enhancing glomerular permeability (Krautkramer et al., 2011). Finally, nucleocapsid (N) proteins of HTNV and PUUV cause impairment of podocyte motility and adhesion capacity (Hagele et al., 2018). Infection of podocytes leads to virus-induced cytoskeletal rearrangements *in vitro*, which could indicate a role for podocyte foot process effacement in observed proteinuria *in vivo* (Boehlke et al., 2014; Hagele et al., 2019). These rearrangements are more prominent for HTNV compared to PUUV, which corresponds with more pronounced proteinuria and kidney injury as observed during HFRS (Hagele et al., 2019).

Liver

Involvement of the liver has mostly been reported in SEOV cases (Kim et al., 1995; Zhang et al., 2011), where it results in acute viral hepatitis-like manifestations with lobular necrosis without viral inclusions, atypical cells, vasculitis, or fibrosis, a painful enlarged liver and distinct elevation of liver enzymes (Kim et al., 1995; Nielsen et al., 2010; Swanink et al., 2018). In addition, focal midzonal necrosis associated with mild mononuclear infiltrates can be observed in the liver during HTNV infection (Elisaf et al., 1993). However, detection of viral antigen in liver tissues has not been specifically reported in HFRS cases. Therefore, elevated liver enzymes seem to be a consequence of inflammatory events rather than direct infection.

Spleen

The spleen contains approximately one third of the body's platelets content illustrating its role in controlling the balance of available blood platelets and hence preventing thrombocytopenia (Bassenge, 1996). Data from a limited number of severe NE patients demonstrates venous congestion, splenomegaly, and variable amounts of antigen-positive ECs in the spleen, presumably sinusoidal lining cells (Hautala et al., 2002; Koskela et al., 2014; Sironen et al., 2017). However, to date, there is no association between enhanced sequestration of blood platelets in the spleen and the pathogenesis of thrombocytopenia during HFRS/NE (Koskela et al., 2014). The most likely explanation of the pathogenesis of thrombocytopenia during HFRS/NE, seems to be peripheral consumption (adherence to ECs), since several bone marrow studies showed a normal morphogenesis of platelets (Lee, 1987; Lutteke et al., 2010).

HCPS IN HUMANS AND DISEASE MODELS

Conducting Airways

In comparison to HFRS, orthohantavirus spread has been described in a wider range of organs for HCPS (**Figure 2**). Similar to HFRS, SNV RNA was found at low abundance in tracheal aspirate in a small number of HCPS patients (Xiao et al., 2006). Unlike other orthohantaviruses, ANDV is associated with

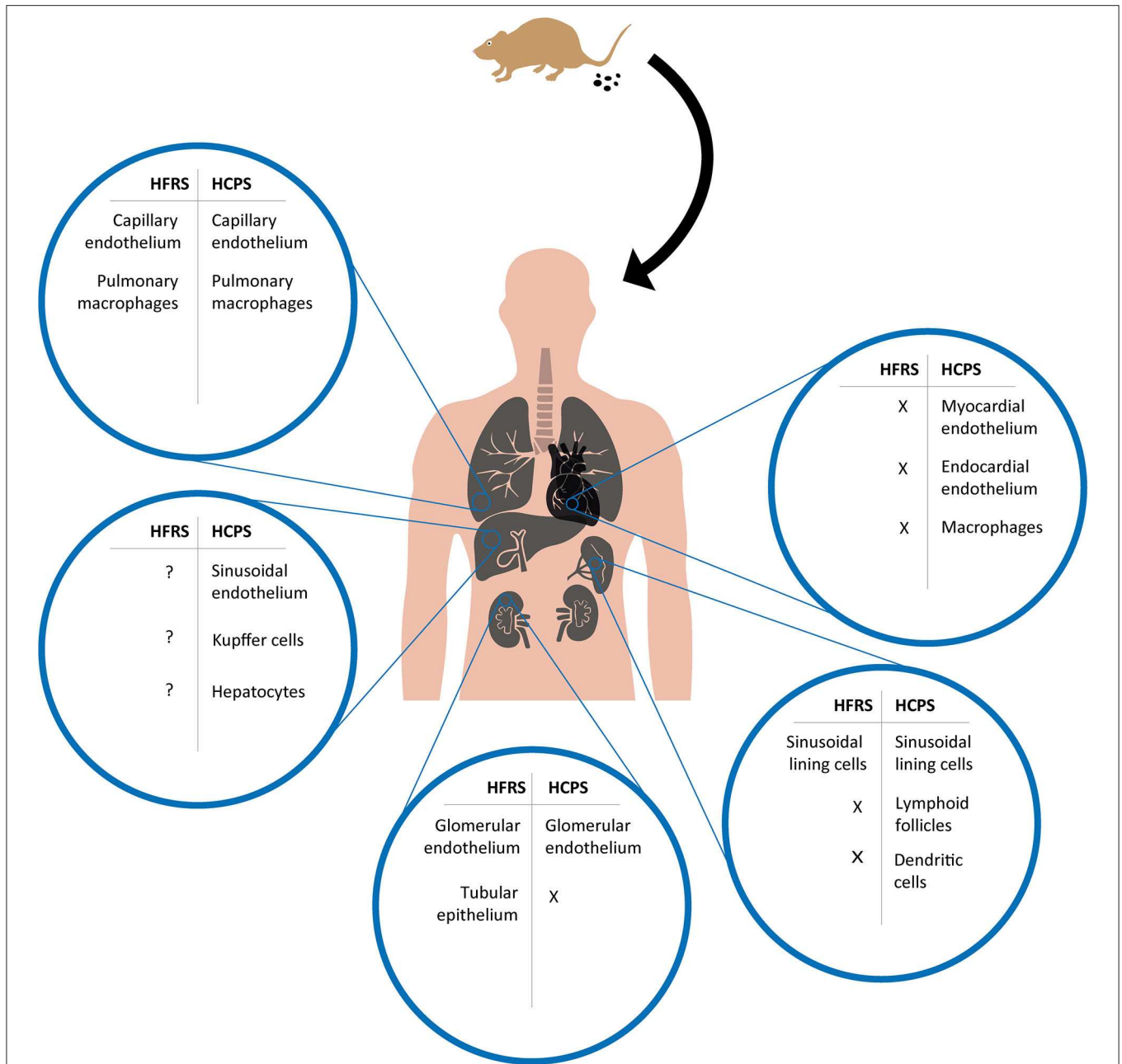


FIGURE 2 | Overview of cell tropism during HFRS and HCPS based on human and experimental disease models. After a human host is infected by inhalation of virus containing aerosolized excreta of an infected rodent, orthohantavirus is able to reach multiple organs and infect different cell types. Potentially infected cell types during HFRS and HCPS are compared for major organs in which viral antigens have been detected in human tissues or experimental disease models; lungs, heart, kidneys, liver, and spleen. X = absence of viral antigen; ? = viral antigen presence not specified.

human-to-human transmission. Efficient infection of the upper respiratory tract favors host-to-host transmission, as has been shown for other respiratory viruses, like influenza (van Riel et al., 2010), suggesting a potential role for respiratory cell infection. This is in line with data from an experimental ANDV infection model in Syrian hamsters in which viral antigen was detected in tracheal tissues following intranasal challenge (Safronetz et al., 2011). This antigen staining was only focal with limited spread

to neighboring cells, and no observed histological abnormalities (Safronetz et al., 2011). *In vitro*, ANDV infects non-ciliated cells (e.g., club and goblet cells) resulting in bidirectional virus release, which could facilitate direct access to infect adjacent respiratory epithelium or systemic spread by infection of respiratory ECs (Rowe and Pekosz, 2006). The exact role of infected non-ciliated cells during initial stages of disease in humans remains to be determined.

Lungs

Since (exudative) thoracic effusions and pulmonary edema are classical hallmarks of HCPS (Duchin et al., 1994; Hallin et al., 1996), pulmonary involvement has been studied to a great extent. Severe SNV infection in HCPS patients causes interstitial pneumonitis with variable mononuclear cell infiltrates, pulmonary edema, and focal hyaline membranes (Zaki et al., 1995). SNV infection leads to an increase of plasminogen activator inhibitor type 1 (PAI-1) in plasma samples of terminal stage patients (Bondu et al., 2018). Upregulation of this fibrinolysis inhibitor may lead to excessive fibrin accumulation, explaining the observed focal hyaline membranes in lungs of HCPS patients (Zaki et al., 1995). In contrast to other respiratory viral infections—like influenza (Kuiken and Taubenberger, 2008)—there is no cellular debris of respiratory epithelial cells and/or type II pneumocyte hyperplasia. This suggests that viral spread to the circulation does not rely on disrupted epithelial layers. Based on samples from end stages of disease, antigens from HCPS causing viruses are predominantly detected in the ECs of small vessels in the lungs and macrophages with almost no cells that remain unaffected (Nolte et al., 1995; Zaki et al., 1995; Green et al., 1998; Toro et al., 1998). Viral antigen was typically not detected in the ECs of large blood vessels in humans (Zaki et al., 1995). Furthermore, high viral load in lung tissue is usually negatively correlated to survival of patients (Zaki et al., 1995). Cell types that may play a role during the early stages of pathogenesis remain unknown due to the lack of early samples from the lungs.

Heart

Cardiac involvement varies in HCPS patients, ranging from mild forward failure with stable blood flow to fulminant shock and rapid death (Bustamante et al., 1997). Severe cases initially display signs of increased vascular permeability leading to non-cardiogenic pulmonary edema which later develops into cardiac complications (Hallin et al., 1996; Peters et al., 1999). In contrast to HFRS viruses, viral antigen is detected in ECs and macrophages in the myocardium and sporadically the endocardium of SNV-infected patients (Nolte et al., 1995; Zaki et al., 1995; Green et al., 1998; Saggiaro et al., 2007). It is believed that direct infection of cardiac tissue (combined with existing pulmonary edema) can lead to cardiac remodeling (flabby wall and mild biventricular dilatation), scattered foci of myofiber necrosis and a mild to moderate interstitial edema with mono-nuclear infiltrate (Saggiaro et al., 2007). This likely causes an atypical form of cardiogenic shock by myocardial dysfunction associated to myocarditis (Saggiaro et al., 2007), which can lead to decreased tissue perfusion, metabolic acidosis, and malignant arrhythmias (Hjelle, 2002). Clinical studies have identified impaired myocardial function instead of hypoxic injury as a leading cause of death in HCPS (Duchin et al., 1994; Hallin et al., 1996).

Liver

Clinical and post-mortem data from HCPS patients suggest that liver contribution to pathogenesis is limited. Still, viral antigen (predominantly SNV) can sporadically be detected in

hepatocytes, sinusoidal ECs, and Kupffer cells (Zaki et al., 1995; Green et al., 1998; Toro et al., 1998). In addition, infiltration of mononuclear inflammatory cells is observed (Nolte et al., 1995; Zaki et al., 1995), like in other organs (e.g., lungs and heart) without histopathology (Zaki et al., 1995).

Kidneys

The lungs are the primary target organ during HCPS, and the majority of HCPS reports actually do not study renal effects. Although a case report showed predominantly renal staining for SNV antigen, suggesting that renal tropism may overrule general pulmonary involvement in SNV infection (Passaro et al., 2001). Additionally, renal symptoms such as polyuria and proteinuria are common findings among a minority of HCPS patients (Jonsson et al., 2010; Clement et al., 2014). A frequent cause for these symptoms is increased glomerular capillary permeability to protein. Accordingly, widespread presence of SNV antigen in glomerular capillary ECs can be detected (Zaki et al., 1995; Green et al., 1998). It is plausible that infection of glomerular ECs during HCPS does not lead to clinical signs as more prominent pulmonary symptoms might arise earlier. Alternatively, tubular reabsorption could also compensate for decreased glomerular filter function, as tubular epithelium is negative for infection by HCPS-causing viruses (Zaki et al., 1995; Green et al., 1998).

Spleen

Mild splenomegaly with atypical mononuclear cells in red pulp and periarteriolar sheaths of the white pulp are common findings in later stages of HCPS (Nolte et al., 1995; Zaki et al., 1995). The white and red pulp of the spleen house a great variety of cell types, such as monocytes, lymphocytes, and dendritic cells. Viral antigen varies from negative to widespread and can be detected in multiple cell types, such as vascular ECs, lymphoid follicles, and splenic dendritic cells (Zaki et al., 1995; Green et al., 1998; Hooper et al., 2001). These data suggest that in addition to splenic ECs, immune cells can be infected during HCPS (e.g., SNV infection). As an essential location of mononuclear phagocyte system activity, viral replication in immune cells might provide an essential route for viral dissemination throughout the body. Altogether, these data suggest that the role of the spleen during HCPS might be more prominent than previously considered.

HFRS/NE-ASSOCIATED VIRUSES IN RESERVOIR RODENTS

Respiratory Tract

Similar to transmission to humans, animal-to-animal transmission in the reservoir host is assumed to occur primarily via the respiratory route. However, unlike in humans, infection in reservoir species results in persistent infection without clinical signs. To our knowledge, no studies have focused on the presence of virus in the conducting airways of orthohantavirus reservoir rodents. So, it remains unclear which cells from the upper respiratory tract can be infected by HFRS viruses in reservoir rodents. Nevertheless, lung tissues are frequently screened for surveillance of orthohantaviruses in reservoir species as highest antigen concentrations can be found here (Lee et al., 1982).

Since the Norway rat (*Rattus norvegicus*) is a model organism for different diseases with many reagents available, SEOV infection in reservoir rodents has been studied more extensively compared to other HFRS viruses (Easterbrook and Klein, 2008a). The lungs are considered the primary site of viral replication during persistent and experimental infection of SEOV in Norway rats (Easterbrook and Klein, 2008b). Following intraperitoneal inoculation of SEOV, viral antigen was mainly detected in pulmonary ECs and alveolar macrophages during persistence (i.e., defined as ≥ 30 days post-infection) (Easterbrook and Klein, 2008b). Although this entry route is distinct from what is expected during natural infection, pulmonary cells are also considered a target early in natural infection. In naturally infected rats, SEOV antigen is indeed primarily detected in interstitial ECs of alveolar septal capillaries, and rarely in ECs of larger blood vessels such as pulmonary veins, similar to human infection (Maas et al., 2019).

Heart

In addition to the lungs, in one study, DOBV and TULV could be detected by polymerase chain reaction (PCR) in hearts of naturally infected animal reservoirs (Michalski et al., 2014). Unfortunately, this study did not identify the infected cell types. Analogous to human data, PUUV is generally absent in cardiac cells of naturally infected reservoir voles (Michalski et al., 2014; Dervovic and Hukic, 2016). Consequently, virus presence in cardiac cells could depend on the specific causative virus.

Kidneys

As the kidneys are the main target organ during HFRS in humans, it is important to identify which (immunological) mechanisms prevent this renal pathology in the reservoir and thus which renal cell types are infected in healthy reservoir animals (Easterbrook and Klein, 2008a). Almost 40 years ago, the first HFRS orthohantaviral antigens were reported in kidneys of wild rodents (Lee et al., 1982; LeDuc et al., 1984). To our knowledge, the infected renal cell types have not been specified in reservoir rodents, other than SEOV in microvascular ECs (Maas et al., 2019). However, HFRS/NE-associated orthohantaviruses are commonly detected in urine of reservoir hosts (Lee et al., 1981; Gavrilovskaya et al., 1983; Yanagihara et al., 1985; Klein et al., 2001; Hardestam et al., 2008; Voutilainen et al., 2015). Orthohantaviruses are much larger than the size of filterable macromolecules. This indicates that viruria is a consequence of viral particles release from the apical membranes of infected renal cells or disruption of glomerular filter function.

Liver

PUUV antigen can be detected in the liver of a minority (4%) of naturally infected wild rodent reservoir hosts (Gavrilovskaya et al., 1983). Intramuscular infections of PUUV in bank voles results in viral antigen in liver ECs and Kupffer cells (Yanagihara et al., 1985). Interestingly, natural SEOV infection in rats primarily targets the microvasculature in the liver and results in a mild hepatitis, characterized by an increase in the number of polymorphonuclear cells within the hepatic parenchyma and

sinusoids (Maas et al., 2019). This suggests that SEOV infects hepatic ECs in both reservoir and diseased host.

Spleen

The spleen is a peripheral immune organ that supports merely low levels of virus replication in reservoir rodents (Lee et al., 1982; Gavrilovskaya et al., 1983; LeDuc et al., 1984; Yanagihara et al., 1985; Compton et al., 2004; Michalski et al., 2014). Although evidence is conflicting and cell types are not consistently specified, splenic endothelium and macrophages seem to be the main target cells (Yanagihara et al., 1985; Maas et al., 2019). During both acute and persistent SEOV infection in spleen tissues, proinflammatory (e.g., IL-1 β , IL-6, and TNF- α) and antiviral responses (e.g., IFN- γ) are elevated to stimulate viral clearance, while regulatory responses (e.g., TGF- β) seem unaltered (Easterbrook and Klein, 2008b). These data differ from local immune reactions in the lungs, where regulatory responses are elevated (Easterbrook et al., 2007; Easterbrook and Klein, 2008b). Altogether, these data suggest that local shifts in the immunological balance might be crucial for controlling virus replication, hence preventing pathogenesis.

HCPS-ASSOCIATED VIRUSES IN RESERVOIR RODENTS

Respiratory Tract

In naturally infected deer mice, the reservoir rodents of SNV, the highest levels of virus can be detected in the lungs (Netski et al., 1999). Mild lung pathology is observed in the majority of wild rodents infected by SNV, as characterized by alveolar septal edema with various levels of SNV antigen in the alveolar and capillary walls (Netski et al., 1999). A transmission study in reservoir rodents naturally infected with ANDV demonstrated viral antigen in most of the epithelium lining the alveoli and some of the capillary ECs (Padula et al., 2004). These observations differ from end stage human infections, during which microvascular ECs are primarily infected (Zaki et al., 1995; Green et al., 1998; Toro et al., 1998). Differences in viral spread could depend on the host's specific ability to clear the virus, differential distribution of the viral entry receptors and the stage of infection, since most data on cell tropism from human cases is based on the end stage of disease (Billings et al., 2010).

Heart

In cardiac tissues of SNV-infected deer mice, only few antigen positive cells can be detected (Green et al., 1998; Botten et al., 2002). Therefore, prominent infection of cardiac tissue with consequent disease manifestations seems specific for human infections, at least for SNV infection (Nolte et al., 1995; Zaki et al., 1995; Green et al., 1998; Saggiaro et al., 2007).

Liver

SNV infection results in immune infiltrates in the hepatic portal zones of reservoir hosts (Netski et al., 1999). These immune infiltrations in infected liver tissue are the second most observed pathological finding after alveolar septal edema in wild deer mice (Netski et al., 1999). These data again imply that SNV is able

to cause pathology within reservoir hosts. However, it remains to be confirmed whether infiltration of immune cells leads to liver function impairment in wild deer mice. As SNV antigen can be found in infiltrating mononuclear cells, Kupffer cells in liver sinuses and hepatocytes (Netski et al., 1999), liver infection by other HCPS orthohantaviruses in their reservoir species should be monitored to exclude the possibility that these observations are specific for persistent SNV infection.

Kidneys

In deer mice, naturally infected with SNV, no gross kidney pathology is observed. Furthermore, focal to no viral antigen can be detected in kidneys (specifically in glomerular tissue) (Green et al., 1998; Netski et al., 1999). It has been described that the

highest levels of virus in urine are shed during earlier stages of infection (Netski et al., 1999).

Spleen

SNV antigen can be detected in mononuclear cells within both red and white pulp of the spleen of wild deer mice in one study (Netski et al., 1999), but not in another (Green et al., 1998). Contradictions between these studies may likely be explained by the unknown timing of natural infection. It remains to be determined whether infection of (immune) cells in the spleen plays an important role in viral dissemination and which local mechanisms aid to persistent infection as opposed to pathogenesis in humans.

TABLE 1 | Organ-specific cell types contributing to orthohantavirus disease *in vivo* summarized for five major organs.

Affected organ	Infected cell type	HFRS		HCPS		Hypothesis on pathology	References
		Human	Reservoir	Human	Reservoir		
Lungs	Pulmonary microvascular endothelium	+	+	+	+	Extensive infection leads to immune cell infiltrations and endothelial cell activation, which causes local inflammation and pulmonary edema	Brummer-Korvenkontio et al., 1980; Lee et al., 1981, 1982; Gavrilovskaya et al., 1983; LeDuc et al., 1984; Yanagihara et al., 1985; Nolte et al., 1995; Zaki et al., 1995; Green et al., 1998; Toro et al., 1998; Netski et al., 1999; Padula et al., 2004; Easterbrook and Klein, 2008b; Rasmuson et al., 2011; Clement et al., 2014
Heart	Myocardial endothelium	-	?	+	+	Infection leads to immune cell infiltrations and endothelial cell activation, causing interstitial edema that contributes to myocardial dysfunction and cardiogenic shock	Nolte et al., 1995; Zaki et al., 1995; Green et al., 1998; Botten et al., 2002; Hautala et al., 2002; Saggiaro et al., 2007; Michalski et al., 2014; Dervovic and Hukic, 2016
Kidneys	Tubular epithelium	+	+	-	?	Infection of endothelium leads to immune cell infiltrations (tubulointerstitial nephritis) with redistribution of tight junction proteins, along with direct tubular necrosis (with possible interstitial hemorrhages) causing functional impairment of tubuli leading to proteinuria, microscopic hematuria	Hung et al., 1992; Kim et al., 1993; Groen et al., 1996; Green et al., 1998; Botten et al., 2002; Hautala et al., 2002; Krautkramer et al., 2011
	Glomerular endothelium	+	+	+	+	Infection of glomeruli causes decrease in glomerular ZO-1 expression relating to reduced function of the glomerulus as molecular filter by enhancing glomerular permeability, leading to proteinuria and microscopic hematuria	Zaki et al., 1995; Groen et al., 1996; Green et al., 1998; Netski et al., 1999; Botten et al., 2002; Krautkramer et al., 2013
Liver	Hepatic sinusoidal endothelium	?	+	+	+	Infection of endothelium leads to immune cell infiltrations (antigen-positive Kupffer cells) and increased vascular permeability, which probably do not lead to significant liver dysfunction as hepatic sinusoidal microvasculature is already relatively permeable	Gavrilovskaya et al., 1983; Yanagihara et al., 1985; Zaki et al., 1995; Green et al., 1998; Toro et al., 1998; Netski et al., 1999
Spleen	Splenic sinusoidal endothelium	+	+	+	+	Infection of immune cells in the spleen may cause over-activation of immature lymphocytes elsewhere and facilitate prolonged virus dissemination throughout the body	Lee et al., 1982; Gavrilovskaya et al., 1983; LeDuc et al., 1984; Yanagihara et al., 1985; Zaki et al., 1995; Green et al., 1998; Netski et al., 1999; Hautala et al., 2002; Klingstrom et al., 2002; Compton et al., 2004; Padula et al., 2004; Sironen et al., 2008, 2017; Michalski et al., 2014

*Viral antigen presence in mononuclear immune cells are not included in table. + = viral antigen present of at least one causative virus species, ? = conflicting data/not tested, - = viral antigen absent of all tested causative virus species, and * = studies did not specify infected cell type within organ.*

CONCLUSION AND FUTURE PERSPECTIVE

While human orthohantaviruses enter the host via the respiratory tract, it remains unknown which cells in the human respiratory tract are the first infected. It has been described that orthohantaviruses are endotheliotropic viruses, however this review demonstrates that additional cell types are infected, which may play a role in the pathogenesis of these viruses (Table 1).

Although the initial target cells are unknown, ECs are an important target later during infection. Interestingly, orthohantavirus infection of ECs does not result in overt cell damage, and infected ECs can be found in most organs. However, orthohantavirus induced pathology is only observed in specific organs, believed to play a key role in pathogenesis, including, lung (HCPS), and kidneys (HFRS). Unlike in humans, orthohantavirus infection in the reservoir host causes a persistent infection with limited pathological changes and no apparent clinical signs. Unraveling the pathogenesis of orthohantaviruses (or any emerging virus) through patient-based research is extremely difficult. Additionally, our understanding of the differential pathogenesis of orthohantaviruses in humans has been hampered by the lack of relevant animal models that allow the comparison of HFRS- and HCPS-causing viruses, the limited availability of *in vivo* and *in vitro* models of the reservoir host, and the requirement of high containment facilities for orthohantaviruses pathogenic to humans.

As reviewed above, ECs of the microvasculature in multiple organs are the main targets for orthohantaviruses both in the reservoir hosts and humans. Here we provide an overview of additional cells targeted by orthohantaviruses in the respiratory tract, heart, kidneys, liver, and spleen and the potential role they play in pathogenesis. These organ systems were chosen as multiple studies have demonstrated viral presence in these organs in human cases. While there are a variety of studies discussing orthohantavirus infection in other organs, such as intestines (Zaki et al., 1995; Green et al., 1998; Latus et al., 2014), endocrine system (Zaki et al., 1995; Green et al., 1998; Bhoelan et al., 2019), and brain (Zaki et al., 1995) in humans, but also brown adipose tissue (Botten et al., 2002) in reservoir rodents, these were not included due to lack of mechanistic studies. Of note, transmission via saliva is suggested to be even more relevant than urine among naturally infected hosts as SEOV and ANDV have been detected more often in either saliva (and salivary glands) compared to urine samples (Padula et al., 2004; Maas et al., 2019).

So far, it remains unknown how viral dissemination occurs in an infected host post-inhalation. Potential mechanisms include

initial infection of respiratory epithelium and either basolateral release or cell-to-cell spread to ECs to reach the circulation, as shown for other respiratory viruses, like measles (Singh et al., 2016). Alternatively, infection of immune cells in the respiratory tract could facilitate systemic spread via the vascular and lymphatic system, as described for another hemorrhagic fever virus; Ebola virus (Bray and Geisbert, 2005).

Interestingly, distinct orthohantavirus species seem to cause different degrees of pathology in various organs. While the use of $\alpha_v\beta_3$ integrins and other (co-)receptors do correlate with pathogenicity in humans, distribution of these viral receptors on human cells does not correspond with the susceptibility and organ tropism of orthohantavirus infection *in vivo*. Therefore, the exploration of additional host cell (co-)receptors that facilitate orthohantavirus entry and/or attachment *in vivo* should continue. In addition, it remains interesting that during HCPS and HFRS ECs of almost all major organs are affected, and yet the clinical signs per organ generally seem to differ per causative virus species, although exceptions have been reported. Therefore, effects of infection by various orthohantaviruses on organ-specific microvascular ECs should be explored. Moreover, the pathogenic mechanisms occurring in other cell types that are infected during HFRS and not HCPS (and vice versa) could also be at the base of understanding why HFRS and HCPS mainly lead to, respectively kidney and lung complications, for instance the potential role of tubular epithelium in kidney disease. In a broader sense, the conclusion that orthohantaviruses cause disease in humans and generally not in their reservoir hosts, while targeting similar cells and organs provides a unique opportunity to identify key host factors that play a role in the observed host-specific pathogenesis. Altogether, addressing these research questions will aid in our understanding of orthohantavirus pathogenesis and will be instrumental in identifying potential therapeutic and prophylactic strategies.

AUTHOR CONTRIBUTIONS

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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