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Review

Emergence and Persistence of Hantavirus in Rodent Reservoirs: Role of Glucocorticoid Hormone

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Abstract

Rodent-borne hantaviruses have received considerable attention in recent years due to the high mortality rate in humans that their infections cause. Anthropogenic stressors are key factors in the emergence of hantavirus-associated diseases. Urbanization, deforestation, noise pollution, artificial lighting and electromagnetic fields are the most common forms of human impact on the environment. An increased systemic concentration of the immunosuppressive class of steroid hormone glucocorticoid is a frequent consequence of chronic anthropogenic stress. Elevated glucocorticoid levels play a crucial role in modulating immune tolerance of rodents, thereby enabling establishment of the host-pathogen interaction. Glucocorticoids support virus persistence in the reservoir host by activating an organ-specific regulatory response mediated by T regulatory lymphocytes to reduce inflammatory and antiviral responses, principally via production of cytokines interleukin-10 and transforming growth factor-β. In-depth analysis of this mechanism would help to understand how rodents maintain a disease-free condition. This may have implications for a cost-effective intervention strategy against hantavirus and other zoonotic human pathogens.

Keywords

hantavirus; viral persistence; anthropogenic stress; glucocorticoid; T regulatory lymphocyte; host-pathogen interaction.

Introduction

Hantavirus, a negative-sensed, enveloped, single stranded RNA virus that belongs to the genus *Hantavirus* and family *Bunyaviridae*, is a deadly zoonotic virus harboured by rodents [1,2]. The RNA genome of hantavirus consists of three elongated and spherical segments, named large (L), medium (M) and small (S), which code for RNA-dependent RNA polymerase (RdRp), envelope glycoproteins (Gn and Gc) and nucleocapsid (N), respectively [2]. Among over 20 distinct hantavirus species at least 11 are responsible for infection of humans [3]. While natural reservoir rodents show no apparent sign of infection, a person may develop potentially fatal clinical disease manifestations [4]. Anthropogenic events followed by anthropogenic stresses to rodents are recognized as a major driving force for the emergence of hantavirus in rodents [5]. These anthropogenic stresses have deleterious effects on a rodent's endocrine, immune, nervous and physiological systems and hence alter the overall functioning of its tissues and organs. Rodents exposed to chronic anthropogenic stress express elevated levels of glucocorticoid (GC) hormone. This is accountable for reducing the resistance of rodents to viruses and increasing their tolerance to viral load of the reservoir host [6]. To facilitate virus persistence in stressed rodents GC activates an organ-specific regulatory mechanism, governed primarily by T regulatory (T_{reg}) lymphocytes and interleukin (IL)-10, to reduce the inflammatory response during infection. This review focuses on why an understanding of factors behind viral emergence is important, discusses the part played by GC hormone in virus persistence and host immune response to infection, and considers current therapeutic measures to both prevent outbreaks and treat cases of hantavirus.

Epidemiology and pathogenesis

Humans are the dead-end host for hantavirus and become infected when coming into close contact with egestion, excretions or secretions, or soiled nesting material, of infected rodents. The most frequent route of transmission is airborne, via inhalation of aerosols containing virus particles [7,8]. The distribution of hantavirus species is determined by the geographical location of their natural reservoir rodents [9]. Individuals living in housing with poor ventilation or containing urine, saliva or fresh droppings from infected rodents, or on agricultural land with an abundant rodent population, are most at risk of infection [9,10]. Long-term forest habitation, such as by military personnel, also increases exposure to the virus [11]. Disturbed natural environments and destruction of habitat promote loss of biodiversity and drive the migration of infected rodents into areas heavily populated by humans, which results in raised rates of pathogen transmission. Russia and China report the most cases of hantavirus infection in Europe and Asia, respectively [12].

Hantavirus-associated clinical syndromes in humans can be classified in either of two categories:

haemorrhagic fever with renal syndrome (HFRS); and hantavirus pulmonary syndrome (HPS). Although HFRS and HPS share some common clinical symptoms, which include overexpression of $CD8^+$ T lymphocytes, increased vascular permeability and elevated leucocytes in peripheral blood, some features, notably mortality rates, differ [13]. As the name indicates, renal involvement with haemorrhagic fever is associated most often with HFRS. The course of clinical development of HFRS is divided into five distinct stages: febrile; hypotensive; oliguric; diuretic; and convalescent. The mortality rate due to HFRS is 5-15% [14]. HPS is characterized by influenza-like symptoms including headache, high fever and myalgia. Hypotension and pulmonary oedema may develop which often deteriorates rapidly into acute respiratory failure, resulting in a high mortality rate of around 50% [14,15].

Role of anthropogenic stressors as a key factor for emergence

A key factor in the emergence of hantavirus as well as of many other emerging infectious diseases is the effect of anthropogenic stresses to wildlife, which is a direct consequence of man-made disturbances to the natural environment[16]. Commonly recognized anthropogenic stressors include urbanization, deforestation, noise pollution, light pollution and electromagnetic radiation. Rodents are considered to serve as a suitable reservoir for more than 60 human-infecting viruses, which should be a serious concern for public health [17].

The most prevalent adverse effects of urbanization are habitat fragmentation, loss of biodiversity, food scarcity, high food competition and deforestation, all of which act as chronic stressors for rodents. In response to such stimuli, rodents express elevated levels of GC which lower their immunity to viruses and alter their endocrine and physiological balance [18,19]. Furthermore, loss of biodiversity increases risks of pathogen transmission [20].

Rodents that are exposed to chronic noise show significant physiological alterations which include increased corticosterone, modulated immunity, and reductions in body weight, gastric secretion and reproductive activity, none of which is observed in rodents kept under conditions of low noise or unbroken silence [21,22]. Significant reductions in T lymphocyte concentration, humoral immune response and phagocytic activity are also experienced by noise-exposed rodents [23].

Prolonged artificial lighting at night reduces body temperature, suppresses circadian activity and initiates sleep deprivation in rodents. This further activates the hypothalamic-pituitary-adrenal axis to produce elevated levels of GC [24-26]. Suppression of cell-mediated and humoral immune responses are also observed in artificial light-exposed rodents [27]. Similarly, extended exposure to electromagnetic fields acts as a chronic stressor of rodents, which causes increased GC production and, subsequently, suppression of cellular immunity [28,29].

Hantavirus outbreaks occur most often in environments that are extensively disturbed due to anthropogenic changes of the type described above. Hence, the impact of anthropogenic stressors on hantavirus emergence should be given consideration because the interaction between endocrine, immune and nervous systems is a significant influence on the outcome of the host-parasite interaction [5,30]. Each class of chronic stressor is capable of reducing a rodent's resistance to infection [31]. A stress response is characterized by increased GC expression, the effects of which in rodents are classified into five categories: increased blood glucose; reduced growth; decreased reproductive performance; altered behaviour; and suppressed immunity [32,33]. Chronic stress-induced GC contributes to a rodent's susceptibility to infection by reducing its antiviral resistance and elevating its tolerance to viruses. This viral persistence mechanism is directed by a complex cytokine cascade orchestrated by T_{reg} lymphocytes [6,34] (Figure 1).

Persistence and immune response – role of glucocorticoid hormone

Understanding the mechanisms of hantavirus persistence and of host immunity to chronic infection is fundamental to development of future antiviral therapies. The means by which rodents support hantavirus without showing any symptoms of disease is just starting to be revealed. Hantavirus-associated clinical manifestations in humans are considered to be due to excessive pro-inflammatory and $CD8^+$ T lymphocyte responses while rodents exhibit lower pro-inflammatory and antiviral responses and elevated regulatory responses [35,36].

During infection, monocytes and macrophages are the first immune cells to become infected. The virus expresses elevated levels of the enzyme matrix metallopeptidase 9 which disrupts the cell membrane, thereby facilitating dissemination into tissues [37]. Reduced expression of antiviral interferon (IFN)-β, IFN-γ and other pro-inflammatory cytokines is observed in chronically infected rodents [36]. Depletion of $CD8^+$ T lymphocytes results in increased viral load and mortality, which is a clear indication of the crucial role of these cells in suppressing hantavirus replication and host infection [38,39]. T_{reg} lymphocytes act to suppress pro-inflammatory and $CD8^+$ T cell activity to maintain host homeostasis and thereby enable viral persistence (Figure 1). Inactivation of T_{reg} lymphocytes reduces expression of viral RNA in rat lungs, which is indicative of T_{reg} involvement in hantavirus persistence [40]. T_{reg} lymphocytes further suppress expression of tumour necrosis factor (TNF)-α and inflammatory responses and promote expression of transforming growth factor (TGF)-β, IL-10 and the transcription factor Foxp3 [41]. T helper (Th) 1 $CD4^+$ lymphocytes express IFN-γ, IL-2 and TNF-α which also activates $CD8^+$ T lymphocytes, NK cells and macrophages [42], while Th2 lymphocytes express IL-4, IL-5, IL-10 and IL-13 and trigger antibody-mediated immunity [43].

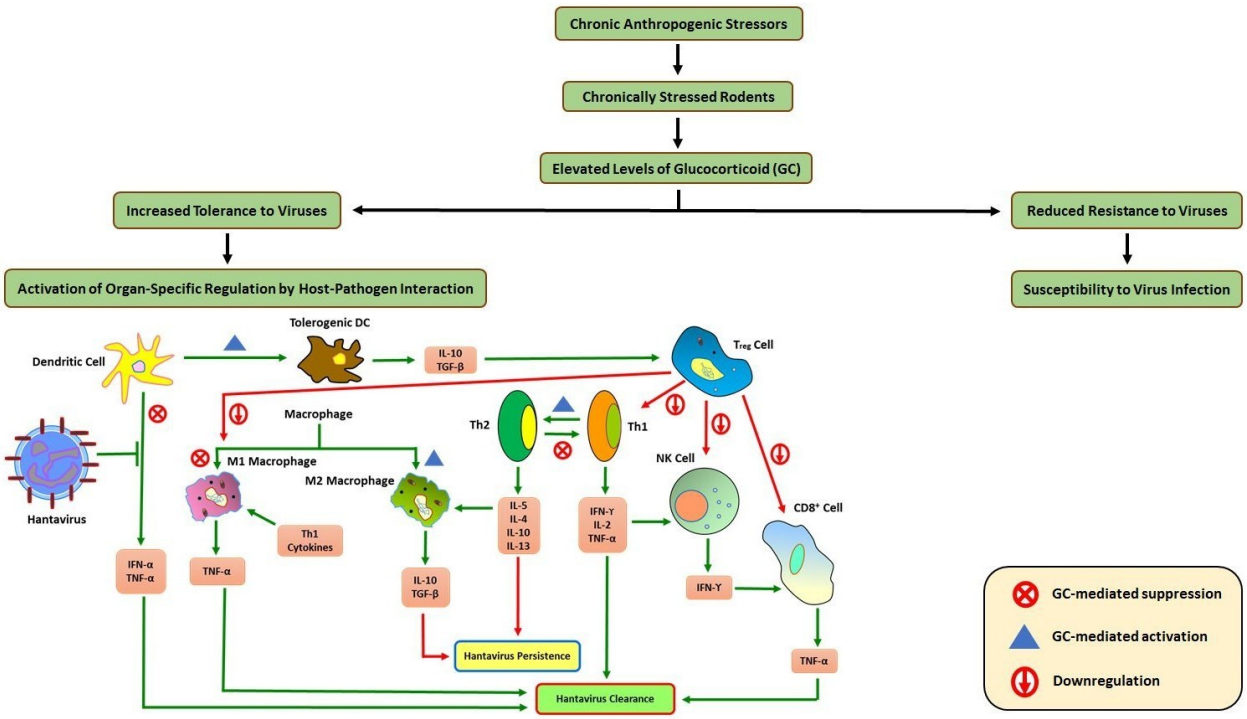

Figure 1 General overview of glucocorticoid-mediated hantavirus emergence and persistence in rodents.

T_{reg} lymphocytes initiate Th1-Th2 pathway polarization and also suppress the activity of antigen-presenting cells, such as dendritic cells (DC), macrophages and B lymphocytes [44-46]. Furthermore, T_{reg} lymphocytes may be activated by immature or tolerogenic DC mediated by TGF-β to exert regulatory activity [45,47].

The anti-inflammatory role of GC is well established. While chronic stress-induced GC is responsible for immune suppression of rodents, it likely activates an organ-specific regulation that supports hantavirus persistence. GC blocks inflammatory pathways and induces apoptosis mediated by T_{reg} lymphocytes [48-50]. GC not only suppresses differentiation of DC but also induces production of tolerogenic DC which express elevated IL-10 and TGF-β. Tolerogenic DC are responsible for generation and activation of T_{reg} lymphocytes to exert a regulatory control over $CD8^+$ lymphocyte-mediated antiviral responses [51,52]. GC initiates a polarization of $CD4^+$ lymphocyte subsets from Th1 to Th2 and increased production of Th2 cytokines which further trigger alternatively activated M2 macrophages [52] (Figure 1). M2 macrophages are characterized by increased production of IL-10 and TGF-β, stimulated mainly by elevated levels of GC, which also suppresses activity of naturally activated M1 macrophages [52,53]. Depletion of GC leads to high mortality rates due to an excessive pro-inflammatory cytokine response despite efficient virus clearance. This is indicative of the critical role of GC in viral persistence and establishing an equitable balance in the host-pathogen interaction [54,55].

Current approaches to therapy and prevention

There is currently no drug that is approved by the US Food and Drug Administration for treatment of hantavirus infection. Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) shows some anti-hantaviral activity both *in vitro* and *in vivo* but not sufficient to consider it further for commercial development [56,57]. Considerable efforts have been invested in designing an efficacious vaccine against hantavirus but progress is slow. A conventional vaccination approach is followed in Asia, which includes rodent brain- and cell culture-derived inactivated vaccines [58] and in Korea mouse brain-derived Hantavax® was marketed commercially [59]. However, none of these is approved in the US for therapeutic use since they do not provide protective immunity against multiple pathogenic species [60,61]. Therefore, current vaccine strategies are focused mainly on developing a DNA vaccine that would protect against a range of pathogenic species. Initial findings indicate that a quadrivalent vaccine could be a promising option for future vaccine research [62].

As successful prophylaxis or treatment for hantavirus-associated clinical syndromes is not an immediate prospect, low technology prevention strategies remain the best tool to minimize the impact of infection. Avoidance of contact with rodents and their secretions is the simplest way to prevent infection. However, farmers and workers in other occupations at risk of exposure to abundant rodent populations are advised to wear a face mask to help prevent acquiring disease via inhalation of infected aerosols. Proper ventilation with fresh air is another way to keep infrequently used accommodation free from risk of transmission [63].

Conclusions

The recent repeated emergence and reemergence of infectious diseases highlight the urgent need for effective public health surveillance and management systems. Anthropogenic stressors to wildlife are

key factors behind viral disease outbreaks, so future research should consider a multi-disciplinary strategy which involves all aspects of the virus life cycle. This includes understanding the host-pathogen relationship in the reservoir, in particular, how wild animals maintain a disease-free condition while supporting virus persistence. In the case of hantavirus, this interaction is governed by GC, so further study should focus on how GC and T_{reg} lymphocytes react under conditions of infection. A systematic comparison of immune responses following infection of human and rodent, and also with respect to immunological profiles of wild rodents, may help to reveal the roles of GC and T_{reg} lymphocytes under different conditions and their interactions in antiviral responses in an organ-specific manner. This may facilitate the development of an effective antiviral therapeutic agent and alleviate issues associated with current therapies.

Competing Interests

The authors have declared no competing interests.

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