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Review

Hendra and Nipah infection: Emerging paramyxoviruses

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ABSTRACT

Since their first emergence in mid 1990s henipaviruses continued to re emerge in Australia and South East Asia almost every year. In total there has been more than 12 Nipah and 48 Hendra virus outbreaks reported in South East Asia and Australia, respectively. These outbreaks are associated with significant economic and health damages that most high risks countries (particularly in South East Asia) cannot bear the burden of such economical threats. Up until recently, there were no actual therapeutics available to treat or prevent these lethal infections. However, an international collaborative research has resulted in the identification of a potential equine Hendra vaccine capable of providing antibody protection against Hendra virus infections. Consequently, with the current findings and after nearly 2 decades since their first detection, are we there yet? This review recaps the chronicle of the henipavirus emergence and briefly evaluates potential anti-henipavirus vaccines and antivirals.

Contents

1. Introduction

Almost two decades ago a lethal and previously unknown disease in horses and humans occurred in Queensland, Australia. The outbreaks occurred within one month of each other in Brisbane and Mackay, which are approximately 1000 km apart. In the Brisbane incident, 21 horses were infected of which 14 died or were euthanised after severe clinical signs of an acute respiratory disease. The causative agent of the deadly disease was later recognised as a new emerging virus, which was named Hendra virus, after the suburb where it emerged first. A few years after the Hendra incident in Australia, a major outbreak of acute febrile encephalitis of humans occurred in Malaysia that resulted in 265 human cases including 105 fatal cases (Chua et al., 2000a). In Singapore, 11 cases and one death were reported among abattoir workers who slaughtered pigs imported from affected areas of Malaysia. The Malaysian outbreak was controlled by the culling of over one million pigs and strict quarantine measures on pig movements (Patton et al., 1997), which was estimated to have costed more than US$450 million

Abbreviations: HeV, Hendra virus; NiV, Nipah virus; IFN, interferon.

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(Tamin and Rota, 2013). Approximately one year after the initial Malaysian outbreak, a new virus was isolated from cerebrospinal fluid (CSF) of an encephalitic patient from a village in Malaysia called Nipah, which is the name that was given to the new virus. Electron microscopy, immunofluoresence and sequence analysis indicated that both of the new viruses are paramyxoviruses and closely related, but not identical to each other.

2. Classification

The *Paramyxoviridae* family includes some of the great and ubiquitous disease-causing viruses of humans and animals, including measles virus, one of the most infectious viruses known (Lamb and Kolakofsky, 2001). Paramyxoviruses are enveloped viruses with a linear non-segmented negative sense RNA genome of approximately 15.5 kb in size (Nagai, 1999) and are clustered with other virus families that are grouped taxonomically in the order *Mononegavirales*. In viruses from this order, genes are arranged in a highly conserved order (Wang et al., 2001; Takeda et al., 2006). The family *Paramyxoviridae* is further classified into two subfamilies *Paramyxovirinae* and *Pneumovirinae* (Lamb and Kolakofsky, 2001; Fields et al., 2007), which not only include a number of older, well studied human and animal pathogens (Nagai, 1999), but also newly emerged agents such as Hendra virus (HeV) and Nipah virus (NiV) (Wang et al., 2001) as well as the most recently identified member Cedar Virus (CedPV) (Marsh et al., 2012). Although these newly emerged viruses appear to retain many of the genetic and biological properties of other members of their subfamily, *Paramyxovirinae*, they also have a number of unique characteristics in their subfamily (Wang et al., 2001); both NiV and HeV share antigenic cross-reactivity with each other but not with any other members of the *Paramyxovirinae* subfamily (Chua et al., 1999).

HeV and NiV genomes are distinctly bigger (18,234 and 18,246 nt, respectively) than those of typical members of the family *Paramyxoviridae* with an average genome length of approximately 15,500 nt (Harcourt et al., 2000). Furthermore, both viruses have an unusually broad host range (Harcourt et al., 2000; Murray et al., 1995a) and their genetic constitution, zoonotic potential and their high virulence set them apart from other Paramyxoviruses (Eaton, 2001).

Harcourt et al. (2000) successfully argued that the unique features of the HeV and NiV genomes, their broad host range and antigenic cross-reactivity clearly indicate that they should be considered members of a new genus within the subfamily *Paramyxovirinae* (Wang et al., 2001; Harcourt et al., 2000). NiV and HeV are now classified into a new genus designated *Henipavirus* (Pringle et al., 2005). As a result, two new genera, *Avulavirus* and *Henipavirus*, were added to the *Paramyxovirinae* subfamily (Eaton et al., 2006). Henipaviruses are the only currently recognised zoonotic Paramyxoviruses and are highly pathogenic with case fatality rates in humans reaching more than 75% (Halpin and Mungall, 2007).

Henipaviruses are also known to infect bats (Field et al., 2001). Bats have been identified or implicated as the natural reservoir host for an increasing number of new and often deadly zoonotic viruses (Field et al., 2001). An extensive serological sampling throughout eastern Queensland revealed that of over 5000 sera collected from 46 species, including 34 species of wildlife, antibodies capable of neutralising HeV have only been detected in bats of the genus *Pteropus* (Young et al., 1996). Furthermore, over 25% of sampled pteropid bats, including representatives of all four main species in eastern Australia (the grey-headed flying-fox, *Pteropus poliocephalus*; the black flying-fox, *Pteropus alecto*; the little red flying-fox, *Pteropus scapulatus*; and the spectacled flying-fox, *Pteropus conspicillatus*) were identified as being seropositive to HeV (Halpin et al., 2000).

3. Hendra virus

Two outbreaks of a previously unknown disease in horses and humans occurred in Queensland in1994. The outbreaks occurred within one month of each other in Brisbane and Mackay, which are approximately 1000 km apart. In the Brisbane incident, 21 horses were infected of which 14 died or were euthanised after severe clinical signs of an acute respiratory disease (Young et al., 1996). The autopsy results were shown to be consistent to that of a viral infection (Murray et al., 1995a), histological findings showed focal necrotising alveolitis with many giant cells, some syncytial formation and viral inclusion bodies (Selvey et al., 1995). Ultrastructural studies of viruses isolated from Queensland horses, from experimentally infected horses and from the kidney of the deceased human indicated that the virus had an envelope and ranged in size from approximately 38 nm to more than 600 nm.

The envelope was covered with 10 and 18 nm surface projections giving the particle a “double-fringed” appearance (Murray et al., 1995a). Furthermore, the supernatant of the cell cultures contained free-lying herringbone nucleocapsids that were 18 nm wide and had a periodicity of 5 nm. These observations were consistent with those described for the family *Paramyxoviridae* and the genera *Paramyxovirus* and *Morbillivirus* (Lamb and Kolakofsky, 2001). Moreover, the translation of the PCR sequence and comparisons with known paramyxovirus matrix proteins revealed 50% similarity with the morbillivirus matrix proteins and 80% similarity if conservative amino acid substitutions were used (Murray et al., 1995b). These initial characterisations led to the identification of the agent as equine morbillivirus [EMV) (Murray et al., 1995b). However, subsequent genetic characterisation revealed it was a novel paramyxovirus and eventually, the newly emerged virus was named Hendra virus (HeV) after the geographical location of the index case (Wang et al., 1998).

HeV has continued to emerge in eastern Australia causing fatal infections of horses in 1999 (Field et al., 2001), twice in 2004 (Fields et al., 2007; Choi, 2004), twice in 2006 (Field et al., 2007) and twice in 2007 (Anonymous, 2008). In one of the 2004 incidents, a veterinarian was also infected and recovered with seroconversion. In 2008 there were two simultaneous HeV outbreaks (Anonymous, 2008), involving a further two human infections. In 2009 an outbreak of Hendra virus caused the death of a veterinarian and four horses at a central Queensland property (Anonymous, 2009; Barbeler, 2009). The virus continued to emerge almost every year since first emergence with an increase in the number of HeV incidence in Australia with approximately 34 reported outbreaks since 2011 bringing the total to 48 reported outbreaks.

4. Nipah virus

A major outbreak of acute febrile encephalitis of humans occurred in Malaysia from late 1998 until 1999, which resulted in 265 human cases including 105 fatal cases (Chua et al., 2000a), and 11 cases and one death were reported among pig abattoir workers in Singapore. The Malaysian outbreak was controlled by the culling of over one million pigs and strict quarantine measures on pig movements (Patton et al., 1997). A close association of human cases with pigs suggested that the causative agent was Japanese encephalitis virus (JEV), which is endemic to the region. However, since vaccination against JEV and mosquito control measures failed to end the outbreak, JEV was discounted as a possible cause of the outbreak (Sawatsky et al., 2007).

In March 1999, a novel virus was isolated from cerebrospinal fluid (CSF) of an encephalitic patient from Sungai Nipah village (Chua et al., 1999). Electron microscopy, immunofluoresence and sequence analysis indicated that the new virus was a

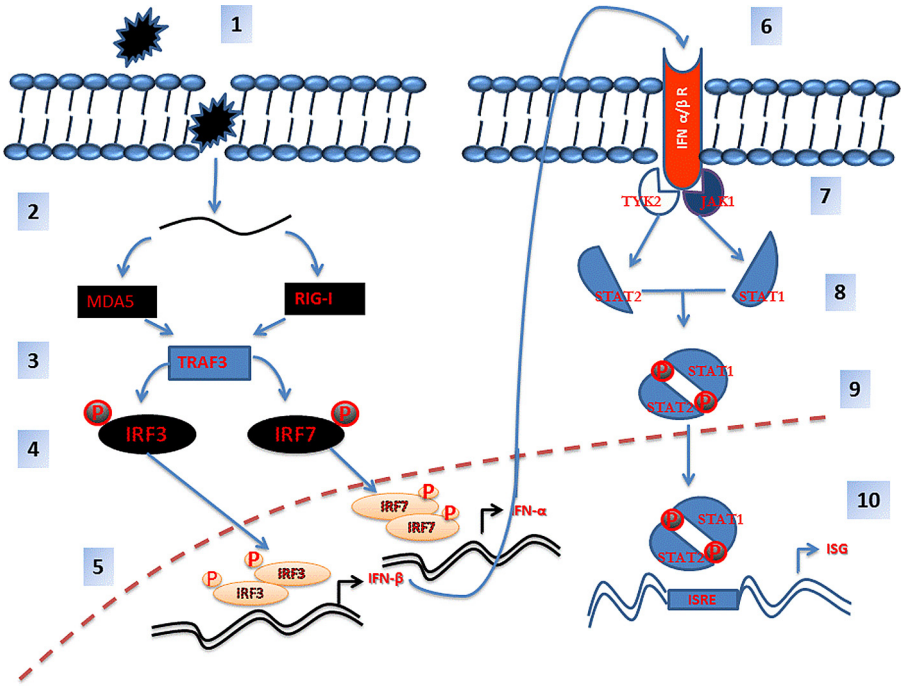

Fig. 1. STAT activation cascade. Upon entry into the cell (Chua et al., 2000a), henipaviruses are recognised by the cytoplasmic receptor RIG I or MDA-5 (Lamb and Kolakofsky, 2001), which will then signal through the adaptor TRAF-3 (Nagai, 1999) and phosphorylate IRF3, which either homodimerises or heterodimerises with IRF-7(Wang et al., 2001) and translocate into the nucleus (Fields et al., 2007), where they activate the transcription of early type I IFNs such as IFN-β. Once released from the cell, IFN-β will bind to the type I IFN receptor (Chua et al., 1999), which will activate a signalling pathway in either an autocrine or paracrine fashion. This will then lead to the phosphorylation of JAK1 and Tyk2 (Harcourt et al., 2000), which results in phosphorylation of STATs (Murray et al., 1995a). Phosphorylated STATs will hetrodimersie (Eaton et al., 2006) and translocate to the nucleus (Eaton, 2001) where they interact with IRF-9 to form ISGF-3, which will then bind to IFN-stimulated response element (ISRE) to activate IFN stimulate genes (ISG) (Pringle et al., 2005). This results in the expression of antiviral proteins and establishing an antiviral state in both infected and neighbouring cells. (Reviewed in Shaw et al., 2004 and Rodriguez et al., 2004).

paramyxovirus closely related, but not identical, to HeV (Sawatsky et al., 2007). The newly emerged virus was named Nipah virus (NiV) after the village of the index case (Chua et al., 2000a; Wang et al., 2001). NiV was shown to be associated with high case fatality rates of approximately 35–75% in humans and roughly 5% in pigs (Sawatsky et al., 2007). The prior knowledge of HeV outbreaks and the similarities between HeV and NiV facilitated the rapid identification of fruit bats as the reservoir hosts of NiV (Field et al., 2001). Furthermore, antibodies to henipaviruses have been detected in five different bat species from Australia, Malaysia, Bangladesh, India, Cambodia, Thailand, Indonesia and Madagascar (Young et al., 1996; Lehle et al., 2007; Peel et al., 2012).

5. Molecular structure

Like all other viruses in the subfamily *Paramyxovirinae*, the Hendra virus and Nipah virus genomes are non-segmented, single-stranded negative sense RNA (Nagai, 1999). Genomes of HeV and NiV are approximately 18.2 kb in size and have genome lengths with multiples of six (Halpin et al., 2004). The "rule of six" stipulates that the paramyxovirus RNA polymerase efficiently replicates only viral genomes counting $6n+0$ nucleotides (Vulliemoz and Roux, 2001). Henipaviruses contain six transcription gene units encoding six major structural proteins, namely the nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G) and large protein (L) or RNA polymerase, in the order 3′-N-P-M-F-G-L-5′ (Lamb and Kolakofsky, 2001; Wang et al., 2001) and three predicted non-structural proteins: C, V and W (7). The V and W proteins are expressed by RNA editing, whereas in other paramyxoviruses, the C protein of NiV and presumably of HeV is expressed from an alternative open reading frame (ORF) within the phosphoprotein (P) gene (Lamb and Kolakofsky, 2001; Harcourt et al., 2000).

5.1. The differences between HeV and NiV

A number of reports have rated the genomic similarities between HeV and NiV to be more than 77% (Wang et al., 2001; Lo and Rota, 2008). Despite the reported similarities between the two viruses, there are many existing features that differentiate each virus. Some of the differences between HeV and NiV include their initial emergence, Australia 1994 and Malaysia 1999, respectively; the amplifying host species, HeV was transmitted via horses, whereas NiV was transmitted through pigs. In contrast, HeV caused a fatal respiratory disease in horses, but it appeared at first that NiV did not cause fatal disease in pigs (Chua et al., 1999, 2000a; Bossart et al., 2002). NiV has been reported to have been transferred from human to human, which was the case in the NiV outbreak in Bangladesh (Gurley et al., 2007a,b). Additionally, direct transmission of virus from flying foxes to humans via contaminated food has been shown (Luby et al., 2006; Harit et al., 2006).

In contrast, HeV was only reported to be transferred from animals to humans with no reports of any human to human cases. Another difference is the fatality rate, while NiV was reported to have a case fatality rate of 75% (Lo and Rota, 2008), HeV showed 57% case fatality rate. This was based on the total reported human fatalities, four, over the total reported number of human infection cases, seven; it is acknowledged that the latter estimate might not be statistically reliable because of the small sample number, the example was used for illustrative purposes.

Bossart et al. (2002), reported a number of interesting differences between the two pathogens, including the functional differences between the efficiencies of the two F glycoproteins in mediating viral fusion, which the authors speculated to be related to the ways in which the HeV and NiV F glycoproteins interact with or engage the G glycoprotein in the fusion process (Bossart et al., 2002). At the genomic level, the NiV and HeV trailer sequence was

reported to be 33 nt long, yet, the two sequences differ by 3 nt (at positions 19, 20 and 21, counting from the 5′ end) (Chan et al., 2001). While it might be argued that these differences are insignificant, but considering the differences in infectivity and lethality that were observed during the outbreaks, we can only speculate about the role that these small differences might have played.

5.2. Molecular mechanism of pathogenicity

Antiviral innate immune induces a signal transduction cascade that results in the production of type I interferon (IFN), other proinflammatory cytokines, and cell-intrinsic factors important for the generation of an antiviral cellular environment (Andreas Pichlmair et al., 2006). IFN induce an antiviral state in uninfected cells and may inhibit virus replication in infected cells as well as enhance the adaptive immune response (Andrejeva et al., 2002). Recognition of viral particles by the pattern recognition receptor [PRR] that bind ligands containing pathogen, stimulate the production and release of IFN-β from infected cells. The released IFN-β then binds to IFN-α/β receptor, which stimulates the JAK/STAT pathway, which upregulates the transcription of IFN stimulated genes (ISGs). This activation results in the production of antiviral proteins such as PKR and Mx that inhibit viral replication in infected cells and halt infection of neighbouring uninfected cells (Shaw et al., 2004) (Fig. 1). A critical component of the JAK/STAT signalling pathway is the signal transducer and activator of transcription 1 (STAT1), which is a member of the STAT family of transcriptional factors. STAT1 is activated by IFN-α/β and other cytokines and growth factors (Stark et al., 1998). STAT activation includes tyrosin phosphorylation by JAK family kinases, resulting in STAT1 and STAT2 hetrodimarisation via SH2 phosphotyrosin interactions (Garcia et al., 2006; Darnell et al., 1994). These will then complex with IFN regulatory factor 9 to create a transcription factor called ISGF-3 (Darnell et al., 1994). Many viruses have evolved molecular mechanisms, by which they avoid cellular antiviral response by targeting IFN production and STAT-dependent IFN signalling.

NiV- P protein, which encodes C, P, V and W, has been shown to supress IFN production and signalling. The proteins display physical interaction with STAT 1 and appear to sequester STAT 1 away from activating Janus Kinases that does not result in degradation (Ciancanelli et al., 2009). Cells transfeceted with NiV P or V proteins and treated with IFN-α/β, were shown to have their STAT 1 retained in its inactive and unphosphorylated form in the cytoplasm. In contrast, the W protein localises the inactive STAT 1 in the nucleus (Shaw et al., 2004, 2005; Rodriguez et al., 2004). However, cells infected with recombinant NiVs containing various mutations in the P gene, showed that multiple elements encoded by the P gene have both distinct and overlapping roles in modulating virus replication and limiting the cellular antiviral response (Lo et al., 2012).

Furthermore, Mathieu et al. (2012) reported that cells stably expressing NiV C showed a reduced level of proinflammatory cytokines production, and that hamsters infected with recombinant virus lacking the expression of NiV C (NiV△C) developed successful inflammatory reactions and anti-NiV immune responses, thus limiting viral infection, which suggests that C protein plays an important role in NiV pathogenesis that the protein achieves by modulating the production of early-induced proinflammatory chemokines, consequently leading to an inappropriate immune response and lethal outcome of the infection.

5.3. Diseases caused by HeV and NiV

5.3.1. Clinical presentation

The first known human infections with NiV were detected during an outbreak of severe febrile encephalitis in peninsular Malaysia and Singapore from the fall of 1998 to the spring of 1999 (Lo and Rota, 2008). There were more than 276 patients reported as having NiV induced viral encephalitis in peninsular Malaysia and Singapore, mostly among adult males who were involved in pig farming or pork production activities, with 105 fatalities (Chua et al., 1999). However, the reported number of patients who survived the acute NiV encephalitis was 160 (Bellini et al., 2005) with 7.5% prevalence of relapsed encephalitis (12/160 patients) more than 24 months after the outbreak. Of the 89 patients previously known to have nonencephalitic or asymptomatic Nipah virus infection, three (3.4%) developed late-onset encephalitis (Tan and Wong, 2003). This might in part be due to the fact that the initial infection was presumably not severe enough to cause neurological manifestations (Tan and Wong, 2003). Most patients presented with a severe acute encephalitic syndrome, but some also had significant pulmonary manifestations (Goh et al., 2000; Patton et al., 1997).

However, the main clinical features at presentation were fever, headache, dizziness, vomiting and reduced levels of consciousness (Goh et al., 2000). Similarly, HeV human clinical presentations included influenza-like illness that can progress to pneumonia, encephalitis type symptoms such as headache, high fever, and drowsiness, which can progress to convulsion or coma. Horses, on the other hand, can develop an acute respiratory or neurological syndrome quickly leading to death in most cases (Anonymous, 2008; Chua et al., 2000b). Seizures occurred in 23 percent of all patients, and all but one of these patients had generalised tonic–clonic seizures; that patient had focal motor seizures with secondary generalisation. Distinctive clinical signs included segmental myoclonus, hypertension, tachycardia, areflexia, and hypotonia (Tan and Wong, 2003). Other pathological features, which are common to both viruses as well, are interstitial pneumonia and encephalitis (Daniels et al., 2001; Hooper et al., 2001).

5.4. Tissue pathology/tropism

One of the main pathological features of both HeV and NiV infections in vitro is the formation of syncytia in vascular epithelial tissues (Fig. 2). Histopathological findings from NiV infected animals and guinea pigs, revealed evidence of endothelial and/or epithelial syncytial cells as well as mural lymphohistiocytic vasculitis with fibrinoid vascular change (Torres-Velez et al., 2008). The autopsy results of the first HeV human victim revealed lesions of congestion in his lungs, haemorrhage and oedema associated with histological chronic alveolitis with syncytia (Murray et al., 1995a,b). Furthermore, a pathological study derived from a series of 32 NiV fatal human cases by Wong (2000), reported a general difficulty in identifying small lesions caused by NiV in central nervous system (CNS); however, they found a few, small, discrete, occasionally haemorrhagic, necrotic lesions (Wong, 2000). The study reported significant histopathological changes in the blood vessels and parenchyma of multiple organs. Additionally, vasculitis was seen in 62% of the tested lungs and fibrinoid necrosis was found in 59% of cases (Wong et al., 2002). However, from animal experiments (guinea pigs), organs such as the spleen, lymph nodes, urinary bladder, ovary, uterus and brain were the most notably affected organs (Torres-Velez et al., 2008).

5.5. Susceptibility of different cell lines to HeV and NiV infections

The fact that henipaviruses are highly pathogenic with a broad range of hosts raises the question of whether they are capable of infecting a broad range of cells in vitro as well. In order to determine this, the susceptibility of different cell lines to henipaviruses infection was investigated in this thesis. Briefly, variable differences in virus replication and giant cell (syncytia) formation amongst different cell lines were observed in the study (Aljofan et al., 2009a).

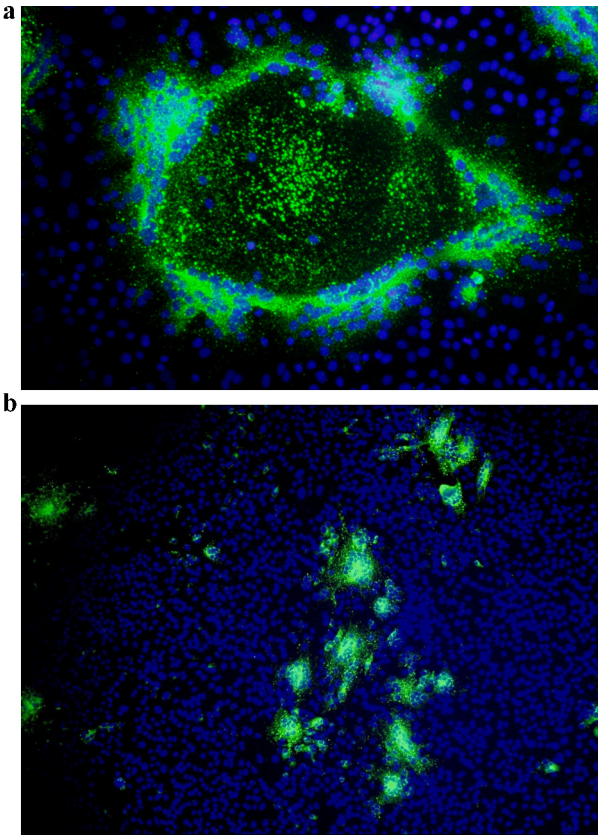

Fig. 2. Monolayer of Vero cells infected with NiV (a) and HeV (b) overnight at 37 °C. Merge of anti-NiV N detected by Alexa-fluor 488 conjugated antibody with DAPI counterstain. The image shows the syncytia formation as a result of viral infection. Images were visualised using an Olympus IX71 inverted microscope coupled to an Olympus DP70 high resolution colour camera with 20× magnification.

While African green monkey (Vero) and baby hamster kidney cells were the most susceptible to henipavirus infections, human bladder cancer cell line and human alveolar basal epithelial cells were the least susceptible cell lines to henipavirus infections. While the Hela cell line was quite susceptible to viral infection, Hela- USU, a modified cell line that lacks the Ephrin protein required for HeV and NiV infection was reported to be very resistant to viral infection (Bossart et al., 2005a,b, 2008; Bonaparte et al., 2005).

Interestingly, at 18 h post infection using Vero cells, NiV was noticed to replicate to a higher titre compared to HeV, a finding that was observed during the process of the development of a High Throughput Screening for antivirals (Aljofan et al., 2008, 2009a). While, the mechanism behind the observed difference is still unclear, it may be valid to speculate that the rapid in vitro replication of NiV is related to its high fatality rate; and that significant differences between the two viruses make one virus generate more viral particles than the other.

However, it is well documented that henipaviruses rapidly (within 24 h) generate large syncytia in monolayers of Vero cells (Fig. 2) and that virus P proteins are detectable in both Hendra and Nipah virus-induced syncytia (Crameri et al., 2002). Syncytium formation is a common effect of paramyxovirus infection (Brooks et al., 2007) and subsequent generalised cell fusion has been reported as a potentially important mechanism of virus-induced cytotoxic effects (Okamoto et al., 1997). Cells expressing the fusion and attachment glycoproteins at their surfaces can mediate the formation of syncytia (Bossart et al., 2002). Therefore, cell fusion of paramyxovirus-infected cells with neighbouring cells to form multinucleated syncytia contributes to the pathogenic effects of paramyxoviruses (Okamoto et al., 1997; Negrete et al., 2005, 2006).

6. Therapy

There are no vaccines or therapeutic remedies available to either prevent or treat patients exposed to henipaviruses (Halpin and Mungall, 2007). Given their high lethality, relative ease of procurement and lack of therapeutics for clinical treatment, henipaviruses are classified as biological safety level 4 (BSL4) pathogens and are listed as National Institute of Allergy and Infectious Diseases (NIAID) category C priority pathogens.

There have been a number of compounds tested against henipavirus infections both in vitro and in vivo (Table 1) shows some of the tested compounds, however, the only antiviral compound with demonstrated clinical efficacy against henipaviruses is ribavirin, a broad spectrum antiviral often used to treat Hepatitis C infection (Siebert and Sroczynski, 2003). A limited non-randomised clinical trial of ribavirin during the initial NiV outbreak in Malaysia indicated a reduction in mortality of acute NiV encephalitis (Chong et al., 2001). An in vitro study of ribavirin showed a more than 50 fold reduction in HeV infection (Wright et al., 2005). Although, these two studies have shown that ribavirin is effective both in vitro and in a clinical trial, there are a number of studies indicating that ribavirin is also associated with a range of side effects such as haemolytic anaemia (De Franceschi et al., 2000). This might result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions (Shakil et al., 2002).

Nonetheless, a number of in vitro studies have reported potential antiviral agents for the treatment of henipavirus infections (reviewed in Vigant et al., 2011), including gentian violet, brilliant green, gliotoxin (Aljofan et al., 2009b) and chloroquine (Porotto et al., 2009), which failed to inhibit the virus in vivo (Pallister et al., 2009). Also, the screening of 18 derivatives of the antibiotic quinolone, have resulted in the identification of five potential antiviral compounds, including two compounds that have inhibited the syncytium formation induced by infectious NiV and showed a low cytotoxicity in Vero cells (Niedermeier et al., 2009). Recently, Porotto et al. (2010) reported antiviral efficacy of an experimental peptide derived from C-terminal heptad repat (HRC) regions in the F-protein of NiV with a cholesterol tag that inhibit NiV fusion in hamster (Porotto et al., 2010). However, a potentially effective post-exposure therapy is the human monoclonal antibody (mAb) known as m102.4. This antibody has been used in humans, and in Queensland, Australia they have a limited licence to use in high risk exposures. Bossart et al. (2011), illustrated that the use of this neutralising human monoclonal antibody in African green monkeys challenged with a lethal dose of HeV, provided 100% survival rate. While, the animal subjects displayed some neurological signs of the disease, they have all survived the infection by day 16 (Bossart et al., 2011; Broder, 2013).

As part of finding a potential treatment against the lethal infections, several vaccine candidates have been tested for potential protection (Table 2). Fortunately, the anti henipavirus vaccine research has been successful in finding a potential vaccine, with two independent groups have announced the discovery of potential Hendra virus therapy. The developed vaccine, the only effective therapy against Hendra or Nipah virus infection, commercially known as Equivac HeV®, is a soluble form of the G glycoprotein, which is licensed for horses only.

The successful discovery of Equivac HeV® is the result of a collaborative research programme between Uniformed Services, University of the Health Sciences and the Henry M. Jackson Foundation, the Australian Animal Health Laboratory and Zoetis, Inc. (Broder et al., 2013). The finding was first announced in 2011 in an

Table 1
Compounds tested against henipavirus infection.

Drug	Target	Test		Outcome		Reference
		In vitro	In vivo	Efficacy	Adverse effect	
Ribavirin	Viral replication	Y	Y	Reduced mortality	Associated with haemolytic anaemia	Siebert and Sroczynski (2003) and De Franceschi et al. (2000)
Gliotoxin	Viral replication/transcription	Y	N	Inhibited viral replication	High toxicity	Aljofan et al. (2009b)
Gentian violet, Brilliant Green	Unknown	Y	N	Inhibited viral replication	Not suitable for systemic use	Aljofan et al. (2009b)
Chloroquine	Cleavage	Y	Y	Inhibited viral cleavage in vitro	Ineffective in vivo	Porotto et al. (2009)
Mibefradil, Verapamil, praziquantel	Replication	Y	N	Inhibited viral replication in cells	Not-tested in vivo can provide potential candidate	Aljofan et al. (2010)
LJ001	Viral entry	Y	N	Inhibited a majority of enveloped viruses	Not-tested in vivo can provide potential candidate	Wolf et al. (2010)

Table 2
Potential vaccines against *henipavirus* infection.

Vaccine	Tests		Efficacy	Licensed	References
	Animal	Human			
Measles virus vaccine expressing NiV G protein	AGM	N	2/2 animals showed no clinical illness	N	Yoneda et al. (2013)
Adeno-associated virus vaccines expressing the NiV G protein	Hamster	N	100% protective against NiV, 50% against HeV	N	Ploquin et al. (2012)
Recombinant subunit HeV G protein vaccine	AGM	N	100% protection	Licensed to be used in horses only	Bossart et al. (2012) and Broder et al. (2013)

AGM: African green monkey.

Australian radio and the study results were later announced in a veterinary meeting in Australia (ABC radio 17/05/2011). While we are hopeful that a reliable treatment might soon appear on the horizon, the recent identification of a potential equine Hendra vaccine revives the question whether is it a light at the end of the tunnel or is it another train?

7. Conclusion

Since their first recognition as newly emerged viruses, almost two decades ago, HeV and NiV continue to possess high risk fatal infections to humans and animals alike both in Queensland and part of East and South East Asia, respectively. While the henipaviruses have only been detected in sub/tropical areas of South East Asia and Oceania, the geographic range of infection is still undefined. Hence, it is essential to evaluate the strategy of potential spread of henipaviruses to other parts of the world, as well as to review research priority with a focused effort on developing vital emergency post exposure antivirals as a defensive means.

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