REVIEW ARTICLE

NOVEL MURINE PARAMYXOVIRUSES.

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Abstract

Many paramyxovirus pathogens jump species, causing resurging or re-emerging diseases in spill-over hosts including humans. Novel murine *J virus* and *Mojiang paramyxovirus* can infect humans causing subclinical and fatal diseases, respectively. This review focuses on seven novel murine paramyxoviruses: *J virus*, *Mojiang paramyxovirus*, *Nariva virus*, *Mossman virus*, Rodent *Paramyxovirus* of Zambia, *Beilong virus,* and *Tailam virus*, that had been isolated since 1960s. The methods for data mining using ProQuest, PubMed, Clinical key and other searches revealed the history of the first isolations, host species, propagation systems and genetics of the novel murine viruses. Further studies will give better understanding on the geographical distributions, evolution and biology of the paramyxoviruses which can be a potentially useful biological resource for disease research, like their well-characterized relative, the murine *Sendai virus*.

Keywords: *Beilong virus, J virus*, *Mojiang paramyxovirus*, *Mossman virus*, *Nariva virus*, *Paramyxoviridae*, *Paramyxovirus*, Rodent *Paramyxovirus* of Zambia, *Sendai virus, Tailam virus*

Introduction

Paramyxoviruses (PMVs), *viz*, *Mumps virus* (MuV), *Measles virus* (MeV), *Respiratory syncytial virus* (RSV), *Human parainfluenza virus* (PIV) *1-4*, *Avian paramyxovirus-1*, *Hendra virus* (HeV), *Menangle virus* (MenPV), *Nipah virus* (NiV), *Tioman virus* (TioPV) and human *Metapneumovirus* cause important zoonoses in humans[1], making them relevant to human health.

Animals PMVs may jump species to have spill-over hosts. *Achimota virus* and *Ghanaian bat henipavirus 1* jumps from bats, *Eidolon helvum* to humans; HeV from fruit bats, *Pteropus alecto*, to horses, humans and dogs; *J virus* (J-V) from rodents, *Mus musculus* to humans, pigs and cattle; MenPV from *Dobsonia magna* to pigs and humans; *Mojiang virus* (MojV) from *Rattus flavipectus*, and NiV from bats, *Pteropus spp*. to pigs, humans, horses, dogs, goats, cattle and cats; *Porcine rubulavirus* from *Sus scrofa* to pigs and humans; *Sosuga virus* from primates, *Homo sapiens*, to humans; TioPV from *Pteropus spp.* to pigs and humans[2].

The two novel murine PMVs, namely, J-V and *Mojiang virus* (MojV) had been reported to infect humans. *J virus* of genus *Jeilongvirus* isolated from rodentia, *Mus musculus*, in Queensland, Australia, had its antibody detected in humans[3, 4]. Serum neutralization tests showed anti-J-V antibody at titres 5 or more in 2/91 humans studied in Australia[5]. *Mojiang virus* found in rats, *Rattus flavipectus*, was associated with severe pneumonia and deaths of three miners in Yunnan Province, China[6].

Nipah virus, MuV and MeV can cause diseases that are undergoing global resurgence and re-emergence, thus threatening the human health. In the USA, measles was declared eliminated in 2000, due to high rates of vaccination coverage, but importations of the disease from endemic regions have led to recent outbreaks of measles in the USA[7]**.** Clinical mumps declines in the USA, since the implementation of the MMR vaccine in 1989; but despite vaccination, resurgence still occurs[8]. Although mumps is a vaccine-preventable disease, resurgence is observed in many locations worldwide due to anti-vaccination sentiment[9]. The first outbreaks of Nipah disease in Bangladesh occurred in 1999, but the disease re-emerged in 2001 and 2003, most likely through close contact with other patients or from exposure to a common source, *Pteropus* bats, that might have transmitted the virus[10].

Seven novel PMVs have emerged from murine species. This review article describes the isolations, host species, propagation and genetics of the novel murine PMVs, namely, J-V [4, 5], MojV[6], *Nariva virus* (NaV) [11, 12], *Mossman virus* (MoV)[13], rodent *Paramyxovirus* of Zambia[14], *Beilong* virus (BeV)[19, 21], *Tailam* virus (TlmPV)[21], highlighting many research findings together with the current knowledge about the subject as well as research gaps that need to be covered. Knowledge on the characteristics of the PMVs may make them a potentially useful biological resource for disease research.

Materials and Methods

The methods used for locating, selecting, extracting, and synthesizing data on the novel murine PMVs since May 2014 include ProQuest, PubMed and clinical key searches.

Results

The data mining revealed reported information on the isolations, host species, propagation and genetics of seven novel murine PMVs: J-V [4, 5], MojV)[6], NaV[11, 12], MoV[13], and rodent *Paramyxovirus* of Zambia[14], BeV[19, 21], and TlmPV[21], that have been isolated since 1960s.

J virus

J virus was isolated by kidney auto-culture from moribund mice, *Mus musculus*, trapped in 1972 in Queensland, Australia[4, 5]. The mice had extensive pulmonary haemorrhage[5]. The PMV produced

cytopathic effect (CPE) in primary mouse kidney (CSL217) and lung, human lines: MRC5 and Hep2, pig kidney (PS), baby hamster kidney (B11K21) and monkey kidney (Vero) cells[5]. The CPE occurred as monolayer destruction with vacuolated syncytium formation and diffuse eosinophilic cytoplasmic inclusions without nuclear changes. No CPE was seen in human lines Hela or Chang liver, bovine kidney (MDBK) cells or rat fibroblasts (RT). The virus multiplied in the cell cultures with CPE, with virus yields that varied between $lO^{5.5}$ and $lO^{6.5}$ tissue culture infectious doses (TCID) per 0.1 ml. RK13 and Vero cell cultures were used for J-V plaque purification or passage[19]. The virus could be stored in culture fluids without loss of titre for 6 months at -20° or -70°C. Effects of lipid solvents, heat and pH on the infectivity titre of Log_{10} $TCID_{50}$/0.1 ml of J-V was comparable with PIV-*3*[5]. Electron microscopy (EM) revealed a virion morphology and herringbone-shaped nucleocapsid structure with a diameter of 15 nm, typical of the PMVs. Haemagglutinin of J-V could not be detected using complement fixation (CF) antigen for J-V at different temperatures with mouse, rat, guinea pig, rabbit, chicken, goose, pig, sheep, cattle, horse or human Type O erythrocytes[5]. A serological survey in Australia detected the presence of serum neutralizing antibodies against J-V in wild rodents, pigs, cattle, and humans[5]; but a similar survey on North American mammals failed to detect antibodies against J-V in laboratory mice, humans, or hamsters[5, 19]. Mouse hyperimmune ascitic fluid to J-V at a selected homologous CF titre was tested against CF antigen from a range of viruses, and J-V CF antigen at a selected titre was tested in parallel against CF reference fluids or antisera to the same range of viruses. No serological relationship was detected to antigens of PIV-1, 2 or 3, *Influenza virus* A, B or C, MeV, MuV, *Newcastle disease virus* (NDV), RSV, NaV, rat *Coronavirus* or lymphocytic choriomeningitis agent. One-way tests of CF reference sera to PIV-4 and MoV against J-V antigens were also negative[5]. During the mid-1970s[5], J-V animal-infection experimentation findings showed that intranasal or subcutaneous inoculation of J-V into weanling laboratory mice and rats was not associated with clinical signs of disease. Post-mortem examination up to 3 weeks post-inoculation revealed various degrees of haemorrhagic interstitial pneumonia, and J-V was isolated from blood, lungs, and pooled liver, kidney, and spleen samples, indicating the presence of viraemia. Intranasal J-V inoculation of pigs did not cause any clinical signs of disease or pathology. No virus was isolated from any of the pigs, although two developed significant serum neutralizing antibody levels. The disease-causing potential of J-V remains somewhat unclear. The complete genome sequence of J-V, had been characterized[19]. Containing 8 genes, the J-V genome has a unique structure and represents a substantial contribution to the genetic diversity of *Paramyxoviridae*. The complete genome sequencing revealed a genome structure unique within the *Paramyxoviridae*[19]. At 18,954 nucleotides (nt), the J-V genome contains 8 genes in the order: 3'-N-P/V/C-M-F-SHTM-G-L-5'. The genomes of the J-V are much larger than most other PMV genomes, contain several novel genes and have an exceptionally large gene for the attachment protein[19, 20]. The J-V G gene has 4,401 nt.

Mojiang paramyxovirus

Mojiang paramyxovirus was detected in rats, *Rattus flavipectus*, in China[6]. In 2012, severe pneumonia without a known cause was diagnosed in three persons who had been working in an abandoned mine in Mojiang Hani County, China; all three patients died. Half a year later, the researchers investigated the presence of novel zoonotic pathogens in natural hosts in the cave. Anal swab samples were collected from bats, *Rhinolophus ferrumequinum*, rats, *Rattus flavipectus*, and musk shrews, *Crocidura dracula* from the mine for virome analysis. On the basis of the non-redundant protein alignment results, the identified 38 sequence reads were classified as *Henipavirus* spp.[6]. However, the sequences

shared low nt and amino acid identities with known henipaviruses. *Mojiang paramyxovirus* shares similar features with known henipaviruses. The virus has a genome length of 18,404 nt. Thus, considering the similar genome features between MojV and other henipaviruses, the researchers confirmed that MojV could be classified as a new species closely related to *Henipavirus* spp. Specific nested primer sets targeting the L gene of MojV were designed to separately re-evaluate the anal swab samples and tissue samples. The anal swab samples from the rats were positive for MojV, and a tissue sample from one MojV-positive rat was also MojV-positive. All samples from the bats and musk shrews were MojV-negative. The MojV-positive anal swab samples were cultured in Vero E6, Hep2, and BHK21 cells for virus isolation; no CPE or viral replication was detected after two blind subculture passages. The presence of a henipa-like virus, MojV, in the rats indicates that *Henipavirus* spp might infect more mammalian hosts than previously thought and that bats may not be the only hosts of henipaviruses[6].

Nariva virus

Nariva virus was isolated from Trinidadian rodents, *Zygodontomys b. brevicauda*, in the early 1960s[11, 15]. The virus grew in suckling mouse brain and formed syncytia in Vero and BHK cells and was identified as a PMV mainly based on the structure of its nucleocapsids of approximately 20 nm in diameter and mean length of 1.8 nm. Its virion is an enveloped, pleomorphic sphere with surface projections[16]. There is no serological cross-reactivity with PIV types 1-4, MuV, NDV and MeV[15]. It resembles respiroviruses and rubulaviruses in that it generates only cytoplasmic inclusion bodies in virus-infected cells[16]; so, it differs from morbilliviruses that produce cytoplasmic and nuclear inclusions in infected cells. Its haemagglutinin (H) could not be detected using CF antigen for J-V at different temperatures with mouse, rat, guinea pig, rabbit, chicken, goose, pig, sheep, cattle, horse or human type O erythrocytes[5, 15]**.** However, haemagglutination and cell-binding studies performed on guinea pig and monkey erythrocytes suggested that NaV, like MeV, does not use sialic acid receptors on red blood cells as do respiroviruses and rubulaviruses[15]. Analysis of the NaV H protein also revealed the lack of the consensus NRKSCS sequence motif known to be important for sialic acid binding for the HN proteins of respiroviruses and rubulaviruses[17]. The NaV genome is 15,276 nt long, conforms to the rule-of-six, and has a genome organization typical of most PMVs, with 6 transcriptional units in the order: 30-N–P-M-F–H-L-50[12]. Post-intracranial inoculation of suckling hamsters, NaV produced acute necrotizing encephalitis, large amounts of infectious virus, and virus antigen in the brain; but weanling hamsters had only small amounts of infectious virus and only early in the disease, when they were well; later, when clinically ill, they had a non-productive infection with continuing evidence of viral antigen, but no detectable infectious virus. Weanlings died later than sucklings with less cerebral parenchymal necrosis.

Mossman virus

Mossman virus was isolated from rats: *Rattus leucopus,* in 1970 near Mossman, Australia and *Rattus fuscipes* in 1971 about 1500 km away at Canungra[13]. Based on the CPE of MoV in cell culture, the structure of virions and nucleocapsids on EM and the lack of reactivity with antisera to a wide range of viruses, including NaV and J-V, it was concluded that MoV was a new PMV. The natural mode of transmission of MoV is not known. A survey in Queensland in 1998 to 1999 showed that the trapped rats were positive for the presence of antibodies against MoV, indicating that MoV (or a closely related virus) was then still in circulation in Queensland's rodent populations approximately 30 years after its first isolation in the same region. This virus was the first member of novel murine PMVs to be characterized at the molecular level by complete genome sequencing[18]. The results of genomic and protein analyses of the MoV confirmed that MoV is a

novel PMV[18]. It appears to be more closely related to shrew *Tupaia paramyxovirus* (TPMV). Together with equine *Salem virus* (SalV), MoV and TPMV make up a new collection of novel murine PMVs situated evolutionally between the genera *Morbillivirus* and *Henipavirus*[18].

Rodent *Paramyxovirus* of Zambia

A high prevalence of PMVs occurs in wild rodents and shrews in Zambia[14]. PCR assays were used to detect the presence of PMV RNA in the animal specimens. Phylogenetic analysis revealed that the viruses were novel PMVs and could be classified as *Morbillivirus*- and *Henipavirus*-related viruses. The findings suggest that there is a circulation of previously unknown PMVs in African rodents and shrews, and provide new information regarding the geographical distribution and genetic diversity of PMVs.

Beilong virus

Beilong virus is most closely related to J-V and TlmPV[19, 21]. Both were found to originate in rodents and BeV was amplifiable from a rat kidney mesangial cell line. A study to evaluate BeV in Hong Kong in 2008 till 2009 used kidney, spleen, respiratory swab, and anal swab samples from asymptomatic rats: brown rats (*Rattus norvegicus*) and black rats (*R. rattus*), bats, cats, cattle, dogs, hamsters and pigs. Results of reverse transcription PCR for a fragment in the large gene of BeV were positive only for the rodent kidney and spleen samples. This study suggests that BeV and its variants are endemic amongst the rats, but it is not known whether transmission is vertical or horizontal[21].

Tailam virus

During an epidemiological study in rodents for PMVs in 2008 till 2009, a novel PMV was isolated from the kidneys and spleens of Sikkim rats, *Rattus andamanensis*, at Tai Lam, Hong Kong[21]**.** The virus was closely related to, but significantly different from BeV and J-V. Named as *Tailam virus* (TlmPV), it contains 8 genes (3’-N-P/V/C-M-F-SH-TM-G-L-5’) of size: 19,152 bases[22]. The complete genome of TlmPV-strain TL8K has been sequenced and submitted to GenBank under accession number JN689227[21].

Discussion

Since the isolations of NaV, J-V and MoV from rodents during the last 40 years, none of which had been characterized at the molecular level until 2003[18]. Both NaV and MoV share a uniform genome structure consisting of six genes in the order: 3′-N-P-M-F-H/HN/G-L-5′[12, 19] but distinctly, the genomes of three other rodent PMVs (BeV, TilmPMV and J-V) contain 8 genes in the order: 3′-N-P/V/C-M-F-SH-TM-G-L-5′[21]. Although J-V/BeV and NaV/MoV represent two quite different groups of murine PMVs in terms of genome size and organization, their proteins do share more sequence identity than any other known PMVs[12]. The only common feature among all known rodent PMVs is the lack of the multibasic cleavage site present in most other PMVs[12].

Sequence comparisons with other PMVs had been carried out both to predict biological properties of murine PMVs and to ascertain its taxonomic position within the family, *Paramyxoviridae*. Phylogenetic and genomic evidences support the grouping of BeV, TimPV, and J-V into a new genus of *Paramyxovirinae*[21]. Until recently, almost all viruses belonging to *Paramyxovirinae* shared a uniform genome structure consisting of 6 genes in the order: 3’-N-P-M-F-H/HN/G-L-5’ [19].

The murine PMVs share many genetic features, not only confirming their murine origin, but also suggesting that they evolved from a common progenitor virus[12, 21]. The ancestor of these closely related PMVs was speculated to have infected the common ancestor of rats and mice, with subsequent co-evolution and divergence with the host[21]. The characterization of the complete genome sequence of rodent PMVs further highlights the great genetic diversity present among the PMVs of wildlife origin, ranging through bats, rodents, reptiles and fish[12].

The genomes of TlmPV, BeV and J-V contain 8 genes in the order: 3'-N-P/V/C-M-F-SH-TM-G-L-5'[21]. Similar to BeV and J-V, the G gene of TlmPV is particularly large, almost twice of those in other PMVs[21]. Taken together, these novel features represent the most significant divergence to date from the common six-gene genome structure of *Paramyxovirinae*. The characterization of the virus genome could also provide valuable information to aid in understanding of virus evolution within *Paramyxoviridae*. Although novel murine PMVs and other members of the family show genetic diversity, they can be a potentially useful biological resource for disease research, like their well-researched relative, *Sendai virus* (SeV), which has many uses that add value to human life. *Sendai virus* remained as the only known member of *Paramyxoviridae* of rodent origin until the later characterization of NaV[12], MoV[18], J-V[19], TlmPV[21] and BeV[21]. *Sendai virus*, a PIV, is a relative of other PMVs described in this review, although it belongs to the genus, *Respirovirus*. The virus was first isolated from a human specimen; but it is believed to have rodents as its natural reservoir[17] and represents the first and best characterized member of *Paramyxoviridae* of rodent origin. As results of intensive research development, SeV finds its many beneficial uses in healthcare industry. It is used in gene transfer and gene therapy and prophylaxis as applications following its role as a virus experimental model. It has been developed as an experimental model of several pathological disorders such as antibody-related nephropathy[24, 25] and asthma[26, 27, 28, 29]. The virus has emerged as a prototype vector for gene transfer approaches[17]. Extraordinary features of SeV that are useful for gene transfer are: (i) the remarkably brief contact time for cellular uptake[23]; (ii) a strong but adjustable expression of foreign genes[30]; (iii) a vector with potent infectivity in most mammalian cells[31, 32 33, 34, 35]; (iv) transduction of target cells being independent of the cell cycle[23]; (v) an exclusively cytoplasmic replication cycle independent of nuclear functions and without a DNA phase[30]; and (vi) the availability of non-transmissible SeV vectors with efficient gene transfer and expression[23]. Many findings from research works using recombinant SeV as a tool, especially as a vector for gene transfer, are applied in gene therapy and prophylaxis. *Sendai virus* vectors have been developed for gene therapy against several pathologies such as respiratory diseases[36], cardiovascular diseases[37], tumours[38], immunological disorders[40], and neurological disorders[41]. The vectors have also been developed for vaccines against melanoma[39], RSV[42], and human PIV [43, 44].

Conclusions

Discoveries of novel murine PMVs in Australia, Japan, China, and Africa have happened since 1960s. Future findings of surveys on novel murine PMVs in other countries may provide valuable information to aid in understanding of the PMV global geographical distributions as well as their biology and evolution. The pathogenicity of rodent PMVs remains somewhat unclear. Further studies are required to determine whether the viruses have the potential or altered pathogenicity to infect and cause diseases in humans and animals. Detection of BeV and TlmPV in rodent kidney and spleen samples, but not respiratory or anal swabs, suggests that they are probably systemic viruses excreted in urine21. Studies on tissue tropism using the novel murine PMVs may add knowledge on their infectivity in experimental animals. Also, established research and therapeutic methodologies using SeV can also be applied in studies on the novel murine PMVs, so that they too can be a potentially useful biological resource for disease research.

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Conflicts of interest / Competing interests

The author discloses that he does not have any and all conflicts of interest that he may have with publication of the manuscript or an institution or product that is mentioned in the manuscript and/or is important to the outcome of the study presented. He also discloses that he has no conflict of interest with products that compete with those mentioned in their manuscript.

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