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Molecular biology, pathogenesis and pathology of mumps virus

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Abstract

Mumps is caused by the mumps virus (MuV), a member of the *Paramyxoviridae* family of enveloped, non-segmented, negative-sense RNA viruses. Mumps is characterized by painful inflammatory symptoms, such as parotitis and orchitis. The virus is highly neurotropic, with laboratory evidence of central nervous system (CNS) infection in approximately half of cases. Symptomatic CNS infection occurs less frequently; nonetheless, prior to the introduction of routine vaccination, MuV was a leading cause of aseptic meningitis and viral encephalitis in many developed countries. Despite being one of the oldest recognized diseases, with a worldwide distribution, surprisingly little attention has been given to its study. Cases of aseptic meningitis associated with some vaccine strains and a global resurgence of cases, including in highly vaccinated populations, has renewed interest in the virus, particularly in its pathogenesis and the need for development of clinically relevant models of disease. In this review we summarize the current state of knowledge on the virus, its pathogenesis and its clinical and pathological outcomes.

Keywords

mumps; mumps virus; pathogenesis; neurovirulence; vaccine

Introduction

Before routine mumps vaccination programmes were introduced, 95% of adults had serological markers of exposure, with peak acquisition during childhood [1–4]. Following the use of mumps vaccine in the USA in the late 1960s, disease incidence declined dramatically, and by the 1980s very few cases were reported. By 2001 the disease was on

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the verge of elimination, with <0.1 cases/100,000 population reported [5], representing a 99.9% decrease in disease incidence compared to the prevaccination era. Similar success in mumps control was achieved in other countries through vaccination. However, within a few years of these historic lows, large, sporadic mumps outbreaks began to appear globally, involving a high percentage of persons with a history of vaccination [6–20]. The reason for the lower than expected efficacy of mumps vaccines is a subject of much debate, ranging from waning immunity to the emergence of virus strains that might be capable of escaping immunity engendered by the vaccine. In addition to questions over vaccine efficacy, safety concerns have come to light following reports of meningitis linked to some vaccine strains used outside the USA. This has led to withdrawal of some vaccine strains and, in some cases, complete cessation of mumps vaccination. In Japan, for example, mumps vaccination was removed from the national immunization programme. Japan now has one of the highest rates of mumps among developed countries, with over a million cases reported annually [21,22]. Considering the numerous issues surrounding mumps, including ongoing outbreaks, a review of MuV pathogenesis is timely.

Humans are the only natural host of MuV. The disease is characterized by painful swelling of the parotid glands, but can involve numerous other tissues and organs, resulting in a wide array of inflammatory reactions, including encephalitis, meningitis, orchitis, myocarditis, pancreatitis and nephritis [23]. Mumps is self-limiting, often with complete recovery within a few weeks of symptom onset; however, long-term sequelae, such as paralysis, seizures, cranial nerve palsies, hydrocephalus and deafness, can occur. The disease is rarely fatal and the lack of autopsy tissue limits opportunities to examine disease pathogenesis and pathology. Our current knowledge of MuV pathogenesis is therefore mostly based on animal studies, often following unnatural routes of infection. Consequently, the pathogenesis of the virus in humans remains in question. This review will summarize the current knowledge of the virus, its inferred pathogenesis, clinical manifestations, and the importance of an understanding of disease pathogenesis as a prerequisite to the development of safer and more efficacious vaccines.

Mumps virus

Mumps was first described by Hippocrates in the fifth century BC, in his first Book of Epidemics, but a viral aetiology was not demonstrated until the 1930s, when Johnson and Goodpasture fulfilled Koch’s postulates by transferring the disease from experimentally infected rhesus macaques (*Macaca mulatta*), to children in his neighbourhood, using a bacteria-free, filter-sterilized preparation of macerated monkey parotid tissue [24,25].

The virus, a member of the family *Paramyxoviridae*, is an enveloped particle containing a non-segmented negative strand RNA molecule of 15,384 nucleotides. Other significant paramyxoviruses that infect humans and livestock include measles virus, canine distemper virus, parainfluenza virus, Newcastle disease virus, respiratory syncytial virus and metapneumovirus. The encapsidated genome (Figure 1) contains seven tandemly linked transcription units, in the order: nucleo- (N), V/P/I (V/phospho-/I proteins), matrix (M), fusion (F), small hydrophobic (SH), haemagglutinin-neuraminidase (HN) and large (L) proteins [26,27]. The template for viral replication and transcription is the ribonucleoprotein

(RNP) complex, which is composed of the negative-strand viral RNA encapsidated by N protein. The RNA-dependent RNA polymerase, a complex of the L and P proteins, acts as a replicase to copy the negative sense (−) RNA to a positive sense (+) RNA and as a transcriptase to generate mRNAs from the (−) RNP by entering at a single promoter at the 3′ end of the genome.

In infected cells the HN and F glycoproteins are transported through the endoplasmic reticulum and Golgi complex to the cell surface. The M protein is involved in localizing the viral RNP to regions of the host cell membrane expressing the F and HN glycoproteins, facilitating budding of the infectious virions from the infected cells [28,29]. The HN glycoprotein is responsible for attachment of the newly budded virus to neighbouring cells via its receptor, sialic acid, which is abundantly present on the surface of most animal cells. The HN glycoprotein, in concert with the F glycoprotein, mediates virus-to-cell fusion and cell-to-cell membrane fusion, facilitating virus spread. The SH protein is thought to play a role in evasion of the host antiviral response by blocking the TNFα-mediated apoptosis pathway [30,31]. This protein is not essential for virus replication, as demonstrated in studies with recombinant (r) MuVs engineered to lack the open reading frame encoding this protein [32]. The V and I proteins are encoded by the same transcriptional unit that encodes the P protein [27,33]. Like the SH protein, the V protein is also involved in evasion of the host antiviral response, where it inhibits IFN production and signalling [34–36]. The role of the I protein is unknown.

Clinical features, pathogenesis and pathology

Given the incidence of mumps in the pre-vaccine era, comparatively little is known about the pathogenesis of the disease. Much is inferred by comparison with related viruses, from experimental infection of laboratory animals, and from the clinical features and pathology of the disease in humans.

Initial infection: targeting of the upper respiratory tract epithelium?

MuV is transmitted via the respiratory route by inhalation or oral contact with infected respiratory droplets or secretions, as suggested by the aforementioned John-son and Goodpasture study, and in a subsequent study by Henle and colleagues, who transmitted the disease to children by both oral and nasal routes of inoculation [37]. MuV has been isolated from children with respiratory disease without parotitis [38] and has been detected by RT–PCR in nasal samples [39]. The spread of mumps among persons in close contact also suggests this mode of transmission. Based on studies of other respiratory viruses, it is assumed that, following exposure, MuV infects the upper respiratory tract, but this has not yet been formally demonstrated. For measles virus, a related paramyxovirus, it was also assumed that the virus initially infects the respiratory epithelium, but this assumption proved to be incorrect when macrophages and dendritic cells in the lung tissue were shown to be the primary target cells infected with this virus [40].

Systemic spread: from epitheliotropic to lymphotropic?

Given the array of symptoms, it is clear that MuV is able to disseminate systemically in the body, which has led to the assumption that, following infection of the upper respiratory mucosa, the virus spreads to regional lymph nodes, resulting in viraemia during the early acute phase (Figure 2). However, despite the high frequency of extra-respiratory symptoms, virus has only rarely been detected in blood [41–43], even in experimentally infected animals [44]. One possible explanation is the coincident development of MuV-specific humoral antibodies.

Approximately one-third to one-half of MuV infections are asymptomatic or result in only mild respiratory symptoms, sometimes accompanied by fever [45–49]. The hallmark of mumps is salivary gland swelling, typically the parotid glands, which forms the basis of a clinical diagnosis. Parotitis is usually bilateral, developing 2–3 weeks after exposure and lasting for 2–3 days, but it may persist for a week or more in some cases [37,50,51]. Submaxillary, submandibular and sublingual glands can be involved, but rarely as the only manifestation of mumps. Viral replication in the parotid gland results in perivascular and interstitial mononuclear cell infiltration, haemorrhage, oedema and necrosis of acinar and epithelial duct cells [52]. Serum and urine amylase levels may be elevated as a result of inflammation and tissue damage in the parotid gland [53]. Virus is excreted in the saliva from approximately 1 week before to 1 week after the onset of salivary gland swelling [37,54,55]. MuV has also been identified in the saliva of asymptomatic persons [37]. Coupled with excretion of virus up to 1 week before symptom appearance, this may explain some of the difficulties in controlling mumps outbreaks.

Orchitis, which is typically unilateral, is the most common extra-salivary gland manifestation of mumps. It occurs in approximately 10–20% of infections in post-pubertal men [46,56,57]. MuV has been recovered from semen and the testis, suggesting that epididymo-orchitis is the result of direct infection of testicular cells [58,59]. However, an indirect immune-mediated mechanism has also been postulated [60]. Both Leydig and germ cells are involved, associated with reduced levels of testosterone production [61–63]. Necrosis of acinar and epithelial duct cells is evident in the germinal epithelium of the seminiferous tubules of the testes. Orchitis is almost always accompanied by epididymitis and fever, all resolving within 1 week. Atrophy of the involved testicle occurs in approximately half of cases and can be associated with oligospermia and hypofertility, but rarely sterility [58,62,64,65]. Mastitis and oophoritis (manifesting as pelvic pain) occurs in 5–10% of mumps cases in postpubertal women [12,46,66]. Oophoritis has been associated with infertility [67] and premature menopause [68], but such cases are extremely rare.

Virus frequently disseminates to the kidneys, as suggested by the frequency of viruria during the established acute phase of the disease (Figure 2) [69,70]. Epithelial cells of the distal tubules, calyces and ureters appear to be primary sites of virus replication [52]. Kidney involvement in mumps is almost always benign, but cases of severe interstitial nephritis have been reported. In such cases, renal biopsy or postmortem necropsy show evidence of immune complex deposition, interstitial mononuclear cell infiltration and fibrosis, oedema and focal tubular epithelial cell damage [71–73]. Pancreatitis, diagnosed as severe epigastric pain and tenderness, has been reported in approximately 4% of cases [6,12,74]. There are

conflicting reports on the association between mumps pancreatitis and diabetes mellitus [75–79] and it is unclear whether there is a causal link.

CNS involvement: from lymphotropic to neurotropic

MuV is highly neurotropic, with evidence of central nervous system (CNS) involvement in up to half of all cases of infection, based on pleocytosis of the cerebrospinal fluid [48,80–82]. Symptomatic CNS infection is less common, but significant. Meningitis occurs in approximately 5–10% of cases and encephalitis in <0.5%. Although these are small percentages, MuV was the leading cause of encephalitis in the USA until 1975, when mumps-containing vaccine gained widespread use [83]. In unvaccinated populations, mumps continues to account for a high percentage of viral encephalitis cases [46,84,85]. Little is known of the CNS pathology, since the disease is rarely fatal. Of the few postmortem cases examined, the pathology includes oedema and congestion throughout the brain with haemorrhage, lymphocytic perivascular infiltration, perivascular glio-sis and demyelination, with relative sparing of neurons. These latter observations suggest that in some cases of mumps encephalitis the inflammation stems from a para-infectious process. However, virus can be recovered from CSF early in the course of meningitis [86,87], as well as from brain tissue in some cases of mumps encephalitis.

Experimental infection in rodents suggests the virus enters the CSF through the choroid plexus, or possibly via transiting mononuclear cells during viraemia. Based on animal data, once in the CSF, virus appears to be carried throughout the ventricular system, resulting in virus replication within ependymal cells that line the ventricles (Figure 3A) [44]. From these locations, virus can penetrate into the brain parenchyma, often infecting pyramidal cells in the cerebral cortex and hippocampus [88]. The infected ependymal epithelia become inflamed, lose their cilia, degenerate and collapse into the CSF (Figure 3B), a postulated cause of the aqueductal stenosis that is believed to be responsible for the occurrence of hydrocephalus, typically of the lateral and third ventricles, a common outcome in intracerebrally injected animals [89–93]. Mumps hydrocephalus has been reported in humans, most often presenting as obstruction of the cerebral aqueduct with dilatation of the lateral and third ventricles. However, obstruction of the foramen of Monro between the lateral and third ventricles, or obstruction of the foramina of Magendie and Luschka between the fourth ventricle and the sub-arachnoid space, have also been reported [94–98]. The finding of ependymal cell debris in the CSF of mumps patients [94,96,99] suggests that the pathogenesis of hydrocephalus in experimentally infected animals is similar to the mechanism of hydrocephalus in humans. However, hydrocephalus has been observed before, or in the total absence of, canal obstruction [88,91,100,101], indicating that such events could be a secondary consequence of external compression by surrounding oedematous tissue and not causally related to the pathogenesis of hydrocephalus.

Deafness has been reported in approximately 4% of mumps cases and is the most frequent cause of acquired unilateral sensorineural hearing loss in children. Hearing loss is typically unilateral and transient, but can be permanent [102–106]. Pathological findings include lesions and degeneration of the stria vascularis, tectorial membrane and organ of Corti [107,108]. MuV infection of the CSF has been implicated in the pathogenesis of deafness in

mumps, given the detection of the virus in perilymph, which freely communicates with the CSF [109]. This is also supported by animal studies, where instillation of the virus into the CSF has resulted in infection of the cochlea [110]. However, deafness does not occur any more frequently in patients with meningitis or encephalitis than it does in patients lacking signs of CNS infection, suggesting that CSF may in fact not be involved in the pathogenesis of deafness. An alternative explanation could be that virus infects the inner ear via a haematogenous route, ie that mumps labyrinthitis occurs as a consequence of viraemia. This is supported by studies in guinea pigs following intravascular inoculation of the virus [111], and clinical findings by Lindsay [107] and Mizushima and Murakami [112] suggesting 'viral endolymphatic labyrinthitis' in the pathogenesis of mumps deafness in humans. Hearing loss caused by indirect effects of virus infection (eg immune-mediated damage) have also been suggested [113]. MuV was also identified in the vestibular ganglia in experimentally infected animals [110], which likely also occurs in humans and explains vestibular symptoms, such as vertigo, which often present in cases of mumps deafness [114,115].

Based on electrocardiographic abnormalities in mumps patients, MuV likely infects cardiac tissue [116]. While this is rarely symptomatic, interstitial lymphocytic myocarditis and pericarditis have been reported [117], which can lead to endocardial fibroelastosis [118]. MuV has also been identified in cardiac muscle from patients with these disorders. Clinically apparent cardiac complications are rare, but can be serious [116,119,120].

Other rare complications include cerebellar ataxia [121,122], transverse myelitis [123,124], ascending polyradiculitis [125], a poliomyelitis-like disease [126,127], arthropathy [128,129], autoimmune haemolytic anaemia [130,131], thyroiditis [132,133], thrombocytopenia [134,135], hepatitis [136,137] and retinitis and corneal endotheliitis [138–140].

Transplacental transmission of the virus has been demonstrated in non-human primates [141] and is suggested by the isolation of virus from the human fetus following spontaneous or planned abortion during maternal mumps [142–144]. Aborted fetal tissue from such cases has been found to exhibit a proliferative necrotizing villitis with decidual cells containing intracytoplasmic inclusions [145]. Virus has also been isolated at birth from infants born to women with mumps [146] and from breast milk [147], but few cases of perinatal mumps have been described [146,148] and it is not clear whether breast milk was responsible for these cases. Mumps virus does not appear to cause congenital malformations [149]. The major morbidity from mumps is from complications of meningitis, encephalitis and orchitis. The case fatality ratio is 1.6–3.8/10,000 [150,151], with most fatalities occurring in persons with encephalitis.

Animal models and molecular determinants of MuV pathogenesis

Historically, the most widely used animal models of mumps have been the hamster and the monkey, and information from these models serves as the basis for much of our current understanding of MuV pathogenesis and disease. However, the relevance of findings in these models for humans is questionable, given the use of unnatural routes of inoculation (eg intracranial, intraperitoneal or intravenous) and the inability of these models to clearly and

reliably discriminate strains that are attenuated for humans from wild-type, virulent strains [152–158]. In the one study where monkeys (rhesus macaques) were inoculated via natural routes (intranasal and intratracheal), only wild-type virus was tested [159]. Nonetheless, this study demonstrated the potential to identify sites of early and late MuV replication, which supports further evaluation of this model. Mice and ferrets were also explored as model systems; however, virus replication in these species is self-limiting, making them poor candidates for pathogenesis studies [159–164].

A key advance in the study of MuV pathogenesis was the development of a rat model predictive of the neurovirulence potential of MuV strains for humans. In this model, 1 month after intracerebral injection of virus into newborn Lewis rats, brains are removed and evaluated for virus-induced hydrocephalus (Figure 4), the severity of which correlates with the neurovirulence potential of the virus for humans [165]. With the advent of plasmid-based reverse genetics systems for MuV, it became possible to examine molecular determinants of virulence, and thus gain a better understanding of virus factors that influence pathogenicity. The first such study was published by Lemon *et al* [166], who generated Jeryl Lynn vaccine strain-based viruses expressing genes derived from the Kilham MuV strain, a hamster brain-adapted laboratory strain. Of the single gene replacements assessed (*M*, *F*, *SH* and *HN*), only the *F* gene was found to significantly increase the neurovirulence potential of the highly attenuated Jeryl Lynn strain [166]. However, in a subsequent study using a different virulent MuV strain, 88-1961, Sauder *et al* [167] found the *F* gene to have no biologically meaningful effect on the neurovirulence potential of Jeryl Lynn. MuV strain-specific molecular determinants of virulence are also highlighted in other studies. For example, Xu *et al* [168] identified the *SH* gene as a virulence factor for the wild-type IA MuV strain, whereas Malik *et al* [32] found no such role for the *SH* gene in 88-1961 virulence. Of additional interest, in the Sauder *et al* study, the Jeryl Lynn genes found to neuro-attenuate the 88-1961 strain (eg *M*, *HN* and *L*), when derived from the 88-1961 strain, did not meaningfully increase the neurovirulence of the Jeryl Lynn virus. Thus, not only do genes that influence virulence of one strain often not affect virulence of another strain, but genes involved in neurovirulence are not necessarily involved in neuroattenuation. Taken together, these results raise doubt as to the prospect of identifying broadly applicable genetic determinants of virulence and attenuation. An alternative, or complementary, approach may be to examine differences between virulent and attenuated strains in terms of sites of primary replication and spread, following infection via natural routes in disease-relevant animal models. To this end, new *in vitro* and *in vivo* model systems that recapitulate the diverse features of a natural infection are needed.

Conclusion

As a re-emerging pathogen, with concerns over vaccine safety and efficacy, elucidation of mechanisms of MuV pathogenesis is of paramount importance, as this information will help direct the development of improved vaccines. The utilization of existing reverse genetic systems alongside the generation of new, clinically relevant systems and the development of robust animal models for other aspects of the disease will allow a more complete understanding of disease. This review has summarized our current understanding of MuV clinical disease, pathology, and how this relates to viral pathogenesis. However, a number of

areas are evidently poorly understood and important questions remain (Figure 5). These include the elucidation of the target cell tropism throughout an infection, the mechanisms by which MuV establishes a systemic infection and the basis of neurotropism. Determination of these likely requires the establishment of a primate model of MuV infection, similar to what has been achieved with measles. The measles system, exploiting a fluorescent reporter-expressing wild-type MV in a clinically-relevant macaque (*Macaca fascicularis*) model has facilitated the elucidation of key features of measles virus pathogenesis relevant to disease, transmission and immunity [40]. Applying what has been learned from the measles model to mumps will provide an ideal basis to understanding determinants of MuV pathogenesis.

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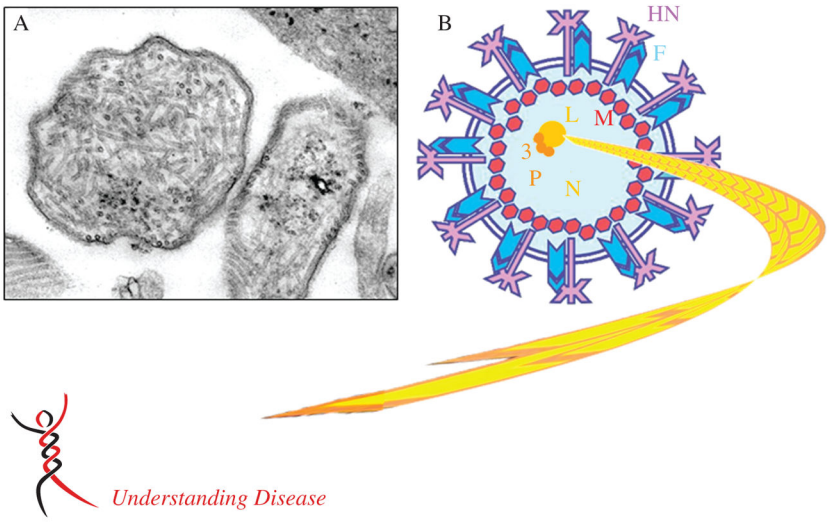

Figure 1.

MuV virion structure. (A) Thin sectioned transmission electron micrograph showing a typical MuV particle alongside (B) a schematic of the particle. The enveloped particles are pleomorphic, in the size range 100–600 nm. Within this structure lies the long, coiled electron-dense ribonucleoprotein (RNP), containing the MuV genome. Small spikes can be observed on the surface of the particle, corresponding to the viral HN and F glycoproteins. The same general features of the MuV particle are shown in the schematic (B). The envelope (blue lines) is studded with the HN (purple) and F (blue) glycoproteins and encases the viral RNP, made up of the RNA genome (3′–5′) in complex with N (yellow), P (orange) and L (gold) proteins. The M protein (red) interacts with the envelope, glycoproteins and the RNP. The V, I and SH proteins are expressed in infected cells, but are not thought to be incorporated within the virion. Photomicrograph courtesy of CDC/A Harrison and FA Murphy (http://phil.cdc.gov/phil/details.asp)

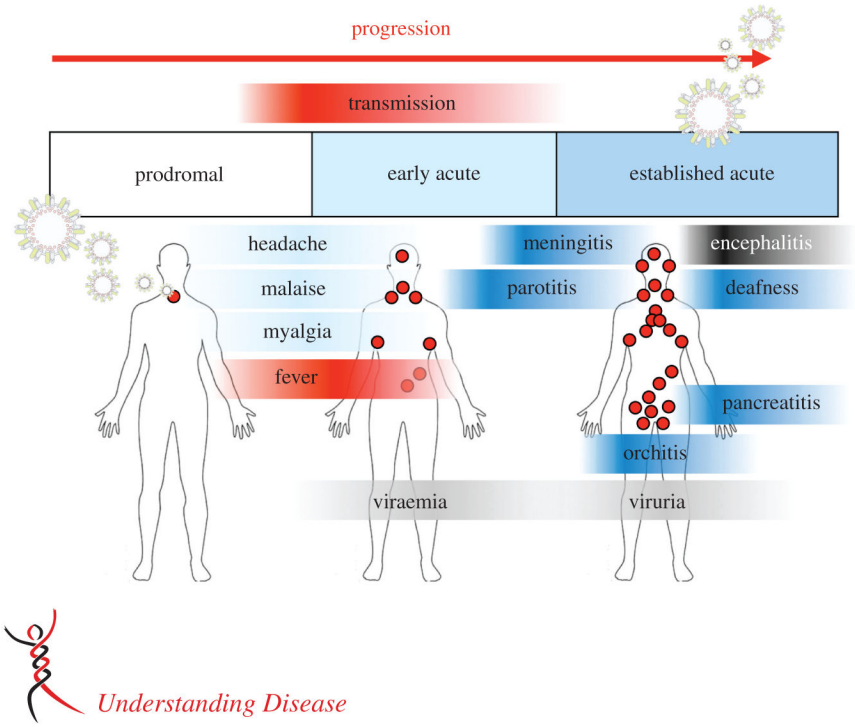

Figure 2.

MuV clinical presentation and pathogenesis. Mumps is a respiratory-spread, acute, inflammatory disease in humans, which causes a range of systemic symptoms. The incubation period is 2–4 weeks. Approximately one-third of infections are asymptomatic. The prodromal phase is characterized by non-specific, often mild symptoms, such as low-grade fever, headache and malaise. An early acute phase follows, likely representing spread of the virus from the respiratory tract and development of systemic symptoms, typically parotitis, which lasts from a few days to 1 week. During the established acute phase, orchitis, meningitis or encephalitis may appear. Symptoms usually resolve within 2 weeks, coincident with the development of a MuV-specific humoral response. Long-term complications and death are rare

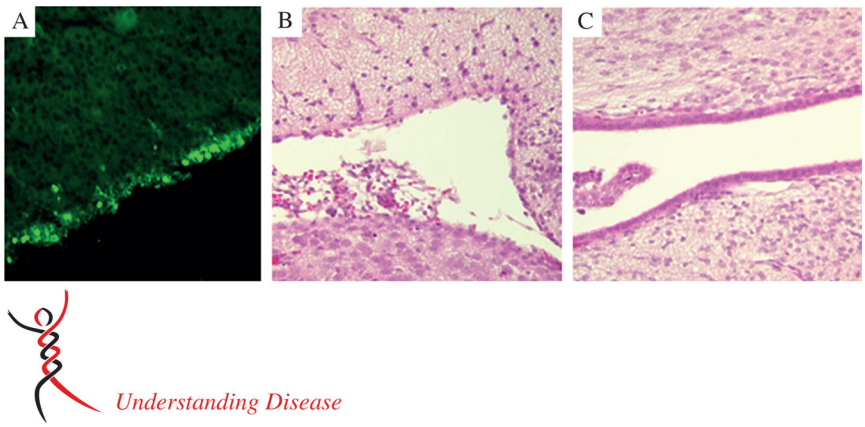

Figure 3.

MuV infection of the rat brain. The most prominent neuropathological outcome following MuV intracranial inoculation in small animal models (hamsters, rats) is enlargement of the lateral and third ventricles, ie hydrocephalus, which has also been reported in cases in humans. The cause of hydrocephalus is postulated to be denuding of virus-infected ependymal cells lining the ventricles. (A) Sagittal section of rat brain tissue immunohistochemically stained for the MuV nucleoprotein, showing extensive infection of the ventricular ependymal cells (green foci). (B) Approximately 3 weeks later, ependymal cell loss is evident in comparison to the well-preserved ependymal cell architecture in rats injected with the Jeryl Lynn vaccine strain (C); haematoxylin and eosin (H&E) stain

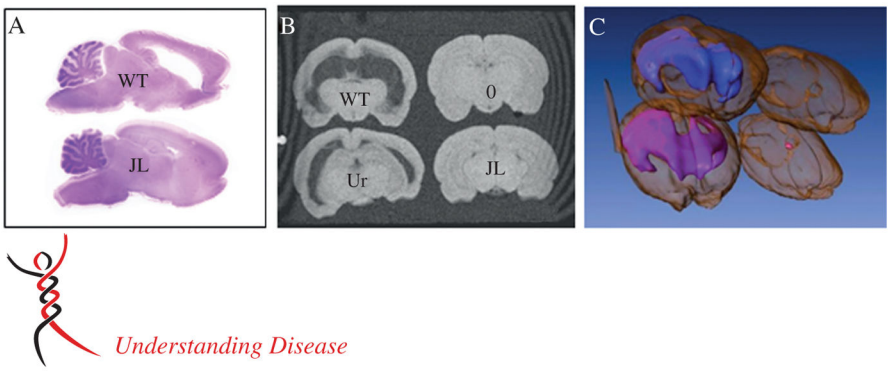

Figure 4.

Hydrocephalus severity in MuV-infected rats. (A) H&E-stained sagittal sections of brain from a representative 30 day-old rat injected with a wild-type (WT) MuV isolate as a newborn (top), compared to a rat similarly injected with the highly attenuated Jeryl Lynn (JL) vaccine strain (bottom). (B) T1 weighted gradient-echo image from MRI of the same brains as in (A) (upper left corner and lower right corner), compared to brain from a rat injected with an insufficiently attenuated vaccine strain, Urabe-AM9 (Ur, lower left corner) and an uninfected rat brain (0, upper right corner). Note that the severity of hydrocephalus tracks with the virus strain's neurovirulence potential for humans. (C) Assembled three-dimensional rendering of MRI slices represented in (B), showing ventricular volume (blue, wild-type; pink, Urabe-AM9)

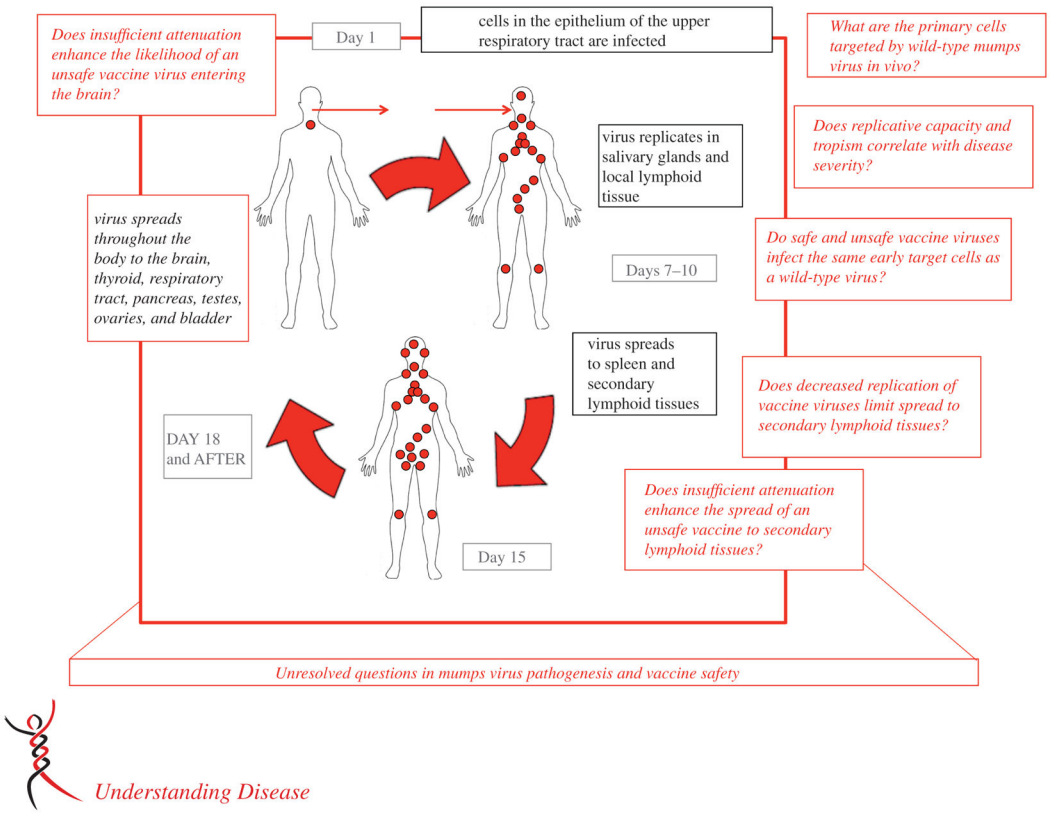

Figure 5.

A number of important questions remain unresolved regarding MuV pathogenesis. This is of particular relevance to renewed efforts towards development of a more efficacious MuV vaccine, in light of the resurgence of mumps in vaccinated populations. The classic method of virus attenuation is extensive blind passage *in vitro*. While this often leads to the desired effect of a loss of virulence and reactogenicity, it can also lead to loss of immunogenicity and efficacy. Clearly, a more rational approach to virus attenuation is needed, and understanding the natural pathogenesis of the infectious agent is a prerequisite to any such endeavour. This figure highlights this issue, showing our current assumptions of pathogenesis (black text) and unresolved questions (red text)