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Viral Disease

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I. INTRODUCTION

The overall prevalence of viral infections in laboratory rats is low and largely relates to global adoption of screening, biosecurity practices, the use of clean air equipment for cage changing and animal manipulation, and housing within individually ventilated cages. Further, the import/export of rats from noncommercial sources has remained low because of the relatively low numbers of genetically engineered rats. However, advances in genetic engineering, including CRISPR technology, could increase the production of genetically engineered rats, resulting in greater infection risks associated with global sharing of unique rats from noncommercial sources. Several serological studies have indicated that paroviruses, coronaviruses, cardioviruses, and pneumoviruses are the most prevalent (up to 13%) (Mahler and Kohl, 2009; McInnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006). Seroconversion to less prevalent viruses, adenoviruses, hantaviruses, Sendai virus, and reovirus, has also been detected in laboratory rats (up to 0.4%). Since the last edition of this book, a new polyomavirus and a new cardiovirus that cause disease in laboratory rats have been described. In addition, advances in metagenomics are enhancing the ability to detect novel organisms. To this end, metagenomic analysis of feces or intestinal contents from wild rats detected viruses from 19 families, many of which are not screened for in laboratory rats and potentially could cause subclinical infections in laboratory rats. The use of metagenomics is likely to expand our knowledge of the virome of laboratory rodents in the coming years. The major sections of this chapter are DNA virus infections (Section II), RNA virus infections (Section III), and the virome (Section IV).

II. DNA VIRUS INFECTIONS

A. Adenoviridae

Adenoviruses are large nonenveloped viruses with 26- to 46-kb linear double-stranded DNA genomes. The genus Mastadenovirus includes adenoviruses that infect humans, nonhuman primates, mice, and several other mammalian hosts. However, advances in genetic engineering, including CRISPR technology, could increase the production of genetically engineered rats, resulting in greater infection risks associated with global sharing of unique rats from noncommercial sources. Several serological studies have indicated that paroviruses, coronaviruses, cardioviruses, and pneumoviruses are the most prevalent (up to 13%) (Mahler and Kohl, 2009; McInnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006). Seroconversion to less prevalent viruses, adenoviruses, hantaviruses, Sendai virus, and reovirus, has also been detected in laboratory rats (up to 0.4%). Since the last edition of this book, a new polyomavirus and a new cardiovirus that cause disease in laboratory rats have been described. In addition, advances in metagenomics are enhancing the ability to detect novel organisms. To this end, metagenomic analysis of feces or intestinal contents from wild rats detected viruses from 19 families, many of which are not screened for in laboratory rats and potentially could cause subclinical infections in laboratory rats. The use of metagenomics is likely to expand our knowledge of the virome of laboratory rodents in the coming years. The major sections of this chapter are DNA virus infections (Section II), RNA virus infections (Section III), and the virome (Section IV).
B. Herpesviridae

Herpesviruses are enveloped icosahedral viruses with large linear double-stranded DNA genomes (125–240 kb). Rats can be infected with rat cytomegaloviruses (RCMVs; genus *Muromegalovirus*). Acidophilic intranuclear inclusions in the salivary glands of rats have been reported since the 1930s (Thompson, 1932). RCMV strain Maastricht (RCMV-M), also known as murid herpesvirus 2, and RCMV strain English (RCMV-E), also known as murid herpesvirus 8, were isolated in primary rat embryo fibroblasts from the salivary glands of wild *R. norvegicus* 50 years later (Bruggeman et al., 1982; Priscott and Tyrrell, 1982). The full genome sequences of these two RCMV isolates indicate that they have genomes of different sizes (230 and 203 kb) and have different genomic organizations (Ettinger et al., 2012; Vink et al., 2000). The RCMV-M genome is substantially different from the genomes of human and mouse cytomegaloviruses (HCMV and MCMV), with only 46%–68% of the ORFs having significant similarities (Vink et al., 2000). Murid herpesvirus 8 genomes (RCMV-E, -B, and -ALL-03) share more similarity with the genome of MCMV (murid herpesvirus 1) than with the genome of RCMV-M (Geyer et al., 2015). Natural infection of laboratory rats with RCMV has not been reported. Given that high levels of RCMV are detected in saliva for several months after experimental infection (Bruggeman et al., 1985), it is likely that transmission of RCMV occurs via exposure to saliva. The prevalence of RCMV is believed to be low, although seroprevalence surveys of laboratory rats have not included RCMV. Metagenomic analyses of rat feces and intestinal contents have not detected RCMV. RCMV appears to be infectious only in rats and there is no published evidence for natural infection of rats with cytomegaloviruses from other species or for infection of other species with RCMV.

Infection of rat embryo fibroblasts and endothelial cells with RCMV results in typical cytomegalovirus-like cytopathic effects: enlarged and multinucleated cells with eosinophilic cytoplasmic and nuclear inclusions (Bruggeman et al., 1982, 1986; Priscott and Tyrrell, 1982). Intracerebral inoculation of newborn rats with RCMV-M resulted in 62% mortality over a 3-week period and virus was detected 14 days postinoculation in the liver, spleen, submaxillary salivary gland, lung, heart, brain, and kidney (Priscott and Tyrrell, 1982). Intraperitoneal inoculation of adult rats with RCMV-M resulted in subclinical infection, with the highest viral titers detected in the salivary glands at 4–5 weeks postinoculation (Bruggeman et al., 1983). Eosinophilic intracytoplasmic inclusions with mild nonsuppurative interstitial inflammation were seen in the salivary glands (Fig. 13.1) at 4 weeks postinoculation, and RCMV-M persisted in the salivary glands for at least 6 months (Bruggeman et al., 1983). The striated duct cells of the submandibular salivary glands were the preferred site of replication in immunosuppressed 6-week-old rats inoculated with RCMV-M, whereas the striated duct cells of the sublingual salivary gland were the preferred site of replication in immunocompetent 3-day-old rats inoculated with RCMV-M (Kloover et al., 2000).

RCMV has been used as a model of HCMV infection of immunocompromised or immunosuppressed human patients, particularly transplant patients, and therefore many experimental infection models use rats that have been immunosuppressed. Transplantation of liver or heart from rats latently infected with RCMV-M to syngeneic and allogeneic rats resulted in passive transfer of the virus to the recipients (Brunning et al., 1986). RCMV infection accelerated transplant vascular sclerosis, obliterator bronchiolitis, and chronic rejection in solid organ (heart, kidney, trachea, and lung) transplants (Koskinen et al., 1996; 1997; Lemstrom et al., 1996; Steinhoff et al., 1996; Streblow et al., 2003; 2005; Yagyu et al., 1993). RCMV has been shown to accelerate the onset of diabetes in rat experimental models of autoimmune diabetes and to exacerbate autoimmune collagen-induced arthritis in rats (Griffiths et al., 1991; Smith et al., 1986; van der Werf et al., 2003). RCMV also has been used as a model of neurodevelopmental disorders in neonates caused by HCMV infection during pregnancy. Infection of immunocompetent and immunosuppressed pregnant rats with a Malaysian strain (ALL-03) of RCMV resulted in infection of the placenta and fetuses (Loh et al., 2006). Intraperitoneal inoculation of rats on the first day of pregnancy with RCMV-M caused abnormalities in the embryonic nervous system, which affected learning and memory in weanlings (Sun et al., 2012).

**FIGURE 13.1** Rat cytomegalovirus infection. Intranuclear inclusions in acinar epithelial cells of a submandibular salivary gland accompanied by mild interstitial inflammation.
C. Parvoviridae

Parvoviruses have a single-stranded, negative-sense DNA genome (5 kb) that is encapsidated in a small (18–26 nm), nonenveloped icosahedral virion particle (Siegl, 1976; Tattersall and Cotmore, 1986). The genome contains two large open reading frames: ORF1, which encodes the nonstructural regulatory proteins (NS1 and NS2), and ORF2, which encodes the structural proteins (VP1 and VP2) that make up the virion. The small genome size makes parvoviruses highly dependent on cellular factors expressed in mitotically active cells for replication. Parvoviruses arrest the cell cycle (at G2/M for rodent parvoviruses) and regulate cell signaling pathways for their benefit. Parvoviruses are released from infected cells during apoptotic or lytic cell death.

Laboratory rats are naturally infected by four types of parvoviruses. The prototype parvovirus of rats is rat virus (RV), which was isolated from a transplantable tumor of rats by Kilham and Olivier (1959). Therefore, it also has been called Kilham RV. An antigenically distinct virus (H-1) was isolated in the following year by Toolan from a human tumor cell line that had been passed through rats and caused deformities in neonatal hamsters (Toolan et al., 1960). A third antigenically distinct virus, rat parvovirus (RPV), was isolated more recently from asymptomatic naturally infected rats (Ball-Goodrich et al., 1998). A similar parovirus was identified by Japanese workers who initially referred to it as “rat orphan parvovirus” (Ueno et al., 1996). Three strains of a fourth parvovirus of rat were identified by polymerase chain reaction (PCR) and they have been named minute virus of rats (RMV) (Wan et al., 2002). Metagenomic analyses of feces or intestinal contents from wild R. norvegicus collected in New York City, Germany, and China have revealed infection of rats with other types of parvoviruses: rat bufavirus, rat bocaparvovirus, and rat chapparvovirus (Firth et al., 2014; Lau et al., 2017; Sachsenroder et al., 2014; Yang et al., 2016a, 2016b), though at present there is no evidence of infection of laboratory rats with bufaviruses, bocaparvoviruses, or chapparvoviruses.

The nonstructural (NS1 and NS2) proteins of RV, RPV, RMV, and H-1 are highly conserved, account for the immunologic cross-reactivity among rodent paroviruses, and are targets of generic parvovirus diagnostic tests. The capsid (VP1, VP2, and VP3) proteins are less conserved than the NS proteins and are used to distinguish the four types of rat paroviruses serologically and molecularly. Serological surveys indicate that parvovirus infections are the first or second most common viral infection of rats, with seroprevalence of 0.26%–13% (Mahler and Kohl, 2009; Marx et al., 2017; McInnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006). Determining the relative prevalence of RV, RPV, RMV, and H-1 has been complicated by the use of generic antigens for serologic testing, though a 2009 study indicates that the serotype-specific prevalences of RV, RPV, RMV, and H-1 are similar, ranging from 1.21% to 1.46% (Pritchett-Corning et al., 2009).

1. Clinical Signs

Spontaneous parvovirus infections in contemporary laboratory rat facilities are usually asymptomatic. RV and H-1 are pathogenic after experimental inoculation of pregnant or infant rats. In initial reports, spontaneous infections and experimental intraperitoneal or intracranial inoculations with RV and/or H-1 caused fetal deaths resulting in partial or complete loss of litters in dams that appeared otherwise clinically normal, and neonatal rats inoculated with H-1 or RV developed a fulminant generalized disease that was fatal (Kilham and Ferm, 1964; Kilham and Margolis, 1966, 1969; Margolis et al., 1968). Pregnant dams inoculated intraperitoneally with high doses of RV-Y (gestation days 12–18) failed to deliver pups, and fetuses were resorbed, macerated, or mummified, whereas pregnant dams inoculated oronasally delivered normal litters (Gaertner et al., 1996b; Jacoby et al., 1988). Fetuses from pregnant dams inoculated intraperitoneally or oronasally with high doses of RV-UM on gestation days 9–12 developed multisystemic necrosis (Gaertner et al., 1996b). A lower dose of RV is needed to infect 2-day-old and 4-week-old Sprague–Dawley rats via the intraperitoneal route compared with the oronasal route (Jacoby et al., 1987). Two-day-old Sprague–Dawley and athymic nude rats inoculated with RV-Y via the intraperitoneal or oronasal route developed anorexia, stunted growth, icterus, diarrhea, oily pelage, dehydration, tremors, and ataxia that often resulted in death between 7 and 28 days postinoculation while 4-week-old rats were asymptomatic (Gaertner et al., 1989; Jacoby et al., 1987). Resistance to RV-induced disease appears to develop by 1 week postpartum and has been attributed to a decline in mitotic activity in target tissues and postnatal development of the immune system (Gaertner et al., 1996b). Therefore, clinical signs induced by RV and H-1 are rarely seen in rats older than 1 week of age. But, paralysis has been reported in adult rats immunosuppressed with cyclophosphamide and then exposed to RV, and fatal hemorrhagic disease has been reported in weanling rats exposed to RV (Coleman et al., 1983; Eldadah et al., 1967). Hepatitis has been reported in adult rats with partial hepatectomy that were infected with H-1 (Ruffolo et al., 1966). RPV is not pathogenic after experimental inoculation (Ball-Goodrich et al., 1998; Ueno et al., 1997) and experimental inoculation with RMV has not been done.
2. Epidemiology

*R. norvegicus* is the only known natural host for RV, RPV, and RMV. It is not clear what the natural host of H-1 is, as it was originally isolated from hamsters and rats transplanted with human tumors. Based largely on studies with RV, parvovirus infections in rats should be considered highly contagious. Natural postnatal infections with RV and RPV appear to be due to direct contact with infected rats or by ingestion of virus-contaminated fomites, such as animal bedding (Jacoby et al., 1988; Ueno et al., 1996; Yang et al., 1995). Airborne transmission of RV has not been detected (Yang et al., 1995), even though RV can be detected for a month in the lungs of rats infected as neonates (Jacoby et al., 1987). RV has been detected in the kidneys (renal tubular epithelium and interstitium of the kidney) (Fig. 13.2), in urine, and in the intestines of rats infected as neonates (Gaertner et al., 1996b; Jacoby et al., 1987; Novotny and Hetrick, 1970), suggesting that transmission by urine or feces may be possible. RPV also infects renal tubular epithelium (Fig. 13.3) and has been detected in urine (Ball-Goodrich et al., 1998; Ueno et al., 1997). While RV can infect intestinal mucosa and lead to fecal excretion (Lipton et al., 1972), the intestine does not appear to be a prominent target of RV. Intestinal infection is prominent with RPV, affecting predominantly the lamina propria, and RPV has been detected in feces (Ball-Goodrich et al., 1998; Ueno et al., 1996). RMV has been detected by PCR in the spleen, kidney, cecum, and mesenteric lymph nodes of naturally infected rats (Wan et al., 2006), suggesting RMV transmission occurs via urine or feces. Prenatal transmission of RV and H-1 is secondary to maternal infection (Gaertner et al., 1996b; Jacoby et al., 1988, 2001; Kajiwara et al., 1996; Kilham and Ferm, 1964; Novotny and Hetrick, 1970). However, it appears to require exposure of dams to large doses of RV or H-1. Prenatal infection is uncommon during natural outbreaks in breeding colonies, presumably because dams are exposed to only a low dose of virus.

The risk of transmission is prolonged by persistent RV and RPV infections. There is no evidence that host genotype affects susceptibility to infection of rats with parvoviruses (Jacoby and Ball-Goodrich, 1995). But, susceptibility to persistent RV infection depends on age and immunologic status. Infection in adult immunocompetent rats with RV is usually resolved within 4 weeks, whereas prenatal or perinatal infection can lead to persistent infection lasting at least 6 months, despite the onset of antiviral humoral immunity (Gaertner et al., 1989; Jacoby et al., 1991). Rats persistently infected with RV can transmit virus for 10 weeks (Jacoby et al., 1988). Preexisting humoral immunity can prevent infection, but development of antiviral antibodies does not eliminate the infection (Gaertner et al., 1991; Paturzo et al., 1987). Maternally acquired immunity protects rats born to RV-infected dams from infection and disease (Gaertner et al., 1991; Jacoby et al., 1988; Novotny and Hetrick, 1970). Passive immunization with RV immune serum protects neonatal and juvenile rats from disease and is most effective if it occurs prior to infection, as antibody administered even 1 day after viral exposure provides only partial protection against infection (Gaertner et al., 1991, 1995). Immunodeficient (athymic) rats are susceptible to persistent RV infection at any age and the duration of the infection is longer, suggesting an important role for T lymphocytes in eliminating infection (Gaertner et al., 1989). Higher morbidity and
mortality were observed in infant athymic rats inoculated oronasally with RV-Y than in euthymic rats, and included anemia and thrombocytopenia (Gaertner et al., 1989). Infectious RPV has been detected, following infection of infant, weanling, and adult rats, for 3 weeks, and viral DNA has been detected for up to 24 weeks (Ball-Goodrich et al., 1998; Ueno et al., 1997, 1998), a finding consistent with persistent infection.

3. Pathology and Pathogenesis

Initial studies in the 1960s showed that the predilection of RV and H-1 virus for mitotically active cells was responsible for pathogenic infections in fetal and infant rats, especially in the liver, central nervous system, and lymphopoietic tissues (Kilham and Ferm, 1964; Kilham and Margolis, 1966, 1969; Margolis et al., 1968; Novotny and Hetrick, 1970; Toolan et al., 1960). Many of these early descriptions of RV- and H-1-induced pathology were based on experimental infections often caused by parenteral inoculation with high doses of virus as models of virus-induced birth defects. In addition, it is not clear whether the rats were coinfected with other, as yet undiscovered, infectious agents that might have altered the pathology observed.

RV replication in the liver caused intranuclear inclusions followed rapidly by degenerative changes, including ballooning degeneration, intensified cytoplasmic eosinophilia, dissociation of histoarchitecture, nuclear pyknosis and karyorrhexis, and cell lysis (Fig. 13.4) (Jacoby et al., 1987; Kilham and Margolis, 1966; Margolis et al., 1968). Associated lesions may include focal hemorrhage, bile stasis, and formation of blood-filled spaces resembling peliosis hepatis (Jacoby et al., 1987; Margolis et al., 1968). These changes are reflected by gross lesions that may include icterus and yellow-red mottling of the liver accompanied by distorted lobular contours caused by necrosis (Jacoby et al., 1987). Persistent infection can incite chronic active hepatitis. Portal triads in affected livers may sustain chronic inflammation with infiltration by mononuclear cells, fibrosis, nodular hyperplasia, and biliary hyperplasia (Fig. 13.5).

Necrosis and hemorrhage induced by RV can occur anywhere in the central nervous system but are most prominent in the cerebellum (Coleman et al., 1983; Jacoby et al., 1987; Kilham and Margolis, 1966). Intranuclear inclusion bodies, followed by lysis and segmental or pancerebellar depletion of the external germinal layer (Fig. 13.6), lead to granuloprival cerebellar hypoplasia (Jacoby et al., 1987; Kilham and Margolis, 1966). Hemorrhage may be significant in the cerebellum, brainstem, rhombencephalon, and mesencephalon and may result in fatal infarcts (Jacoby et al., 1987). Mild focal necrosis of the lymphoreticular system (thymus, lymph nodes,
and spleen) and of the renal tubular endothelium was also observed (Jacoby et al., 1987). Intrauterine infection often results in necrosis of fetuses, placentas, and fetal resorption (Gaertner et al., 1996b; Jacoby et al., 1988; Kilham and Ferm, 1964). Corresponding gross lesions may vary from a reduction to a total loss of viable fetuses and include segmental reddish-black discoloration of the uterus and accumulation of necrotic debris at placentation sites.

The prevalence of hemorrhagic lesions illustrates the importance of vasculotropism in pathogenic parvovirus infections. Hemorrhage during acute infection appears to result from viral-induced endothelial injury. Inclusion bodies, viral DNA, and viral antigens have been demonstrated in the endothelium (Fig. 13.7) (Gaertner et al., 1993a; Jacoby et al., 1987, 2000; Margolis and Kilham, 1970). Endothelial infection can disrupt vascular integrity, can exacerbate viremia, and may facilitate fetal infection through involvement of placental and fetal vasculature. Vascular and intestinal smooth muscle cells (SMCs) appear to be major sites of persistent infection (Gaertner et al., 1993a; Jacoby et al., 2000). Persistent vascular SMC infection may be accompanied by perivascular mononuclear cell infiltrates, which most often are found in kidney and liver. Viral DNA can be seen in adjacent vessels (Fig. 13.8) (Jacoby et al., 2000). It is believed that SMCs sequester nonreplicating RV. RV replication also may continue among mitotically quiescent SMCs (Jacoby et al., 2000). Persistent infection of SMCs does not cause prominent necrosis, but may provoke focal myolysis. Focal SMC infection may exacerbate mitotic activity during cellular repair and may provide additional targets for viral infection.

Contemporary studies with RV have emphasized inoculation by natural (oronasal) routes at various ages in both immunocompetent and immunodeficient rats to resemble more closely exposure during natural outbreaks (Gaertner et al., 1989, 1993a, 1995, 1996b; Jacoby et al., 1987, 1988, 1991, 2001). RV-Y infection of immunocompetent 2-day-old rats was seen in the blood, kidney, liver, spleen, thymus, lung, intestine, salivary glands, genitalia, and brain, and RV-Y infection of immunocompetent 4-week-old rats was seen in the kidney, liver, spleen, thymus, lung, intestine, salivary glands, and genitalia (Gaertner et al., 1993a; Jacoby et al., 1987), indicating that oronasal exposure leads to viremic dissemination. RV infection in infant rats caused hepatic necrosis, granulopraliv cerebellar hypoplasia, and hemorrhagic encephalopathy, while infection was asymptomatic in juvenile rats (Gaertner et al., 1993a; Jacoby et al., 1987). Intraperitoneal inoculation of juvenile immunodeficient athymic rats with RV-Y resulted in infection of the kidney, liver, and spleen, but not the brain (Jacoby et al., 1987).

In contrast to RV and H-1 virus, RPV is nonpathogenic even in infant rats (Ball-Goodrich et al., 1998). However,
it does express similar tissue tropisms. In particular, it infects vascular endothelium and renal tubular epithelium (Fig. 13.3) as well as regional lymph nodes and lamina propria of intestinal mucosa (Fig. 13.9) (Ball-Goodrich et al., 1998).

4. Diagnosis

Clinical signs can be dramatic, but occur rarely. Standard pathologic examination can be useful, especially to detect inclusions and/or lesions compatible with pathogenic infection. However, the diagnostic sensitivity and specificity of histopathology are enhanced by immunohistochemistry or in situ hybridization of tissue sections (Gaertner et al., 1993a; Jacoby et al., 1987).

Traditionally, serology has been the primary method for detecting parvoviruses in laboratory rat colonies. Enzyme-linked immunosorbent assays, immunofluorescence assays, and multiplexed fluorescence immunoassays using recombinant antigens, virions, or infected cells as generic antigens can be used to detect all known serotypes. Alternatively, serotype-specific (capsid) antigens can be used to distinguish infections with RV, RPV, RMV, and H-1 (Xu et al., 2017).

Molecular diagnostics are effective at detecting parvoviruses of rats in tissues, excreta, cultured cells, and the environment. As with serology, PCR assays that target the NS region of the genome can detect all parvoviruses of rats, whereas PCR assays that target the capsid region of the genome can be used to distinguish among parvoviruses of rats (Besselsen et al., 1995; Taylor and Copley, 1994; Wan et al., 2006).

Virus isolation can be accomplished by inoculation of cell lines or explant cultures (Paturzo et al., 1987). RV and H-1 virus grow well in primary rat embryo cells and C6 rat glial cells. RV also replicates in continuous cell lines such as 324K (human embryonic kidney), NRK (normal rat kidney), and BHK21 (hamster kidney) cells. H-1 virus also can be propagated in rat nephroma cells (Paturzo et al., 1987; Tattersall and Cotmore, 1986). RPV replicates well in 324K and C58(NT)D cells (Ball-Goodrich et al., 1998; Ueno et al., 2001). Productively infected cells usually develop cytopathic effects, beginning with intranuclear inclusions and proceeding rapidly to cytolysis. Cultures that contain actively dividing cells are more susceptible to viral infection and replication than confluent cultures (Tennant et al., 1969).

5. Control and Prevention

Because parvoviruses are small, nonenveloped viruses, they are highly resistant to inactivation and can persist in the environment. RV is highly heat resistant, retains infectivity after exposure to lipid solvents, is stable over a pH range of 1–12, and is resistant to ultrasonication and treatment with RNase, DNase, papain, and trypsin (Kilham and Olivier, 1959; Siegl, 1976). RV remained infectious for at least 5 weeks in saline or bedding (Yang et al., 1995). Because parvoviruses also persist in rats, extensive testing is required to identify all persistently infected rats during an outbreak. Cell lines, transplantable tumors, and other biological products can be a source of parvovirus infection. Based on reports with mouse parvovirus, nonsterilized food may also be a source of parvovirus infection (Watson, 2011).

6. Interference with Research

The primary way that parvovirus infections interfere with research is by disrupting biological responses that rely on cell proliferation. RV is lymphocytotropic and can induce immune function alterations, such as disruption of T cell responses in diabetes-resistant rat strains leading to autoimmune diabetes or lymphocytic insulitis (Brown et al., 1993; Chung et al., 2000; Ellerman et al., 1996; Guberski et al., 1991), interference with T cell responses to transplantable neoplasms (Campbell et al., 1977), and diminished proliferative and cytolytic responses of T cells (McKisic et al., 1995). H-1 is oncolytic in rat and human tumors (Geletneky et al., 2010, 2017; Kiprianova et al., 2011; Raykov et al., 2007) and is being considered as a novel therapeutic agent against both solid tumors and hematological malignancies in humans (Akladios and Aprahamian, 2016; Angelova...
et al., 2017; Marchini et al., 2015). Chronic RPV infection has been reported to improve hind-limb locomotor recovery following induction of moderate spinal cord contusion injury (Kjell et al., 2016).

D. Polyomaviridae

Polyomaviruses are nonenveloped icosahedral viruses with small circular double-stranded DNA genomes (5 kb). A polyomavirus serologically distinct from *Mus musculus* polyomavirus was detected in rats in 1984 (Ward et al., 1984). It was found initially in athymic rats that developed a wasting disease with parotid sialoadenitis and in some cases tracheitis, bronchitis, or bronchiolitis (Ward et al., 1984). Basophilic intranuclear inclusions consistent with papovavirus infection occurred in ductal epithelial and acinar cells of the parotid salivary glands (Ward et al., 1984). Immunohistochemistry detected papovavirus antigens in salivary glands, respiratory airway mucosa, and kidney, and electron microscopy detected intranuclear crystalline arrays of virus particles (Ward et al., 1984). A 2017 study reported the presence of intranuclear paracrystalline arrays of 45-nm nonenveloped icosahedral virions in the prostatic epithelial cells of a Wistar–Han rat with prostatitis in a chronic toxicity study using an immunomodulatory agent (Masek-Hammerman et al., 2017). Although the microscopic findings were consistent with polyomavirus, PCR from formalin-fixed paraffin-embedded tissues did not detect polyomavirus DNA.

*R. norvegicus* polyomavirus 1 (RnorPyV1) was detected by PCR in the spleens of 22 feral or feral-derived *R. norvegicus* in Germany and the complete genome sequence of RnorPyV1 is most similar to *Mesocricetus auratus* polyomavirus 1 (genus *Alphapolyomavirus*) (Ehlers et al., 2015). PCR from an additional 388 Norway rats collected in five European countries detected RnorPyV1 in 23% of the spleen samples (Heuser et al., 2017).

*R. norvegicus* polyomavirus 2 (RnorPyV2) was initially detected in the parotid salivary gland of an X-linked severe combined immune deficiency rat that had a genetically disrupted interleukin-2 receptor γ gene (X-SCID) (Rigatti et al., 2016). RnorPyV2 was also detected in a breeding colony of immunodeficient F344–SCID rats (FSG) (Besch-Williford et al., 2017). The sequence of the RnorPyV2 genome is divergent from that of RnorPyV1 and most similar to human polyomaviruses WU and KI and vole polyomavirus (genus *Betapolyomavirus*) (Besch-Williford et al., 2017; Rigatti et al., 2016).

Decreased fecundity was observed in X-SCID rats infected with RnorPyV2 (Rigatti et al., 2016). Rats had no overt clinical signs. Intranuclear inclusion bodies were detected in the lung epithelium of all 12 X-SCID rats examined and several rats also had intranuclear inclusion bodies in the nasal cavity, Harderian and salivary glands, prostate, and uterus (Rigatti et al., 2016). Lesions characterized as severe were detected in the Harderian glands, salivary glands, and prostate of adult rats and in the lung and nasal cavity of weanling rats (Rigatti et al., 2016).

Decreased fecundity, adult-onset wasting, and mortality of dams and pups were observed in FSG rats infected with RnorPyV2 (Besch-Williford et al., 2017). Salivary, lacrimal, and Harderian gland atrophy was observed. RnorPyV2 is epitheliotropic, and basophilic intranuclear inclusions were seen in the epithelium of salivary, lacrimal, Harderian, prostate, endometrial, and thyroid glands; lung; and kidney (Fig. 13.10). By in situ hybridization, signal intensity was greatest in the epithelium of glands, followed by respiratory tract, reproductive tract, urinary tract, and gastrointestinal tract (Besch-Williford et al., 2017). Nude rats cohoused

![FIGURE 13.10](image-url)  
*Rattus norvegicus* polyomavirus 2 infection in an FSG rat. Intranuclear inclusions (arrows) within (A) acinar and ductal cells of the parotid salivary gland and (B) bronchiolar epithelium of the lung. Hematoxylin and eosin–stained sections. *Images provided by Cynthia Besch-Williford and modified by Carmen Booth.*

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with infected FSG rats for 10–15 weeks had lesions similar to the naturally infected FSG rats (Besch-Williford et al., 2017). Thirty-two percent of immuno-competent rats were reported to have antibodies to RnorPyV2 DNA and 0.7% of feces collected from immuno-competent rats were positive for RnorPyV2 DNA (Besch-Williford et al., 2017), suggesting that RnorPyV2 infection in laboratory rat colonies is widespread. It was postulated that RnorPyV2 is spread by direct contact with respiratory and salivary secretions.

E. Poxviridae

Orthopoxviruses have large, linear, double-stranded DNA genomes (185–225 kb), which are encapsidated in large complex virions. Cowpox virus (CPXV), ectromelia virus, monkeypox virus, vaccinia virus, and variola virus are all members of the Orthopoxvirus genus (Essbauer et al., 2010). The first report of poxvirus infection in rats was in a white rat breeding colony used to supply a zoo in Moscow, Russia, in which over 12,000 rats became severely ill or died (Marennikova et al., 1978). The virus was determined to be distinct from ectromelia virus and vaccinia virus and was considered a CPXV variant. Affected rats developed pulmonary and dermal lesions. Rats with the pulmonary form of the disease had weight loss, became flaccid, were dyspneic, and had increasing abdominal distension and died within 4 days. Deaths in rats with the dermal form of the disease were rare, and rats had rhinitis, conjunctivitis, and a red papular rash on their tail, paws, and/or muzzle, which sometimes led to necrosis of the affected part. Rats that had the mixed form of the infection with both pulmonary and dermal lesions died in 2–3 days. Subclinical infection was reported in many of the rats.

Experimental infection of 4- to 6-week-old Wistar rats with CPXV resulted in clinical symptoms and dermal lesions in 6–11 days; rats had detectable virus in oropharyngeal secretions on day 5 and the majority of rats had detectable viral DNA in the nose, lung, esophagus, liver, spleen, skin, and brain on day 10 (Kalhoff et al., 2011). Severity of disease is related to the route of infection. Intranasal or combined intranasal/intradermal inoculation resulted in severe disease, and rats died peracutely with severe dyspnea and lethargy, whereas rats inoculated intradermally or infected by exposure to CPXV-infected rats had less severe disease characterized primarily by dermal lesions and survived until the end of the experiment (11 or 36 days) (Breithaupt et al., 2012). Rats inoculated with cowpox were reported to have proliferative and necrotizing dermatitis and folliculitis, ulcerative–necrotizing rhinitis and pharyngitis, bronchointerstitial pneumonia, pulmonary edema, and emphysema. Contact sentinel rats had dermal lesions but did not develop upper or lower respiratory lesions (Breithaupt et al., 2012). Histologically, all poxviruses produce basophilic intracytoplasmic inclusions (type A, or Guarnieri bodies) in infected epithelial cells, while CPXV and ectromelia virus also produce eosinophilic/acidophilic intracytoplasmic inclusions (type B). Serology using vaccinia virus can be used to detect cowpox antibodies. PCR is used to definitively distinguish CPXV from other poxviruses, such as ectromelia virus and vaccinia virus.

Small rodents are believed to be the reservoir of CPXV, with cows, cats, humans, and elephants being the default hosts (Essbauer et al., 2010). Yet, a 2017 PCR-based survey of wild rats in Norway failed to detect CPXV DNA (Heuser et al., 2017). While human CPXV infection is a rare zoonosis, transmission of CPXV from wild and pet rats to humans has been reported several times since 2002 (Becker et al., 2009; Campe et al., 2009; Elsendoorn et al., 2011; Honlinger et al., 2005; Vogel et al., 2012; Wolfs et al., 2002). Transmission of CPXV from rats to Barbary macaques in an exotic animal sanctuary has also been documented (Martina et al., 2006). Therefore, CPXV needs to be ruled out as the cause of pox-like lesions of the tail, paw, or muzzle in laboratory rats.

III. RNA VIRUS INFECTIONS

A. Arenaviridae

Lymphocytic choriomeningitis virus (LCMV), a Mammarymavirus, is an enveloped spherical virus that contains two segments of negative-stranded RNA totaling 11 kb. LCMV was originally isolated from a human patient and usually causes aseptic meningitis (Armstrong and Lillie, 1934). The primary host for LCMV is mice and fetal or neonatal infection of mice with LCMV is lifelong. Hamsters, guinea pigs, and rats can also be infected with LCMV but only mice and hamsters have been linked to outbreaks of LCMV in humans (Bowen et al., 1975; Centers for Disease Control and Prevention (CDC), 2005; Hirsch et al., 1974; Martinez Peralta et al., 1990). Serological surveys of laboratory rats have not detected LCMV (McInnes et al., 2011; Pritchett-Corning et al., 2009) and LCMV was not detected in a serological survey or in metagenomic analyses of wild rat feces and intestinal contents (Easterbrook et al., 2008; Firth et al., 2014; Sachsenroder et al., 2014). But, LCMV is still a concern in laboratory rats because of its zoonotic potential.

Rats have been used as a model of the neuropathological abnormalities of human congenital LCMV infection. Intracerebral inoculation of neonatal Wistar and Long–Evans rats with LCMV caused nonfatal, acute, severe,
and permanent cerebellar hypoplasia and retinitis leading to abnormalities in movement, coordination, vision, and behavior (Monjan et al., 1971, 1972, 1973, 1975). Intracerebral inoculation of neonatal Lewis rats with LCMV has been linked to urolithiasis (Mook et al., 2004). Vertical transmission of LCMV from rats infected as neonates has been reported and led to congenital retinitis in their offspring (del Cerro et al., 1984). Infection of adult diabetes-prone BB rats with LCMV reduced the incidence of insulin-dependent diabetes mellitus (Schwimmbeck et al., 1988).

B. Coronaviridae

Coronaviruses are enveloped, pleomorphic viruses with large positive-sense single-stranded RNA genomes (27–32 kb). They replicate in the cytoplasm and are released by budding through the endoplasmic reticulum (Compton et al., 1993). Coronaviruses are widespread among mammals and birds, including laboratory rats and mice. Coronaviruses are largely species specific. Parker and associates isolated a coronavirus from the lungs of clinically normal rats, which became known as Parker’s rat coronavirus (RCV) (Parker et al., 1970). Within a few years, a second coronavirus was isolated by Bhatt and coworkers from rats with sialodacryoadenitis and it was named sialodacryoadenitis virus (SDAV) (Bhatt et al., 1972). RCV and SDAV are different strains of a coronavirus indigenous to rats and called, most inclusively, RCV (Percy and Williams, 1990). Additional RCV strains have been reported since the initial isolations by Parker and Bhatt. These include Japanese isolates—CARS (Kojima et al., 1980; Maru and Sato, 1982)—and US isolates RCV-BCMM, RCV-W, and RCV-NJ (Compton et al., 1999a; 1999b).

The replication of single-stranded RNA viruses is more error prone than the replication of DNA viruses, resulting in the emergence of divergent RCV strains during natural infections (Compton et al., 1993). RCV replicates in vitro in primary rat kidney cells, forming multinucleate syncytia typical of coronaviral infection (Bhatt et al., 1972). Virus can be detected antigenically in infected cells within 12 h and cytopathic effects can develop within 24 h. Mouse L2 fibroblasts and sublines, as well as rat LBC cells and intestinal RCV-9 cells, can also be infected (Gaertner et al., 1996a; Hirano et al., 1986; Ohsawa et al., 1996; Percy et al., 1989, 1990b), and L2 sublines and LBC cells can also be used for plaque assays and plaque purification (Gaertner et al., 1993b).

1. Clinical Signs

Clinical signs may vary with RCV strain, but are characteristic of coronavirus infection. Mild infection can be clinically silent and revealed by serology or RT-PCR of sentinel or index rats. But clinical signs are common in many outbreaks and can occur in nonimmune rats of any age, usually lasting about a week (Bhatt and Jacoby, 1985; Jacoby et al., 1975). Early signs, especially in suckling pups, include squinting, photophobia, and lacrimation. Older rats frequently develop audible sneezing and palpable enlargement of cervical salivary glands. Red-tinted discharges containing porphyrin (chromodacryorrhea) may stain periorbital and perinasal skin. Severe ocular inflammation can initially present as keratoconjunctivitis, which may resolve quickly or become chronic. Chronic ocular inflammation can lead to corneal opacities and ulcers, pannus, hypopyon, hyphema, and megaloglobus (Lai et al., 1976). Ancillary effects attributable to the discomfort of infection include transient anorexia and weight loss (Sato et al., 2001) and disruption of estrus (Utsumi et al., 1980, 1990, 1991). In addition, birth rates and fertility in breeding colonies have been observed to markedly decline during acute RCV epizootics. Morbidity frequently reaches 100% among rats housed in open cages, but RCV infection rarely causes mortality. Most rats recover, with the most frequent long-term sequelae being ocular disease.

2. Epidemiology

RCV spreads primarily by direct contact with infected rats or by aerosol, and RCV remains infectious for at least 2 days when dried on plastic surfaces (Gaertner et al., 1996a). Experimental studies have demonstrated the ease of horizontal transmission of RCV (La Regina et al., 1992), but there is no evidence for intrauterine transmission. Colony infections often occur in either of two patterns: explosive epizootics among nonimmune animals or endemic infection in rooms where young rats are protected transiently by maternal antibody. Nonimmune, immunocompetent rats excrete virus in oronasal and lacrimal discharges for about 1 week (Bhatt and Jacoby, 1985). The onset of antiviral immunity terminates infection and is most easily detected by seroconversion. Immunity offers protection against recurrence of clinical disease, but protection is relatively short-lived (<6 months) and does not preclude transient reinfection, virus shedding, and a resultant increase in antibody titer (Percy and Williams, 1990; Percy et al., 1990a, 1991; Weir et al., 1990a). Reinfection of seropositive animals implies exposure to an antigenically variant strain of RCV. This risk is inherent to coronavirus infections because of spontaneous mutations leading to the emergence of variant strains, especially during endemic infection. Infection of immunodeficient (e.g., athymic) rats is persistent, with chronic necrosis and inflammation in the salivary and lacrimal glands and the respiratory tract (Hajjar et al., 1991; Weir et al., 1990b). In addition, athymic rats can excrete virus for prolonged...
periods and can develop urinary tract infection, which makes transmission by contaminated urine likely, whereas immunosuppression with prednisolone had a negligible effect on the course of infection, and treatment with cyclophosphamide resulted in only a modest prolongation of infection (Hanna et al., 1984).

Rats appear to be the sole hosts for naturally occurring infection, although there is experimental evidence that mice develop transient infection and interstitial pneumonia after inoculation with RCV or contact exposure to infected rats (Barthold et al., 1990; Bhatt et al., 1977; La Regina et al., 1992). Mice experimentally inoculated with large doses of RCV can transmit infection to mice in close contact; however, RCV infection does not appear to spread mouse to mouse under natural conditions.

The overall RCV seroprevalence is low (<1%), with the exception of one study conducted in India where the seroprevalence was reported to be 16% (Manjunath et al., 2015). However, it remains among the top four viruses detected by serology (Mahler and Kohl, 2009; McInnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006).

3. Pathology and Pathogenesis

The lesions of RCV reflect acute inflammation of the salivary and lacrimal glands, lymphoid tissue, respiratory tract, and eye (Bhatt et al., 1977; Jacoby et al., 1975). The submandibular and parotid salivary glands and adjacent cervical connective tissue are often edematous and the glands proper may be pale yellow to white, with red spots caused by vascular congestion. The cervical lymph nodes may be enlarged and edematous and contain multiple red foci. The exorbital and infraorbital lacrimal glands may be pale and enlarged, whereas the Harderian lacrimal gland located on the dorsolateral and posterior aspects of the eye globe may be flecked with yellow-gray foci. Reddish-brown mottling of the Harderian gland, indicative of porphyrin pigment, is a normal finding. The thymus may be small (as a result of stress atrophy) and the lungs may contain small gray foci. The external nares and eyes may reveal serous exudate and staining of adjacent skin by porphyrin pigment. Acute ocular inflammation includes corneal opacities and swollen conjunctiva, whereas advanced ocular disease may, as noted above, include pannus, hypopyon, hyphema, and megaloglobus (Lai et al., 1976).

Histologic lesions of RCV infection develop initially in the nasopharynx. They include necrosis of respiratory epithelium (Fig. 13.11) and submucosal glands with inflammatory edema of the lamina propria. Similar changes also affect the vomeronasal organ. The nasal meatus often contains neutrophils, cell debris, and mucus (Bhatt et al., 1977; Bihun and Percy, 1995; Jacoby et al., 1975). Mild, nonsuppurative tracheitis with focal necrosis of respiratory epithelium may occur and hyperplastic peribronchial lymphoid nodules may develop. Pulmonary lesions are less frequent and are characterized by focal, interstitial pneumonia presenting as infiltration of alveolar septae by mononuclear cells and neutrophils (Fig. 13.12). More severe lesions may be accompanied by alveolar exudates containing exfoliated pneumocytes, macrophages, and edema fluid. Although such lesions are typically not associated with clinical disease, Parker and colleagues demonstrated that RCV can induce lethal interstitial pneumonia in neonatal rats (Parker et al., 1970).

Salivary gland lesions occur in serous or mixed parenchyma and are, therefore, most easily visualized in the submandibular and parotid salivary glands, although smaller serous glands lining the oral cavity.
also are susceptible. Mucous salivary glands are not affected. Lesions begin as necrosis of the ductular epithelium (Fig. 13.13), which progresses rapidly to diffuse acinar necrosis. Moderate to severe interstitial inflammatory edema also develops within glandular parenchyma and in periglandular connective tissues. The combined effects of necrosis and inflammation often lead to regional or panacinar effacement of affected glands. Lacrimal gland lesions develop in a similar pattern (Fig. 13.14).

Histologic lesions in immunodeficient (athymic) rats are characterized by chronic active inflammation in the respiratory tract, salivary glands (Fig. 13.15), and lacrimal glands. As noted earlier, viral antigen has been detected in the urinary tract of athymic rats, indicating that defective immunity leads to altered tissue tropism and the likelihood of prolonged urinary excretion (Fig. 13.16) (Weir et al., 1990b).

Immunohistochemistry has shown that, irrespective of immune status, lesions result from initial infection of the respiratory tract, which extends to the salivary and lacrimal glands. It is not clear how this transition occurs. No viremic phase has been detected during experimental infections, but detection of viral antigen in salivary excretory ducts suggests that retrograde infection from the pharynx may occur. Retrograde infection of nasolacrimal ducts also could account for lacrimal gland infection. Cervical lymph nodes often sustain focal necrosis and inflammatory edema succeeded by hyperplasia as immunity develops. Mild thymic necrosis with widening of interlobular septae is viewed as a nonspecific response to the stress of infection.
Tissue repair in immunocompetent rats commences 5–7 days after infection begins. Reconstitution of respiratory mucosa and alveolar parenchyma is rapid and uneventful, although transient squamous metaplasia may occur in respiratory epithelium. Healing in salivary and lacrimal glands is characterized by prominent squamous metaplasia of the ductular epithelium, including the tubuloalveolar epithelium of the Harderian gland, and proliferation of hyperchromatic regenerating acinar cells (Fig. 13.17). Restoration of cytoarchitecture is substantially complete in 4–6 weeks, facilitated by the survival of basement membranes, which provide an effective framework for parenchymal regeneration. Residual lesions include focal lymphocytic infiltrates and mild fibrosis.

Keratoconjunctivitis does not result from direct RCV infection of the eye. It is attributed to impeded tear production by compromised lacrimal glands resulting in keratitis sicca. Changes are characterized by focal or diffuse interstitial keratitis with superficial corneal ulceration and associated conjunctivitis. These lesions may resolve within 4–6 weeks without further complication or progress to permanent scarring or more severe sequelae in a small number of rats. Severe outcomes include transmural corneal ulceration, hypopyon, hyphema, synechia, and glaucoma with lenticular and retinal degeneration. Keratitis also may facilitate secondary bacterial infection and increase the severity of ocular lesions.

4. Diagnosis

Clinical signs, serology, lesions, and RT-PCR-based environmental testing are used to diagnose RCV. In addition, immunohistochemistry on and virus isolation from tissues collected during acute infection can aid in diagnosing an RCV infection, keeping in mind that the virus is eliminated rapidly with the onset of host immunity. Gross and microscopic lesions, particularly necrosis and inflammation of the salivary and lacrimal glands, are virtually pathognomonic for RCV infection, as they are not duplicated in other known diseases of rats. The course of infection and tissue repair is sufficiently prolonged (4–6 weeks) to facilitate detection of acute or reparative stages. Because acute lesions develop within 5 days of exposure to the virus and are often reflected in clinical signs, it is best to select animals for pathologic study that have active clinical signs or that have been in recent contact with rats with clinical signs. Serology is used routinely to detect or confirm infection. However, it generally takes 7–10 days after initial exposure to virus before an individual rat becomes seropositive. Because RCV is antigenically related to mouse hepatitis virus (Barker et al., 1994), mouse hepatitis virus antigens can be used in serologic testing to detect RCV infection (Percy et al., 1991; Peters and Collins, 1981; Smith and Winograd, 1986). RT-PCR of cage surfaces also has been used to identify cages housing infected rats rapidly—and prior to seroconversion (Compton et al., 1999b).

5. Differential Diagnosis

RCMV can cause mild, asymptomatic lesions of the salivary glands, but corresponding lesions can be differentiated from RCV lesions. Cytomegalovirus infections are characterized by enlargement of ductal epithelial cells that may contain herpetic, intranuclear inclusions (Bruggeman et al., 1983). RnorPyV2 infection in immunodeficient rats can result in basophilic intranuclear inclusions in the epithelium of salivary, lacrimal, and Harderian glands and is accompanied by ductal and acinar degeneration with a mixed inflammatory infiltrate (Besch-Williford et al., 2017). Porphyrin-tinged nasoocular discharges can occur when rats are subject to other stressors, or during other infectious diseases of the respiratory tract, such as mycoplasmosis. Irritants such as ammonia can cause photophobia and lacrimation. Respiratory tract lesions due to RCV should be differentiated from those caused by Sendai virus, pneumonia virus of mice (PVM), or pathogenic bacteria. One cannot exclude, in this regard, the potential for RCV to facilitate or exacerbate secondary bacterial infection (Michaels and Myerowitz, 1983).

6. Control and Prevention

Typical bioexclusion and biocontainment practices prevent the introduction and spread of RCV, taking into account the potential for fomite, direct contact, and/or aerosol spread and contamination of biological materials (La Regina et al., 1992; Shek and Gaertner, 2002). RCV infection is eliminated by the immune
system in immunocompetent rats. However, it can remain endemic in any colony where naive nonimmune rats are regularly added. If an RCV infection is detected and it is determined that it will not interfere with research objectives, an alternative strategy to culling of infected rats is to exploit RCV’s highly transmissible nature for control. By purposefully exposing all rats to RCV, under strict biocontainment practices, immunocompetent rats will develop immunity that protects against reinfection with a homologous RCV strain. If there are breeding rats in the affected colony, production should cease in breeding colonies for about 6 weeks. After this interval, seropositive rats can be moved to a different room to resume breeding, because they should no longer be contagious (Brammer et al., 1993). Here, as well, purposeful exposure of breeding stock will accelerate colony-wide immunity, which also will lead to protection of normally susceptible litters by maternally acquired immunity.

Because RCV is relatively labile, routine disinfection will inactivate the virus. Sanitation of caging and equipment should include thorough washing at 83°C, but need not require autoclaving. Similarly, room surfaces can be sanitized with standard disinfectants, such as chlorine dioxide, followed by enforced vacancy for 2–3 days (Saknimit et al., 1988).

7. Interference with Research

RCV infection may hamper studies involving the respiratory system, salivary glands, lacrimal glands, immune system, and eye. Furthermore, acutely infected rats may be at increased risk for death during inhalation anesthesia, as inflammatory exudate in the airways and enlarged salivary glands may impede normal respiration. Published reports include other diverse effects upon research, including altered feeding behavior (Sato et al., 2001), inhibition of phagocytosis and interleukin-1 production by pulmonary macrophages (Boschert et al., 1988), enhancement of nasal colonization with *Haemophilus influenzae* type B (Michaels and Myerowitz, 1983), depletion of salivary gland epidermal growth factor (Percy et al., 1988), and graft-versus-host disease in rats with transplanted bone marrow (Rossie et al., 1988). A natural SDAV infection in rats undergoing tibial nerve transection was shown to severely impair axonal regeneration and functional recovery and negated the positive effects of FK506 treatment (Yu et al., 2011).

8. Rat Coronavirus as a Model of Respiratory Viral Infection

Understanding the interactions between the immune response and coronavirus infections in the lungs has been spurred by the severe respiratory disease induced by the emergence of severe acute respiratory syndrome-related coronavirus (SARS-CoV) and, more recently, by Middle East respiratory syndrome-related coronavirus (MERS-CoV). Serially passaged SARS-CoV was used to intranasally infect young and aged F344 rats. Aged rats had more severe lesions, which included pulmonary edema, bronchiolitis obliterans organizing pneumonia, and diffuse alveolar damage, similar to what is observed in early human SARS infections. Neutrophils and activated macrophages were the predominant inflammatory cell infiltrate. There were no histopathologic lesions in extrapulmonary tissue. The authors demonstrated that advanced age and virus adaptation are required for SARS development (Nagata et al., 2007). More generally, RCV is used to better understand the host–pathogen relationship in pulmonary disease. The primary target of RCV in the alveoli is the type 1 alveolar epithelial cells (Funk et al., 2009; Miura et al., 2007). Using an in vitro model system, RCV infection induced proinflammatory cytokines and, specifically, CXC chemokines that inhibit polymorphonuclear leukocyte (PMN) apoptosis in type 1-like alveolar epithelia (Miura and Holmes, 2009; Rzepka et al., 2012). Furthermore, it was shown that RCV-infected rats deficient in PMNs have more severe and prolonged disease, indicating PMNs are required for an effective antiviral response but also contribute to the lung pathology (Haick et al., 2014).

9. Emergence of Novel Rat Coronaviruses

Increased interest in coronavirus reservoirs occurred after SARS and MERS outbreaks, since they infect both humans and animals. Two novel rat coronaviruses were detected using RT-PCR of tissues in wild rats trapped in China; Lucheng Rn rat coronavirus (LRNV) and Longquan R1 rat coronavirus (LRLV). LRNV is the first rodent coronavirus assigned to the genus *Alphacoronavirus*. It is genetically distinct enough to be considered as a new species of coronavirus and, importantly, has a recombination origin, implicating recombination among coronaviruses of different genera. LRLV is assigned to the *Betacoronavirus* genus along with RCV and mouse hepatitis virus. Tissues sampled included liver, spleen, lung, kidney, and rectum, but the specific tissue in which LRLV was detected was not identified (Wang et al., 2015). Another rat coronavirus, HKU24, was also detected by RT-PCR of alimentary tract samples from wild Norway rats collected from public areas in China. Although distinct from the murine coronaviruses, phylogenetic analysis of HKU24 suggests it represents a murine origin betacoronavirus that underwent interspecies transmission from rodents to other mammals prior to the emergence of human coronaviruses (Lau et al., 2015). These studies demonstrate the potential for novel rat coronavirus infections to emerge/reemerge.
C. Flaviviridae

Hepaciviruses are enveloped icosahedral viruses with positive-sense single-stranded RNA genomes of approximately 10 kb. The prototype hepacivirus is human hepatitis C virus (hepacivirus C). Six species of hepaciviruses have been found in rodents (hepaciviruses E–J). In 2014, RNA from hepacivirus G and hepacivirus H, also called Norway rat hepaciviruses 1 and 2 (NrHV 1 and 2) or rodent hepacivirus—R. norvegicus (RHV-rn 1 and 2), was detected by RT-PCR in the livers and sera from six Norway rats (Firth et al., 2014).

Clinical illness has not been reported in natural infections of rats with hepacivirus G, although Sprague–Dawley rats inoculated with a serum sample from a wild rat infected with hepacivirus G developed a high-titered viremia, which persisted for at least 80 days (Trivedi et al., 2017). Brown Norway rats inoculated intrahepatically with a molecular clone of hepacivirus G and Holtzman, Long–Evans, and Wistar rats inoculated intravenously with hepacivirus G also became persistently infected (Trivedi et al., 2017). Histopathology of liver biopsies from infected rats showed moderate hepatic inflammation with dense lymphoid aggregates focused on the portal tracts on day 85 and macrovesicular and microvesicular steatosis with diminished portal tract inflammation on day 287 (Trivedi et al., 2017). Hepacivirus G infection results in chronic infection with pathology similar to that seen in humans with hepacivirus C infection. Intravenous inoculation of immunocompetent mice with hepacivirus G results in an acute infection, whereas a chronic liver infection was established in immunocompromised mice (Billerbeck et al., 2017).

D. Hantaviridae

Hantaviruses are enveloped, spherical viruses with trisegmented, negative-sense, single-stranded RNA genomes (18 kb total). There are over 40 known species of hantaviruses, each of which is closely associated with its reservoir host (Forbes et al., 2018; Schmaljohn and Hjelle, 1997). Infections in reservoir species are generally subclinical and persistent. R. norvegicus and Rattus rattus serve as the reservoir hosts for Seoul virus. In contrast, virtually all hantaviruses are zoonotic, with varying degrees of pathogenicity in humans, causing asymptomatic to lethal infections (Hart and Bennett, 1999).

In humans, Seoul virus and Hantaan virus cause a hemorrhagic fever with renal syndrome known as Korean hemorrhagic fever. While Korean hemorrhagic fever has been reported since the 1950s, Seoul virus was not isolated from rats until the 1980s (Kitamura et al., 1983; LeDuc et al., 1984; Lee et al., 1982). Over 100 cases of transmission of Seoul virus from laboratory rats to laboratory personnel have been reported (Desmyter et al., 1983; Kawamata et al., 1987; Lloyd et al., 1984; Lloyd and Jones, 1986; Umemai et al., 1979; Wong et al., 1988). Since the implementation of biosafety level 3 practices for in vivo and in vitro research with hantaviruses, laboratory-acquired infections are rare. The seroprevalence of Seoul virus in laboratory rats is low (0%–0.07%) (Liang et al., 2009; McInnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006). Several reports of Seoul virus infection of pet rats have been reported (Duggan et al., 2017; Fill et al., 2017; Jameson et al., 2013a, 2013b; McElhinney et al., 2016, 2017). Seoul virus is found worldwide and its prevalence in wild rat populations is high (12%–58%) (Cueto et al., 2008; Dupinay et al., 2014; Easterbrook et al., 2007b). Therefore, exposure of laboratory rats to feral or pet rats should be avoided.

Rat-to-rat transmission of Seoul virus in the wild occurs primarily through direct contact and bite wounds, although indirect contact by fomites contaminated with urine, feces, or saliva is possible (Easterbrook et al., 2007a; Glass et al., 1988; Hinson et al., 2004; Kariwa et al., 1998; Klein et al., 2000). Experimental aerosol transmission using a nebulizer has been reported (Nuzum et al., 1988). Seoul virus is not transmitted in utero in rats and maternal antibodies protect neonatal rats from infection (Dohmae and Nishimune, 1998; Morita et al., 1993; Zhang et al., 1988). Transmission to cage mates has been seen with neonatal mice and adult nude rats (Dohmae et al., 1994; Morita et al., 1985).

Most studies of Seoul virus pathology in rats have used experimental intraperitoneal inoculation (Compton et al., 2004; Lee et al., 1986). In 1- to 7-day-old rats inoculated with Seoul virus, infection of the central nervous system can lead to ataxia, limb paralysis, tremors, and in some cases death 2–3 weeks postinoculation (Compton et al., 2004; Mori et al., 1991; Zhang et al., 1989). Virus was detected in the lung, brain, spinal cord, salivary glands, pancreas, spleen, kidney, liver, and skin for 25 weeks in rats inoculated as neonates (Compton et al., 2004; Mori et al., 1991; Tanishita et al., 1986; Yamanouchi et al., 1984; Zhang et al., 1989). In situ hybridization of tissues from rats inoculated at 6 days of age detected viral RNA in SMCs, endothelial cells, and glandular and renal epithelium (Compton et al., 2004). Infection does not cause significant tissue damage, but can provoke mononuclear cell infiltrations in affected tissues, including lung, salivary gland, pancreas, and kidney. Pancreatic lesions may cause insulitis with at least transient elevations in blood glucose.
Infection of immunocompetent weanling and adults rats with Seoul virus causes a subclinical infection. A transient viremia was seen 2–3 days postinfection (Kariwa et al., 1996) The distribution of virus was similar to that seen in neonates, with the highest titers of virus found at 2 weeks (Hannah et al., 2008). By 6 weeks post-inoculation, virus titers were low and were less consistently detected in lung, spleen, kidney, and salivary glands (Compton et al., 2004; Klein et al., 2001; Tanishita et al., 1986). Persistent infection occurs in the presence of a strong humoral immune response (Compton et al., 2004). Infection of immunodeficient adult nude rats with Seoul virus caused a disease similar to that seen in neonatal mice, resulting in limb paralysis, ataxia, convulsions, and sudden death within 10 weeks, indicating a role for T cells in the control of Seoul virus infection (Dohmae et al., 1994). The role of the immune response in the persistent Seoul virus infections in rats is unclear, but the activation of regulatory T cells and the ensuing suppression of proinflammatory responses by Seoul virus could contribute to persistence of the virus (Easterbrook et al., 2007a; Easterbrook and Klein, 2008a, 2008b). Male rats are more susceptible to Seoul virus infection, producing higher and longer antibody responses, shedding virus for longer, and consistently having higher viral titers in the lung, spleen, and saliva (Klein et al., 2000, 2001, 2002). Innate and cell-mediated immune responses differ between Seoul virus–infected male and female rats (Easterbrook and Klein, 2008b; Hannah et al., 2008). Increased testosterone and aggression have been associated with high levels of Seoul virus in male rats (Easterbrook et al., 2007a).

E. Hepeviridae

Hepeviruses are nonenveloped icosahedral viruses with positive-sense single-stranded RNA genomes of approximately 7 kb (Johne et al., 2014). The prevalence of hepatitis E virus (HEV) antibodies in wild R. norvegicus in the 1990s in the United States ranged from 44% to 90% (Favorov et al., 2000; Kabrane-Lazizi et al., 1999). In 2010 and 2011, two novel HEVs were detected by RT-PCR in wild R. norvegicus in Germany and the United States (Johne et al., 2010; Purcell et al., 2011). HEV RNA and antigens were detected in the liver of the wild rats (Johne et al., 2010). HEV from wild rats was transmissible to Sprague–Dawley and nude rats (Purcell et al., 2011). Sprague–Dawley rats inoculated with rat HEV seroconverted and shed HEV in their feces, and mild hepatitis characterized by foci of necrosis in the liver parenchyma and aggregates of lymphocytes and Kupffer cells in the hepatic lobules was seen (Purcell et al., 2011). Nude rats inoculated with rat HEV had high levels of rat HEV RNA in feces and serum but not in urine on days 1–28 (Li et al., 2017). Immuno-competent Wistar rats inoculated with rat HEV had high levels of rat HEV RNA in feces on days 5–15, and the development of anti–HEV antibodies by 2 weeks seemed to have resulted in clearance of the infection (Li et al., 2017). The genome sequences of over 50 strains of rat HEV (orthohepevirus C) have been elucidated from rats in the United States, Europe, and Asia (Ryll et al., 2011). Rat HEVs are genetically distinct from human and porcine HEVs (orthohepevirus A) and from avian HEV (orthohepevirus B) (Ryll et al., 2017). Experimental infections of rats with orthohepevirus A have been unsuccessful and experimental infection of pigs and nonhuman primates with orthohepevirus C were also unsuccessful (Li et al., 2013a; 2013b; Purcell et al., 2011). As of this writing, rat HEV infection in laboratory rats has not been reported.

F. Paramyxoviridae

1. Sendai Virus

Sendai virus (murine respirovirus) is an enveloped, pleomorphic virus with a 15-kb single-stranded negative-sense RNA genome. Sendai virus was previously known as murine parainfluenza virus and can be differentiated serologically from human, porcine, and bovine parainfluenza viruses (respiroviruses). While mice are the primary targets of Sendai virus infection, there have been reports of natural outbreaks in rats (Burek et al., 1977; Makino et al., 1973). Sendai virus also is infectious for hamsters and guinea pigs (Parker et al., 1978). Sendai virus seroprevalence in laboratory rats is very low (0%–0.4%) (McInnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006). Seroprevalence in wild rats in Baltimore in 2005–06 was 4.2% but recent metagenomic analyses of feces or intestinal contents from wild rats did not detect Sendai virus (Easterbrook et al., 2008; Firth et al., 2014; Sachsenroder et al., 2014).

Sendai virus is highly contagious and transmitted by aerosols. Rapid spread throughout rat colonies was common prior to the advent of individually ventilated caging (Burek et al., 1977; Makino et al., 1973). During an epizootic of Sendai virus in mice in the Netherlands, multifocal interstitial pneumonia was observed in rats that seroconverted to Sendai virus, but virus could not be isolated from the rat lungs (Burek et al., 1977). Also, during several rounds of Sendai virus infection in a facility in Japan, signs of respiratory disease and retarded growth in suckling rats were observed (Makino et al., 1973). Epizootic infection was punctuated by fresh clinical outbreaks, typical for acute viral infections in which
recovery leads to transient maternally derived immunity, followed by renewed susceptibility (Makino et al., 1973). Antibody responses to Sendai virus in both outbreaks remained high for several months, but declined to low or undetectable levels within 9 months (Burek et al., 1977; Makino et al., 1973).

Immunocompetent rats of all ages are susceptible to experimental intranasal Sendai virus infection. Sendai virus infection of young adult Sprague–Dawley rats caused rhinitis, bronchiolitis, and pneumonia. Lesions were confined to the nasal cavity, trachea, and lung, with sporadic involvement of the middle ear (Giddens et al., 1987). Rhinitis was maximal on days 4–6 and persisted for 3 weeks, with viral antigen detectable in the columnar epithelial cells of the nasal cavity from day 1 to 7 (Giddens et al., 1987). Histologically, lesions were characterized by epithelial necrosis with mucosal infiltration by neutrophils and lymphoid cells. Bronchiolitis and interstitial pneumonia were observed starting on day 1 and viral antigen was detected in the bronchial/bronchiolar/alveolar epithelium from day 1 to 5 (Giddens et al., 1987). The epithelium underwent necrosis and erosion, which may be accompanied by epithelial hyperplasia (Fig. 13.18). Peribronchial lymphoid infiltrates were detectable through day 42. Lesions in the trachea were similar to those seen in the bronchi (Giddens et al., 1987). Infectious Sendai virus was recovered from the lungs and nasal cavity through day 8 and antiviral antibodies were detected for 9 months (Garlinghouse et al., 1987). Resolution of pneumonia in immunocompetent rats begins within 2 weeks after exposure and is largely complete within 3 weeks (Sorden and Castleman, 1991). Residual lesions include perivascular and peribronchial accumulations of mononuclear cells, which may last up to several weeks. Rat strain differences in susceptibility to Sendai virus have been reported. Brown Norway rats infected with Sendai virus have prolonged viral replication and produce much higher viral titers than Fischer 344 rats (Sorden and Castleman, 1991). Young Brown Norway rats infected with Sendai virus also develop increased airway resistance and hyperresponsiveness with bronchial fibrosis that is associated with increased bronchiolar mast cells (Uhl et al., 1996). More severe rhinitis, tracheitis, bronchitis, bronchiolitis, and alveolitis were observed in Lewis rats compared with Fischer 344 rats (Liang et al., 1995).

The pattern of infection and lesions in neonatal and weanling rats was similar to that seen in young adult rats (Castleman, 1983; Castleman et al., 1987). Sendai virus was detected by electron microscopy in bronchiolar ciliated and nonciliated cells, alveolar type I and II epithelial cells, and macrophages of weanling rats infected with Sendai virus (Castleman et al., 1987). Pneumonia was maximal in weanling rats at 5 days and in neonatal rats at 8 days. Infectious Sendai virus was recovered from the lungs of weanling rats for 6 days and from the lungs of neonatal rats for 10 days (Castleman et al., 1987). Elimination of virus coincides with the onset of antiviral immunity and the delay in Sendai virus clearance from neonatal rats is associated with the delayed onset of antiviral antibodies and interferon response (Castleman et al., 1987; Liang et al., 1999). Passive transfer of anti-Sendai virus antibodies protected rats from lower airway but not from upper airway infection (Liang et al., 1999). Sendai virus infection impaired postnatal alveolar and bronchiolar growth, resulting in alveolar and bronchiolar hypoplasia (Castleman, 1984; Castleman et al., 1988).

Infection of pregnant rats with Sendai virus resulted in resorption of embryos, increased neonatal mortality, or decreased neonatal weights (Coid and Wardman, 1971, 1972). Virus was not recovered from the fetuses or neonates, and the fetal/neonatal effects were concluded to be the indirect result of infection of the dam (Coid and Wardman, 1971, 1972). Embryonic deaths were also reported during an outbreak of Sendai virus and Pasteurella pneumotropica in rats (Carthew and Aldred, 1988). Athymic rats inoculated with Sendai virus had extensive pneumonitis with necrosis and hyperplasia of the bronchiolar epithelium and virus was detectable for at least a month (Carthew and Sparrow, 1980). Sendai virus has been reported to increase the severity of Mycoplasma pulmonis–induced lung, tracheal, nasal, and inner ear lesions in gnotobiotic Fischer 344 rats (Schoeb et al., 1985). It was noted that natural infection of Sendai virus in conjunction with M. pulmonis increased susceptibility to neurogenic inflammation in the trachea (McDonald, 1988). Experimental Sendai

![FIGURE 13.18 Sendai virus infection. Bronchopneumonia with necrosis of bronchial epithelium.](image-url)
virus infection alone was able to potentiate neurogenic inflammation in the trachea (Piedimonte et al., 1990).

2. Other Paramyxoviruses

Several other members of the Paramyxoviridae family have been detected in wild rat species. Mossman virus was isolated from Rattus leucopus and Rattus fuscipes in Queensland (Miller et al., 2003). Beilong virus was amplified from cultured rat kidney mesangial cells and from kidney and spleen samples from R. norvegicus and R. rattus (Li et al., 2006; Woo et al., 2012). Tailam virus was detected in kidneys and spleens of Rattus andamanensis in Hong Kong (Woo et al., 2011). Mojiang virus, a novel henipavirus, was detected in three miners in China that died from severe pneumonia and was detected in anal swabs from Rattus flaviviridis collected from the mine (Wu et al., 2014). A 2014 metagenomic analysis targeting unclassified morbillivirus-related viruses in the Southwestern Indian Ocean Islands detected paramyxovirus RNA in 62% of R. norvegicus and 23% of R. rattus tissue samples (Wilkinson et al., 2014). As of this writing, none of these other paramyxoviruses have been reported to cause disease in rats.

G. Picornaviridae

1. Cardioviruses

Cardioviruses are nonenveloped icosahedral viruses with single-stranded positive-sense RNA genomes of approximately 8 kb. Three species of cardioviruses infect rats: cardiovirus A (encephalomyocarditis virus [EMCV]/mengovirus), cardiovirus B (rat theilovirus [RTV], also known as Thera virus), and cardiovirus C (Boone cardiovirus). Serological surveys indicate that cardiovirus infections are one of the top four most common viral infections of rats, with seroprevalences of 0.08%–2.3% (Mahler and Kohl, 2009; Marx et al., 2017; McInnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006).

ECMV (cardiovirus A) causes lethal infections in a broad range of species, including pigs, nonhuman primates, and elephants, and has a worldwide distribution (Doi, 2011). Mice and rats serve as reservoirs for EMCV and have been linked to several outbreaks in zoos and pig farms. Young rats are more susceptible to EMCV than adult rats. Intraperitoneal or intranasal inoculation of 3- to 25-day-old rats with mouse brain stocks of EMCV resulted in paralysis and death within 8 days, whereas inoculation of 35- to 40-day-old rats resulted in asymptomatic infection (Findlay and Howard, 1951). In rats inoculated intraperitoneally with EMCV at 2–14 days of age, acute meningoencephalitis with small foci of neuronal necrosis in the cerebral cortex, hippocampus, and thalamus was observed, whereas in rats inoculated intracerebrally at 28 or 56 days of age, no lesions were observed (Ikegami et al., 1997). EMCV was efficiently transmitted from 8-week-old rats inoculated oronasally to contact rats, with infectious EMCV detectable in the feces of inoculated and contact rats between days 2 and 29 (Spyrou et al., 2004). EMCV was isolated on days 11–22 from the heart, spleen, lung, pancreas, thymus, Peyer’s patches, and liver of over 80% of inoculated and contact rats, but on days 57–62, EMCV was isolated only from the thymus and Peyer’s patches (Spyrou et al., 2004). While the infection was subclinical, histologically focal interstitial pancreatitis, depletion of thymus and Peyer’s patches, and interstitial pneumonia were evident, and ECMV antigen was detected in the cardiac muscle cells, pancreatic acinar cells, hepatic epithelial cells, and macrophages in the spleen, lung, and thymus (Psalla et al., 2006). Experimental Trichinella spiralis infection of rats increases the severity of EMCV disease (crippling and death) in 2-month-old rats (Kilham and Olivier, 1961).

The cardiovirus B species includes Saffold virus, which infects humans; Theiler’s encephalomyelitis virus (TMEV), which infects mice; and RTV, which infects rats (Liang et al., 2008). In 1961, a neurotropic TMEV-like cardiovirus called MHG virus was isolated from Sprague–Dawley rats and it infected intestine, lung, and brain after experimental inoculation (McConnell et al., 1964). In 1991, another TMEV-like cardiovirus (NGS910) was isolated from intestinal homogenates from clinically normal sentinel rats seropositive for TMEV (Ohsawa et al., 2003). Sequencing of NGS910 revealed that it had only 74% identity with TMEV (Ohsawa et al., 2003). Inoculation of neonatal rats with intestinal homogenates from clinically normal sentinel rats seropositive for TMEV resulted in paralysis (Rodrigues et al., 2005). RTV1 was isolated from neonatal rats exposed to solid bedding from rats seropositive for TMEV and has 95% identity with NGS910 (Drake et al., 2008). Four-week-old Sprague–Dawley rats were more susceptible than CD rats to RTV1 infection in that they shed virus in feces for longer (56 days vs. 14 days) and seroconverted earlier (14 days vs. 56 days), though lesions were not seen in either rat strain (Drake et al., 2008). Shedding of RTV in feces from immunocompromised nude rats and immunocompetent (Brown Norway and Fischer 344) rats infected as weanlings was high for the first 2 weeks, with persistent shedding in nude rats but not in immunocompetent rats (Drake et al., 2011). RTV persisted in the mesenteric lymph nodes and spleen of nude rats but not those of immunocompetent rats (Drake et al., 2011). Serum antibody responses in Brown Norway and Sprague–Dawley were significantly higher than those in Fischer 344 and CD1 rats (Drake et al., 2011).
Metagenomic analysis of rat intestinal contents/feces detected a novel species of cardiovirus, *cardiovirus C*, also called Boone cardiovirus (Firth et al., 2014; Hansen et al., 2016).

2. Other Picornaviruses

Metagenomic analysis of rat intestinal contents/feces has detected several other genera of picornaviruses (*Enterovirus, Hmunivirus, Kobavirus, Parechovirus, Rabovirus*, and *Rosavirus*) in rats (Firth et al., 2014; Hansen et al., 2016; Ng et al., 2015; Sachsenroder et al., 2014).

H. Pneumoviridae

PVM(species *murine orthopneumovirus*) is a member of the family Pneumoviridae along with human respiratory syncytial virus (species *human orthopenovirus*). Pneumoviruses have enveloped pleomorphic virions containing a 15-kb negative-sense, single-stranded RNA genome. PVM cause rhinotracheitis and interstitial pneumonia in mice, but also causes asymptomatic infections in rats, cotton rats, guinea pigs, hamsters, and rabbits (Eaton and VanHerick, 1944; Horsfall and Curnen, 1946). Seroconversion of rats to PVM has been reported since 1978 but PVM was not isolated from rats until 1995 (Miyata et al., 1995; Payment and Descoteaux, 1978). Reports of seroprevalence of PVM in laboratory rats range from 0.1% to 1.6%, ranking it among the top four most prevalent agents in rats (Mahler and Kohl, 2009; Mclnnes et al., 2011; Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006). PVM infection in immunocompetent rats is generally asymptomatic, though PVM infection in F344 rats has been associated with decreased body weight and lower prevalence of spontaneous leukemia. PVM infection in F344 rats has also been reported to cause multifocal nonsuppurative vasculitis and acute pneumonia in the lung at day 6 postinoculation (Vogtsberger et al., 1982). Pulmonary lesions were reported in F344 nude rats after PVM infection (Miyata et al., 1995).

I. Reoviridae

1. Reoviridae

Reoviruses (genus *Orthoreovirus*) are nonenveloped double-shelled icosahedral viruses that contain 11 segments of double-stranded RNA that total 22 kb. Mammalian orthoreoviruses infect a wide range of species, including humans, nonhuman primates, cattle, swine, mice, and rats. There are no documented reports of natural reovirus infection in rats, although, in rare cases, rats develop antibodies to reoviruses (Pritchett-Corning et al., 2009; Schoondermark-van de Ven et al., 2006). Metagenomic analyses of rat feces did not detect reovirus RNA (Firth et al., 2014; Sachsenroder et al., 2014).

There are three serotypes of reovirus, and reovirus 3 (REO3) is of most concern in rodents. Most newborn Wistar rats inoculated with REO3 died between 6 and 15 days and had small spleens, thymuses, and lymph nodes, and the surviving rats were runted (Bennette et al., 1967). Two other studies using infant Sprague–Dawley rats inoculated intracerebrally or subcutaneously with REO3 produced an acute fatal hemorrhagic encephalitis within 2 weeks (Raine and Fields, 1974; Spandidos and Graham, 1976). The initial targets in 22- to 30-day-old rats inoculated intravenously with REO1 or REO3 were the liver and lungs (Verdin et al., 1988). Rats (25–28 days of age) inoculated intratracheally with REO1 or REO3 have been used as models of viral pneumonia (Farone et al., 1996; Morin et al., 1996). Parenteral inoculation of pregnant rats with REO3 resulted in maternal viremia and placental infection, but clinical signs were not observed in dams and neonates (Margolis and Kilham, 1973).

2. Rotavirus

Rotaviruses are nonenveloped triple-shelled icosahedral viruses that contain 11 segments of double-stranded RNA that total 22 kb. The eight species of rotaviruses are classified as groups A–H. Infectious diarrhea of infant rats (IDIR), a nonlethal illness in rats that resembles rotavirus-caused epizootic diarrhea of infant mice (Vonderfecht et al., 1984), is caused by a group B rotavirus antigenically distinct from epizootic diarrhea of infant mice virus (group A) (Vonderfecht et al., 1985). Group B rotaviruses infect humans, rats, piglets, lambs, and calves (Vonderfecht et al., 1985). Suckling rats inoculated with IDIR develop clinical signs within 2 days, which include diarrhea for up to 1 week accompanied by cracking and bleeding of the perineal region; dry, flaky skin; and transient weight loss (Salim et al., 1995; Vonderfecht et al., 1984). Gross lesions included distended ilea and colons (Vonderfecht et al., 1984). One day postinoculation, small intestinal villous epithelial syncytia, villous epithelial necrosis, and villous shortening were evident, and cytoplasmic inclusions of viral particles were seen in syncytial cells (Huber et al., 1989; Vonderfecht et al., 1984). Three days postinoculation, syncytia and necrosis were not observed, but the villous epithelium was disorganized and vacuolated and crypt epithelium was hyperplastic (Huber et al., 1989). Virus was detected in intestinal washings only between 18 and 72 h postinoculation (Salim et al., 1995). Although rats of all ages are susceptible to infection, clinical disease did not occur in rats 2 weeks or older (Vonderfecht et al., 1984).

Natural infection of laboratory rats with group A rotaviruses has not been documented. But experimental
infections of suckling rats with simian, human, bovine, and laprine group A rotaviruses have been used as models of rotavirus infection of infants (Ciarlet et al., 2002; Crawford et al., 2006; Perez-Cano et al., 2007), and metagenomic analysis of wild rat intestinal contents detected a group A rotavirus (Sachsenroder et al., 2014).

IV. RAT VIROME

With the growing interest in the role of the microbiome in rodent research, the role of the virome also needs to be considered. Metagenomic analyses have identified infections with several genera of viruses, several of which are not routinely tested for, though at present none of the newly detected viruses have been associated with clinical disease. In a metagenomic analysis of the intestinal contents of 20 wild R. norvegicus in Germany, paroviruses (protoparovirus, bocaparovirus, and/or dependoparovirus) were found in all rats (Sachsenroder et al., 2014); picobirnavirus, mastadenovirus, and circo-like viruses were found in 80%–90% of rats; and rotavirus and stool-associated circular single-stranded RNA virus were found in 50%–60% of rats (Sachsenroder et al., 2014).

Metagenomic analysis of serum and feces from 133 R. norvegicus from five sites in New York City detected Seou virus, anellovirus, bocaparovirus, mastadenovirus, parovirus, calchevirus, cardiovirus, circovirus, hunnivirus, mamastrovirus, rotavirus, arterivirus, hepacivirus, orbivirus, pegivirus, pestivirus, kobavirus, parechovirus, phlebovirus, picobirnavirus, rosavirus, and sapovirus (Firth et al., 2014). A metagenomic analysis of feces from 29 R. norvegicus collected in Malaysia, China, and Denmark detected vertebrate viruses from the following families in decreasing order of prevalence: Paroviridae, Picornaviridae, Retroviridae, Astroviridae, and Polyomaviridae (Hansen et al., 2016).

More focused studies to identify members of specific viral genera in rodents have also been performed. Anelloviruses have been detected in R. norvegicus by PCR (Nishiyama et al., 2015). Astroviruses have been detected by RT-PCR in feces or rectal swabs collected from R. norvegicus in Hong Kong and China (Chu et al., 2010; To et al., 2017). Three novel genogroup V noroviruses have been detected by RT-PCR in feces collected from R. rattus in Hong Kong and Japan (Tse et al., 2012; Tsunesumi et al., 2012). Picobirnavirus RNA was detected in 14 captive Wistar rats and it had the greatest homology with human genogroup I picobirnavirus Hu/104-FL-97 (Fregolente et al., 2009). A novel papillomavirus was isolated from the oral cavity of an R. norvegicus (RnPVI), sequenced, and determined to be a member of the Pipapillomavirus genus (Schulz et al., 2009). A second and third rat papillomavirus (RnPVI2 and RnPVI3) isolated from a rectal smear and from feces were sequenced and determined to be a members of the Iotapapillomavirus genus (Hansen et al., 2015; Schulz et al., 2012).

In summary, viral infections of rats are likely to gain higher visibility in laboratory rats given the potential for genetically engineered rats, including those with immune deficiencies, to become easier to generate. As has occurred with mice, the demand for the worldwide exchange of unique rat strains will probably increase, as will the unintended consequences of exposure to and spread of “classical” and new viral infections. Although quarantine and biosafety practices have advanced, these safeguards are likely to be challenged given the known rat viruses and, perhaps more importantly, the unknown viruses lurking within both the laboratory and the wild populations of rats.

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