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ANIMAL CORONAVIRUSES: LESSONS FOR SARS

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The emergence of severe acute respiratory syndrome (SARS) illustrates that coronaviruses (CoVs) may quiescently emerge from possible animal reservoirs and can cause potentially fatal disease in humans, as previously recognized for animals. Consequently the focus of this review will be on the emergence of new CoV strains and the comparative pathogenesis of SARS CoV with those CoVs that cause enteric and respiratory infections of various animal hosts. A review of animal CoV vaccines recently has been compiled (Saif, in press), so this topic will not be addressed.

Emergence of New Coronaviruses

The medical community was amazed by the emergence of a new coronavirus associated with SARS in healthy adults in 2003 (Drosten et al., 2003; Ksiazek et al., 2003; Peiris et al., 2003b; Poutanen et al., 2003). Historically human CoV infections (229E and OC43 CoV strains) were mild and associated with only common cold symptoms although reinfections, even with the same strain, occur (Callow et al, 1990; Holmes, 2001). However, veterinary coronavirologists had previously recognized the potential for coronaviruses to cause fatal enteric or respiratory infections in animals and for new CoV strains to emerge from unknown reservoirs, often evoking fatal disease in naïve populations. For example, the porcine epidemic diarrhea CoV (PEDV) first appeared from an unknown source in Europe and Asia in the 1970s and 1980s, causing severe diarrhea and widespread deaths in baby pigs before becoming endemic in swine (Pensaert, 1999). The PEDV is absent in U.S. swine. Interestingly, PEDV is genetically more closely related to human CoV 229E than to the other animal group I CoV (Duarte et al., 1994), and unlike the other group I CoV, it grows in Vero cells like SARS CoV (Hoffman and Wyler, 1988). These observations raise intriguing, but unanswered, questions about its origin.

Alternatively new CoV strains differing in tissue tropism and virulence may arise from existing strains. The less virulent porcine respiratory coronavirus (PRCV) evolved as a spike

(S) gene deletion mutant of the highly virulent enteric CoV, transmissible gastroenteritis virus (TGEV) (reviewed in Laude et al., 1993; Saif and Wesley, 1999). Curiously, differences in the sizes of the 5′ end S gene deletion region (621–681 nucleotides) between European and U.S. PRCV strains provided evidence for their independent origin on two continents within a similar time frame (1980s). Deletion of this region (or in combination with deletions in ORF 3a) presumably accounted for altered tissue tropism from enteric to respiratory and reduced virulence of the PRCV strains (Ballesteros et al., 1997; Sanchez et al., 1999). The ability of certain CoVs to persist in their host also provides a longer opportunity for new mutants to be selected with altered tissue tropisms and virulence from among the viral RNA quasispecies (or swarm of viruses). An example is the virulent systemic variant, the feline infectious peritonitis virus (FIPV), which likely arises from persistent infection of cats with the less virulent feline enteric CoV (Herrewegh et al., 1997; Vennema et al., 1995).

Furthermore, animal CoVs may acquire new genes via recombination, as exemplified by the acquisition of an influenza C-like hemagglutinin by bovine CoV or its ancestor CoV (Brian et al., 1995). Recombination events among CoVs may also generate new strains with altered tissue or host tropisms. For example, targeted recombination between feline and mouse S proteins enables feline CoV to infect mice (Haijema et al., 2003). Recent phylogenetic analysis suggests that SARS CoV may have evolved from a past recombination event between mammalian-like and avian-like parent strains with the S gene representing a mammalian (group 1)–avian origin mosaic (Stavrinides and Guttman, 2004). This recognition that CoVs can further evolve in a host population to acquire new tissue tropisms or virulence via mutations or recombination suggests that similar events may occur if SARS CoV persists in humans.

Interspecies Transmission of Coronaviruses

The genus *coronavirus* is composed of at least three genetically and autigenically distinct groups of CoV that cause mild to severe enteric, respiratory, or systemic disease in domestic and wild animals, poultry, rodents, and carnivores and mild colds in humans (Table 3-1) The SARS CoV is genetically distantly related to known CoVs and comprises a provisional new group (IV) (Drosten et al., 2003; Marra et al., 2003; Rota et al., 2003) or alternatively, using rooted tree phylogenetic analysis, belongs to a subgroup of group II (Snijder et al., 2003). Coronaviruses from two wild animal species (civet cats and raccoon dogs) recently have been characterized genetically as members of the SARS CoV group (Guan et al., 2003). Coronaviruses within each group share various levels of genetic and antigenic relatedness and several show cross-species transmission. Thus the likelihood that SARS CoV is a zoonotic infection potentially transmitted from wild animals to humans is not unprecedented based on previous research on interspecies transmission of animal CoV and wildlife reservoirs for CoV. As examples, the porcine CoV, TGEV, and canine and feline CoVs can cross-infect pigs, dogs, and cats with variable disease expression and levels of cross-protection in the heterologous host (Saif and Wesley, 1999; Saif and Heckert, 1990). These three related CoVs appear to be host range mutants of an ancestral CoV. Wildlife reservoirs for CoVs were recognized prior to SARS. Captive wild ruminants harbor CoVs antigenically closely related to bovine CoV and CoV isolates from the wild ruminants experimentally infected domestic calves (Tsunemitsu et al., 1995; Majhdi et al., 1997). The promiscuousness of bovine CoV is evident by infection of dogs and also humans by genetically similar (>97 percent identity) CoV strains (Erles et al., 2003; Zhang et al., 1994). Even more dramatic than infection of mammalian hosts by bovine CoV is the finding that bovine CoV can experimentally infect and cause disease (diarrhea) in phylogenetically diverse species such as avian hosts,

including baby turkeys, but not baby chicks (Ismail et al., 2001b). It is notable that in the latter study, the bovine CoV-infected baby turkeys also transmitted the viruses to unexposed contact control birds. The reasons for the broad host range of bovine CoV are unknown, but may relate to the presence of a hemagglutinin on bovine CoV and its possible role in binding to diverse cell types.

Recent data suggest that SARS CoV may also have a broad host range besides humans. Genetically similar CoVs were isolated from civet cats and raccoon dogs (Guan et al., 2003). In experimental studies, the SARS CoV infected and caused disease in macaques and ferrets and infected cats subclinically (Fouchier et al., 2003; Martina et al., 2003). In the latter two species, the SARS CoV was further transmitted to exposed contacts, documenting transmission within the new host species. Consequently, although previous data document the emergence of new animal CoV strains and the broad host range of several CoVs, the determinants for host range specificity among CoVs are undefined. In addition, we understand little about CoVs circulating in wildlife and relatively few animal CoV strains have been fully sequenced for comparative phylogenetic analysis to trace their evolutionary origins.

Pathogenesis of Animal Enteric and Respiratory Coronaviruses

Pathogenesis of Group I TGEV and PRCV CoV: Models of Enteric and Respiratory Infections

Because both pneumonia and diarrhea occur in SARS patients, an understanding of the tissue tropisms and pathogenesis of respiratory and enteric animal CoVs should contribute to our understanding of similar parameters for SARS. The TGEV targets the small intestinal epithelial cells leading to severe villous atrophy, malabsorptive diarrhea, and a potentially fatal gastroenteritis (Table 3-1). The virus also infects the upper respiratory tract with transient nasal shedding (Van Cott et al., 1993), but infection or lesions in the lung are less common. In adults, TGEV is mild with transient diarrhea or inappetence, but pregnant or lactating animals develop more severe clinical signs and agalactia (Saif and Wesley, 1999).

The PRCV, an S gene deletion mutant of TGEV, has an altered tissue tropism (respiratory) and reduced virulence (Laude et al., 1993; Saif and Wesley, 1999). Like SARS, PRCV spreads by droplets and has a pronounced tropism for the lung, replicating to titers of 10^7-10^8 $TCID_{50}$ and producing interstitial pneumonia affecting 5 to 60 percent of the lung (Cox et al., 1990; Halbur et al., 1993; Laude et al., 1993; Saif and Wesley, 1999). Although many uncomplicated PRCV infections are mild or subclinical, lung lesions are invariably present. Like SARS, clinical signs of PRCV include fever with variable degrees of dyspnea, polypnea, anorexia, and lethargy, and less coughing and rhinitis (Cox et al., 1990; Halbur et al., 1993; Hayes, 2000; Laude et al., 1993; Saif and Wesley, 1999). Further resembling SARS, PRCV replicates in lung epithelial cells, although viral antigen is also detected in type I and II pneumocytes and alveolar macrophages. In lungs, bronchiolar infiltration of mononuclear cells, lymphohistiocytic exudates, and epithelial cell necrosis leads to interstitial pneumonia. PRCV induces transient viremia with virus also detected from nasal swabs and in tonsils and trachea, similar to SARS (Drosten et al., 2003; Ksiazek et al., 2003; Peiris et al., 2003b). The PRCV further replicates in undefined cells in the gut lamina propria, but without inducing villous atrophy or diarrhea and with limited fecal shedding (Cox et al., 1990; Saif and

Wesley, 1999). Recently, however, fecal isolates of PRCV were detected with consistent, minor point mutations in the S gene compared to the nasal isolates from the same pig (Costantini et al., in press). Such observations suggest the presence of CoV quasispecies in the host with some strains more adapted to the intestine, a potential corollary for the fecal shedding of SARS CoV (Drosten et al., 2003; Ksiazek et al., 2003; Peiris et al., 2003a). Of further relevance to SARS was the displacement of the virulent TGEV infections by the widespread dissemination of PRCV in Europe and the disappearance of PRCV from swine herds in summer with its reemergence in older pigs in winter (Laude et al., 1993; Saif and Wesley, 1999).

Group II Bovine CoV (BCoV): Models of Pneumoenteric Infections

The shedding of SARS in feces of many patients and the occurrence of diarrhea in 10 to 27 percent of patients (Peiris et al., 2003a), but with a higher percentage (73 percent) in the Amoy Gardens, Hong Kong, outbreak (Chim et al., 2003) suggests that SARS may be pneumoenteric like BCoV. BCoV causes three distinct clinical syndromes in cattle: calf diarrhea; winter dysentery with hemorrhagic diarrhea in adults; and respiratory infections in cattle of various ages, including cattle with shipping fever (Table 3-1) (Clark, 1993; Lathrop et al., 2000a; Lathrop et al., 2000b; Saif and Heckert, 1990; Storz et al., 1996, 2000a, Tsunemitsu et al., 1995). Based on BCoV antibody seroprevalence, the virus is ubiquitous in cattle worldwide. All BCoV isolates from both enteric and respiratory infections are antigenically similar in virus neutralization (VN) tests, comprising a single serotype, but with two to three subtypes identified by VN or using monoclonal antibodies (MAbs) (Clark, 1993; Hasoksuz et al., 1999a; Hasoksuz et al., 1999b; Saif and Heckert, 1990; Tsunemitsu and Saif, 1995). In addition, genetic differences (point mutations but not deletions) have been detected in the S gene between enteric and respiratory isolates, including ones from the same animal (Chouljenko et al., 2001; Hasoksuz et al., 2002b). Nevertheless, inoculation of gnotobiotic or colostrum-deprived calves with calf diarrhea, winter dysentery, or respiratory BCoV strains led to both nasal and fecal CoV shedding and cross-protection against diarrhea after challenge with a calf diarrhea strain (Cho et al., 2001b; El-Kanawati et al., 1996). However, subclinical nasal and fecal virus shedding detected in calves challenged with the heterologous BCoV strains (Cho et al., 2001b; El-Kanawati et al., 1996) confirmed field studies showing that subclinically infected animals may be a reservoir for BCoV (Heckert et al., 1990). Cross-protection against BcoV-induced respiratory disease has not been evaluated.

Calf Diarrhea and Calf Respiratory BCoV Infections

Calf diarrhea BCoV strains infect the epithelial cells of the distal small and large intestine and superficial and crypt enterocytes of the colon, leading to villous atrophy and crypt hyperplasia (Saif and Heckert, 1990; Van Kruiningen et al., 1987). One- to 4-week-old calves develop a severe, malabsorptive diarrhea, resulting in dehydration and often death. Concurrent fecal and nasal shedding often occur. BCoV are also implicated as a cause of mild respiratory disease (coughing, rhinitis) or pneumonia in 2- to 24-month-old calves and are detected in nasal secretions, lungs, and often the intestines (Clark, 1993; Heckert et al., 1990; Heckert et al., 1991; Saif and Heckert, 1990). In studies of calves from birth to 20 weeks of age, Heckert and colleagues (1990, 1991) documented both fecal and nasal shedding of BCoV, with repeated respiratory shedding episodes in the same animal with or without respiratory disease, and subsequent increases in their serum antibody titers consistent with these reinfections. These findings suggest a lack of long-term mucosal immunity in the upper

respiratory tract after natural CoV infection, confirming similar observations for human respiratory CoV (Callow et al., 1990; Holmes, 2001).

Winter Dysentery BCoV Infections

Winter dysentery (WD) occurs in adult cattle during the winter months and is characterized by hemorrhagic diarrhea, frequent respiratory signs, and a marked reduction in milk production in dairy cattle (Saif, 1990; Saif and Heckert, 1990; Van Kruiningen et al., 1987). Intestinal lesions and BCoV-infected cells in the colonic crypts resemble those described for calf diarrhea. The BCoV isolates from WD outbreaks at least partially reproduced the disease in BCoV seropositive nonlactating cows (Tsunemitsu et al., 1999) and in BCoV seronegative lactating cows (Traven et al., 2001). Interestingly, in the later study, the older cattle were more severely affected than similarly exposed calves, mimicking the milder SARS cases seen in children versus adults (Kamps and Hoffmann, 2003a).

Shipping Fever BCoV Infections

More recent studies done in 1995 have implicated BCoV in association with respiratory disease (shipping fever) in feedlot cattle (Lathrop et al., 2000a, Storz et al., 1996). BCoV was isolated from nasal secretions and lungs of cattle with pneumonia and from feces (Hasoksuz et al., 1999a, 2002a; Storz et al., 2000a, b). In a subsequent study, a high percentage of feedlot cattle (45 percent) shed BCoV both nasally and in feces by ELISA (Cho et al., 2001a). Application of nested RT-PCR detected higher BCoV nasal and fecal shedding rates of 84 percent and 96 percent, respectively (Hasoksuz et al., 2002a).

Cofactors That Exacerbate CoV Infections, Disease, or Shedding

Underlying disease or respiratory coinfections, dose and route of infection, and immunosuppression (corticosteroids) are all potential cofactors related to the severity of SARS. These cofactors can also exacerbate the severity of BCoV, TGEV, or PRCV infections. In addition, these cofactors may play a role in the superspreader cases seen in the SARS epidemic (Kamps and Hoffmann, 2003b) by enhancing virus transmission.

Impact of Respiratory Co-Infections on CoV Infections, Disease, and Shedding

Shipping fever is recognized as a multifactorial, polymicrobial respiratory disease complex in young adult feedlot cattle with several factors exacerbating respiratory disease, including BCoV infections (Lathrop et al., 2000a,b; Storz et al., 1996; Storz et al., 2000a; Storz et al., 2000b). Shipping fever can be precipitated by several viruses, alone or in combination, including viruses similar to common human respiratory viruses (BCoV, bovine resiratory syncytial virus, parainfluenza-3 virus), bovine herpesvirus, and viruses capable of mediating immunosuppression (bovine viral diarrhea virus, etc.). The shipping of cattle long distances to feedlots and the commingling of cattle from multiple farms creates physical stresses that overwhelm the animal's defense mechanisms and provides close contact for exposure to new pathogens or strains not previously encountered. Such factors are analogous to the physical stress of long airplane trips with close contact among individuals from diverse regions of the world, both of which may play a role in enhancing an individual's susceptibility to SARS. For shipping fever, various predisposing factors (viruses, stress) allow commensal bacteria of

the nasal cavity (*Mannheimia haemolytica, Pasteurella* spp., *Mycoplasma* spp., etc.) to infect the lungs, leading to fatal fibrinous pneumonia (Lathrop et al., 2000a,b; Storz et al., 1996, 2000a,b). Like PRCV or SARS infections, it is possible that antibiotic treatment of such individuals with massive release of bacterial lipopolysaccharides (LPS) could precipitate induction of proinflammatory cytokines, which may further enhance lung damage. For example, Van Reeth et al. (2000) showed that pigs infected with PRCV followed by a subclinical dose of *E. coli* LPS within 24 hours developed enhanced fever and more severe respiratory disease compared to each agent alone. They concluded that the effects were likely mediated by the significantly enhanced levels of proinflammatory cytokines induced by the bacterial LPS. Thus there is a need to examine both LPS and lung cytokine levels in SARS patients as possible mediators of the severity of SARS. Bacteria (*Chlamydia* spp.) have been isolated from SARS patients, but their role in enhancing the severity of SARS is undefined (Poutanen et al., 2003).

Interactions between PRCV and other respiratory viruses may also parallel the potential for concurrent or preexisting respiratory viral infections to interact with SARS CoV (such as metapneumoviruses, influenza, reoviruses, respiratory syncytial virus [RSV], OC43 or 229E CoV). Hayes (2000) showed that sequential dual infections of pigs with the arterivirus (order Nidovirales, like CoV) PRRSV followed in 10 days by PRCV significantly enhanced lung lesions and reduced weight gains compared to each virus alone. The dual infections also led to more pigs shedding PRCV nasally for a prolonged period and surprisingly, to fecal shedding of PRCV. The lung lesions observed resembled those in SARS victims (Nicholls et al., 2003).

In another study, Van Reeth and Pensaert (1994) inoculated pigs with PRCV followed in 2 to 3 days by swine influenza A virus (SIV). They found that SIV lung titers were reduced in the dually compared to the singly infected pigs, but paradoxically the lung lesions were more severe in the dually infected pigs. They postulated that the high levels of IFN-alpha induced by PRCV may mediate interference with SIV replication but may also contribute to the enhanced lung lesions. Such studies are highly relevant to potential dual infections with SARS CoV and influenza virus and potential treatments of SARS patients with IFN alpha.

Impact of Route (Aerosols) and Dose on CoV Infections

Experimental inoculation of pigs with PRCV strains showed that administration of PRCV by aerosol compared to the oronasal route, or in higher doses, resulted in higher virus titers shed and longer shedding (Van Cott et al., 1993). In other studies, high PRCV doses induced more severe respiratory disease. Pigs given $10^{8.5}$ $TCID_{50}$ of PRCV had more severe pneumonia and deaths than pigs exposed by contact (Jabrane et al., 1994), and higher intranasal doses of another PRCV strain (AR310) induced moderate respiratory disease whereas lower doses produced subclinical infections (Halbur et al., 1993). By analogy, hospital procedures that could potentially generate aerosols or exposure to higher initial doses of SARS CoV may enhance SARS transmission or lead to enhanced respiratory disease (Kamps and Hoffman, 2003a,b).

Impact of Treatment with Corticosteroids on CoV Infections of Animals

Corticosteroids are known to induce immunosuppression and reduce the numbers of CD4 and CD8 T cells and certain cytokine levels (Giomarelli et al., 2003). Many hospitalized SARS patients were treated with steroids to reduce lung inflammation, but there are no data to

assess the outcome of this treatment on virus shedding or respiratory disease. A recrudescence of BCoV fecal shedding was observed in one of four winter dysentery BCoV infected cows treated with dexamethasone (Tsunemitsu et al., 1999). Similarly, treatment of older pigs with dexamethasone prior to TGEV challenge led to profuse diarrhea and reduced lymphoproliferative responses in the treated pigs (Shimizu and Shimizu, 1979). These data raise issues for corticosteroid treatment of SARS patients related to possible transient immunosuppression leading to enhanced respiratory disease or increased and prolonged CoV shedding (superspreaders). Alternatively, corticosteroid treatment may be beneficial in reducing proinflammatory cytokines if found to play a major role in lung immunopathology (Giomarelli et al., 2003).

Group I Feline CoV (FCoV): Model for Systemic and Persistent CoV Infection

The spectrum of disease evident for FCoV (feline infectious peritonitis virus) exemplifies the impact of viral persistence and macrophage tropism on CoV disease progression and severity. Historically, two types of FCoVs have been recognized: feline enteric CoV (FECoV) and FIPV. Current information suggests that the FECoV that causes acute enteric infections in cats establishes persistent infections in some cats, evolving into the systemic virulent FIPV in 5 to 10 percent of cats (deGroot and Horzinek, 1995; Herrewegh et al., 1997; Vennema et al., 1995). The relevance of this model to SARS is whether similar persistent CoV infections might occur in some patients, leading to the emergence of macrophage-tropic mutants of enhanced virulence and precipitating systemic or immune-mediated disease. The initial site of FCoV replication is in the pharyngeal, respiratory, or intestinal epithelial cells (deGroot and Horzinek, 1995; Olsen, 1993), and clinical signs include anorexia, lethargy, and mild diarrhea. The prolonged incubation period for FIPV and its reactivation upon exposure to immunosuppressive viruses or corticosteroids suggested that FCoVs could cause chronic enteric infections in cats (deGroot and Horzinek, 1995; Olsen, 1993). Recent reports of chronic fecal shedding and persistence of FCoV mRNA or antigen in infected cats confirm this scenario (Herrewegh et al., 1997).

A key pathogenetic event for development of FIPV is productive infection of macrophages followed by cell-associated viremia and systemic dissemination of virus (deGroot and Horzinek, 1995; Olsen, 1993). Stress (immunosuppressive infections, transport to new environments, cat density) leading to immune suppression may trigger FIP in chronically infected cats, similar to its role in shipping fever CoV infections of cattle. Two major forms of FIP occur: (1) effusive, with a fulminant course and death within weeks to months, and (2) noneffusive, progressing more slowly (deGroot and Horzinek, 1995; Olsen, 1993). The effusive form is characterized by fibrin-rich fluid accumulation in peritoneal, pleural, pericardial, or renal spaces, with fever, anorexia, and weight loss. Noneffusive FIP involves pyogranulomatous lesions with thrombosis, central nervous system, or ocular involvement. Fulminant FIP with accelerated early deaths appears to be immune mediated in FCoV seropositive cats. At least two mechanisms implicating IgG antibodies to FCoV S protein in FIP immunopathogenesis have been described. In the first, circulating immune complexes (IC) with C' depletion in sera and IC in lesions are evident in cats with terminal FIP (deGroot and Horzinek, 1995). In the second, antibody dependent enhancement (ADE) of FCoV infection of macrophages in vitro is mediated by neutralizing IgG MAbs to the S protein of FIPV, or of interest, to the antigenically-related CoV, TGEV (Olsen et al., 1993). Similar accelerated disease was seen in vivo in cats inoculated with recombinant vaccinia virus expressing the S protein (but not the M or N proteins) of FIPV (deGroot and Horzinek, 1995;

Olsen et al., 1993). Thus the FIPV model provides a frightening glimpse of the severity and potential complications associated with a persistent, systemic CoV infection.

Group III CoVs: Infectious Bronchitis Virus (IBV): Model for Respiratory CoV Infection with Other Target Tissues

The IBV is a highly contagious respiratory disease of chickens, like SARS, spread by aerosol or possibly fecal-oral transmission, and distributed worldwide (Cavanagh and Naqi, 2003; Cook and Mockett, 1995). Genetically and antigenically closely related CoV have been isolated from pheasants and turkeys (Guy et al., 1997; Ismail et al., 2001a), but in young turkeys, they cause mainly enteritis. Respiratory infections of chickens are characterized by tracheal rales, coughing, and sneezing, with the disease most severe in chicks (Cavanagh and Naqi, 2003; Cook and Mockett, 1995). The IBV also replicates in the oviduct, causing decreased egg production. Nephropathogenic strains can cause mortality in young birds. In broilers, severe disease or death ensues from systemic *E. coli* co-infections after IBV damage to the respiratory tract or *Mycoplasma* sp. co-infections with IBV. The IBV is recovered intermittently from the respiratory tract for about 28 days after infection and from the feces after clinical recovery, with the cecal tonsil being a possible reservoir for IBV persistence, similar to the persistence of FCoV in the intestine of cats (Herrewegh et al., 1997). The IBV was recovered from both tracheal and cloacal swabs in chickens at onset of egg production, suggesting re-excretion of IBV from chronically infected birds, as also demonstrated for fecal shedding of FCoV or BCoV after induction of immunosuppression (Olsen, 1993; Tsunemitsu et al., 1999).

The IBV replicates in epithelial cells of the trachea and bronchi, intestinal tract, oviduct, and kidney, causing necrosis and edema with small areas of pneumonia near large bronchi in the respiratory tract and interstitial nephritis in the kidney (Cavanagh and Naqi, 2003; Cook and Mockett, 1995). Of interest for SARS is the persistence of IBV in the kidney and its prolonged fecal shedding because SARS CoV is detected in urine and shed longer term in feces. However, it is unclear if SARS CoV shedding in urine is a consequence of viremia or a kidney infection like IBV. Both diagnosis and control of IBV are complicated by the existence of multiple serotypes and the occurrence of IBV recombinants (Cavanagh and Naqi, 2003; Cook and Mockett, 1995). This is unlike the scenario for most group 1 or 2 respiratory CoVs in which only one or two (FCoV) serotypes are known. Also relevant to SARS CoV is the finding that IBV strains also replicate in Vero cells, but only after passage in chicken embryo kidney cells (Cavanagh and Nagi, 2003).

In summary, studies of animal CoV infections in the natural host provide enteric and respiratory disease models that enhance our understanding of both the similarities and divergence of CoV disease pathogenesis and targets for control. Unanswered questions for SARS pathogenesis, but highly relevant to the design of strategies for prevention and control, include the following: What is the initial site of viral replication? Is SARS CoV pneumoenteric like BCoV, with variable degrees of infection of the intestinal and respiratory tracts and disease precipitated by the co-factors discussed or unknown variables? Alternatively, is SARS primarily targeted to the lung like PRCV, with fecal shedding of swallowed virus and with undefined sequelae contributing to the diarrhea cases? Does SARS CoV infect the lung directly or via viremia after initial replication in another site (oral cavity, tonsils, upper respiratory tract) and does it productively infect secondary target organs (intestine, kidney) via viremia after replication in the lung?

Finally, the persistent, macrophage tropic, systemic FIPV CoV infection of cats presents yet another CoV disease model and a dilemma for attempted control strategies. In this disease scenario, induction of neutralizing IgG antibodies to the FIPV S protein not only fails to prevent FIPV infections, but actually potentiates the immunopathogenesis of FIPV (Olsen, 1993).

The suspected zoonotic origin of SARS CoV (Guan et al., 2003) and the recognized propensity of several CoV to cross species barriers illustrate the need for additional animal studies of the mechanisms of interspecies transmission of CoVs and adaptation to new hosts. The possible animal reservoir for SARS remains undefined. At present we understand very little about CoVs or other viruses circulating in wildlife or their potential to emerge or recombine with existing CoVs (Stavrinides and Guttman, 2004) as public or animal health threats. Hopefully the SARS epidemic will generate new interest and funding for these fundamental research questions applicable not only to SARS CoV, but also to the estimated 75 percent of newly emerging human diseases arising as zoonoses (Taylor, 2001).

Tables

TABLE 3-1Coronavirus Groups, Target Tissues, and Diseases

Genetic Group	Virus	Host	Disease/Infection Site		
			Respiratory	Enteric[a]	Other[b]
I	HCoV-229E	Human	X upper		
	TGEV	Pig	X upper	X S1	
	PRCV	Pig	X upper/lung		Vitremia
	PEDV	Pig		X SL, colon	
	F1PV	Cat	X upper	X	Systemic
	FCoV	Cat		X S1	
	CCOV	Dog		X S1	
	RaCoV	Rabbit			Systemic
11	HCoV-OC43	Human	X upper	?? (BCoV?)	
	NUN	Mouse		X	Hepatitis, CNS, systemic
	RcoV (sialodocry-adenitis)	Rat	X		Eye, salivary glands
		Pig	X		CNS
	BEV	Cattle	X upper/lung	X S1, colon	
	BCoV				
III	IBV	Chicken	X upper	X	Kidney, oviduct
	TCoV (TECoV)	Turkey		X S1	
IV??	SARS	Human	X lung	X (?)	Viremia, kidney?

Genetic Group	Virus	Host	Disease/Infection Site		
			Respiratory	Enteric[a]	Other[b]
IIA?	Civet cat CoV	Himalayan palm civet	X	X	Subclinical?
		Raccoon dog			
	Raccoon dog CoV		?	X	Subclinical?

a

Sl = small intestine; ?? = BCoV-Iike CoV from a child, Zhang et al. (1994); ? = unknown.

b

CNS = central nervous system.