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Review of Animal Noroviruses

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Review

Animal noroviruses

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Abstract

Among enteric caliciviruses, noroviruses belong to the genus *Norovirus*, one of the four accepted genera in the family *Caliciviridae*. These single-stranded, positive-sense RNA viruses are highly variable both genetically and antigenically. Several animal enteric caliciviruses that are morphologically indistinguishable and genetically closely related to human noroviruses have been identified. The first bovine enteric noroviruses were described in Great Britain and are known as Newbury Agent 2. At least three genetic clusters of porcine noroviruses join together within genogroup II noroviruses. Human noroviruses are the most important cause of acute gastroenteritis illness in people of all ages. In the USA, they are associated with approximately 30–50% of all food-borne outbreaks. Until now, noroviruses have not been associated with gastroenteritis outbreaks in immunocompetent animals. Neither bovine nor porcine noroviruses can replicate in cell culture, although human norovirus can grow in a complex 3D culture system. However, the recently discovered murine noroviruses can replicate in cell culture and are therefore used as model viruses to study human noroviruses.

This review focusses on virus classification, virion structure, pathogenesis, epidemiology, immune response and diagnosis of animal noroviruses in comparison with human noroviruses. The classification of animal enteric caliciviruses within the *Norovirus* genus raises the question of whether transmission from an animal reservoir to humans could occur. Answering this question is important in determining the risk of cross-species infections affecting the epidemiology and evolution of these viruses and so complicating the control of human norovirus infections.

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Keywords: Norovirus; Calicivirus; Animal; Zoonosis

Introduction

Noroviruses (NoVs) belong to the family *Caliciviridae*. Caliciviruses are small non-enveloped viruses approximately 27–35 nm in diameter with a positive-sense, single-stranded RNA genome (Green et al., 2001). They have a broad host range and cause a wide spectrum of diseases and lesions in their respective hosts, including digestive tract infections (humans, pigs, cattle, dogs and mink), vesicular lesions and reproductive failure (pigs, sea lions and other marine mammal species), stomatitis, upper respiratory tract and systemic diseases (cats), and haemorrhagic disease (rabbits) (Bridger, 1990; Green et al., 2000, 2001; Guo et al., 2001; Ohlinger et al., 1993; Smith et al., 1998). Moreover, caliciviruses have also been isolated from calves with clinical respiratory signs (Smith et al., 1983).

The first discovered NoV was associated with a human outbreak of gastroenteritis in Norwalk, Ohio, which gave the name Norwalk virus (NV) to the prototype strain of NoV, in 1968 (Adler and Zickl, 1969). The virus was visualised by immune electron microscopy (IEM) in 1972 in stool samples from volunteers fed with faecal filtrates from children who were affected during the outbreak (Kapikian, 2000). At almost the same time the family *Caliciviridae* was created (Matthews, 1979). Discovery of both Norwalk virus (Kapikian et al., 1972) and rotavirus (Adams and

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Kraft, 1967; Bishop et al., 1973; Bridger and Woode, 1975) as enteric pathogens using IEM stimulated and ultimately led to the discovery of a number of enteric viruses identified as 'small round-structured viruses' (SRSV) for their general appearance under EM (Appleton and Higgins, 1975; Chiba et al., 2000; Madeley and Cosgrove, 1976).

In the early 1990s, the cloning and sequencing of the entire NV genome (strain FIIa) contributed to a new era in the study of these viruses (Jiang et al., 1993; Xi et al., 1990). The NoV virions share several characteristics, namely shedding into the faeces by patients affected with gastroenteritis, a positive-sense single-stranded RNA genome, and buoyant density of 1.33–1.41 g/cm^3 in CsCl (Kapikian et al., 1996). As molecular techniques became available in the 1990s, SRSV were divided into the Norwalk-like viruses (NLVs), now known as noroviruses, the Sapporo-like viruses (SLVs), now called sapoviruses, and the astroviruses.

Meanwhile, through the use of EM, several viruses with typical calicivirus morphology were discovered in stool samples of domestic animal species, namely calves (Woode and Bridger, 1978) and pigs (Bridger, 1980; Saif et al., 1980). Strain SW918, a prototype strain of porcine NoV, was first detected in the caecal contents of a healthy pig in Japan in 1997 (Sugieda et al., 1998). Other porcine strains were then discovered in other continents (van der Poel et al., 2000; Wang et al., 2005). Bovine NoV prototype strains identified so far are the Newbury Agent 2, first identified in the faeces of diarrhoeic calves in 1978 (Woode and Bridger, 1978), and the Jena agent, isolated in the 1980s from cattle in Germany and molecularly characterised in 1999 (Granzow and Schirrmeier, 1985; Gunther and Otto, 1987; Liu et al., 1999).

Two other enteric bovine caliciviruses have been described. These are the Newbury Agent 1 and the Nebraska (NB) strain. Newbury Agent 1 was found with Newbury Agent 2 in diarrhoeic calf samples in Great Britain and was characterised in 1984 (Bridger et al., 1984). The NB strain was detected in cattle in the USA (Smiley et al., 2002). According to Oliver et al. (2006a), the two viruses form a phylogenetically distinct clade in the *Caliciviridae* family and share 98% amino acids identity in their complete capsid protein sequence. Recently, murine NoVs (murine NoV-1, 2, 3, 4) were isolated from both immunodeficient and immunocompetent laboratory mice (Hsu et al., 2006; Karst et al., 2003) (Fig. 1). A norovirus infection was also identified in a dead lion cub in Italy (Martella et al., 2007).

Currently, no NoV has been discovered in other animal species, but some caliciviruses, related to the genus *Vesivirus*, have been found in dog faeces (Matsuura et al., 2002; Mochizuki et al., 2002; Pratelli et al., 2000). Moreover, the presence of vesivirus-specific antibodies was associated with abortion in horses (Kurth et al., 2006b) and serological evidence of vesivirus infection and also vesivirus viremia have been detected in human sera (Smith et al., 2006). Guo et al. (2001) found caliciviruses related to the *Sapovirus* genus in mink. In addition, antibodies specific to human NoVs have been detected in non-human primates (Jiang et al., 2004).

Classification

The classification of caliciviruses was first based on virus morphology. The International Committee on Taxonomy of Viruses (ICTV) proposed a new system for classification and nomenclature of the caliciviruses in 1998 and it has been further updated. The *Caliciviridae* family was divided into four genera (Green et al., 2000; Mayo, 2002): *Vesivirus*, *Lagovirus*, *Norovirus*, and *Sapovirus* and, more recently, a fifth genus, provisionally named *Nabovirus* or *Becovirus*, has been suggested (Oliver et al., 2006a) to include Newbury Agent 1 and NB virus because they show significant differences from the current four genera of the *Caliciviridae* family.

Complete sequencing of the capsid gene has allowed the classification of NoVs into five genogroups (G). Human NoV strains are found in GI, II and IV (Fankhauser et al., 2002; Green et al., 2000; Vinje and Koopmans, 2000). Bovine NoVs fall in GIII (Ando et al., 2000; Oliver et al., 2003; van der Poel et al., 2003), the murine NoVs in GV (Hsu et al., 2007; Karst et al., 2003), the porcine NoVs in GII (Sugieda and Nakajima, 2002) and the lion NoV in GIV based on partial sequencing (Martella et al., 2007).

No consensus has been reached on the classification of NoV strains within each genogroup. However a standardised method was proposed by Zheng et al. (2006) and this provides clear criteria for NoV nomenclature below the genus level using the amino acid sequences of the major capsid protein. They suggested dividing the five genogroups into 29 genetic clusters (genotypes): eight genotypes in GI (GI.1–GI.8), 17 in GII (GII.1–GII.17) – extended to 19 by Wang et al. (2007) using the same method-, two in GIII (GIII.1 and GIII.2), one in GIV and one in GV. Because recombination can affect the correct classification of NoVs (Kageyama et al., 2004), it is not recommended to use partial sequences to classify new NoV strains but rather full capsid sequencing should be performed (Zheng et al., 2006).

Based on phylogenetic analyses (Zheng et al., 2006), porcine NoVs belong to three distinct clusters in GII, which is also the most widely detected genogroup in humans. Porcine NoVs have been classified into GII.11, which is the closest to human strains, and very recently into two novel genotypes, GII.18 and GII.19 (Wang et al., 2005, 2007).

Molecular study of bovine NoVs has clarified their relationship with human NoVs, showing that they form a distinct third genogroup in the NoV genus. Historically, the first genogroup in this genus was composed solely of animal enteric caliciviruses (Oliver et al., 2003). Bovine NoV strains Jena and Newbury Agent 2 are the prototypes of genotypes GIII.1 and GIII.2, respectively (Fig. 1).

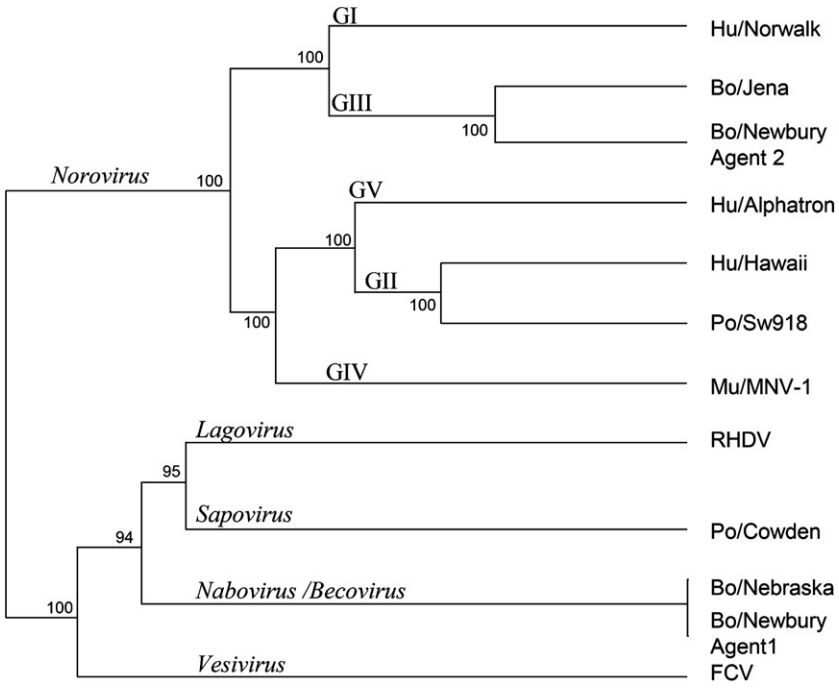

Fig. 1. Phylogenic analysis of *Caliciviridae*. Multiple alignment was performed using the ClustalW program of the partial capsid protein sequence of Alphatron norovirus (NoV) (bases 1–1668) with capsid protein sequences of representative members of the four genera of *Caliciviridae*. The numbers close to the branches indicate bootstrap values. Capsid protein sequences were derived from human NoV Alphatron (GenBank accession no. AF195847), murine NoV 1 (AY228235), porcine NoV SW918 (AB074893), human NoV Hawaii (U07611), bovine NoV Jena (AJ011099), bovine NoV Newbury Agent 2 (AF097917), bovine Newbury Agent 1 strain (DQ013304), bovine Nebraska strain (NC_004064), human NoV Norwalk (M87661), rabbit haemorrhagic disease virus (RHDV; M67473), feline calicivirus (FCV; L40021), porcine sapovirus Cowden (AF182760).

Virus and genomic organisation

Animal and human NoVs are non-enveloped, spherical particles with an indistinct surface structure and a foamy aspect outlined in EM. Studying human NoV, it was shown that the capsid is made of 180 copies of a single protein and its architecture is based on a $T = 3$ icosahedral symmetry with 90 dimers. Its surface shows 32 cup-shaped depressions and protruding arches (Prasad et al., 1999). These properties are conserved across the family *Caliciviridae* but structural variations between different members of the family *Caliciviridae* have been observed and their functional implications studied (Chen et al., 2004) (Figs. 2A and B).

The NoV genome is positive-sense, single-stranded RNA of around 7.5 kb and contains three open reading frames (ORF) (Table 1). At the 5′-end, there is a predicted genome linked viral protein (VPg) (Daughenbaugh et al., 2003). NoV possesses neither ribosomal entry site nor cap structure typical of eukaryotic mRNA but their N-terminal genome extremity is assumed to be bound to VPg, as has been described for other animal caliciviruses (Burroughs and Brown, 1978; Dunham et al., 1998; Herbert et al., 1997; Schaffer et al., 1980). In vitro, this predicted VPg interacts with components of the translation machinery (eIF3, eIF4GI, eIF4E, and S6 ribosomal protein) through unique protein–protein interactions and may play a role in initiating translation of NoV RNA (Daughenbaugh et al., 2003). There is no experimental proof of the linkage of the predicted VPg to genomic NoV RNA except for murine NoV (Daughenbaugh et al., 2006) (Fig. 3).

At the 5′-end of the genomic RNA, ORF1 encodes a polyprotein of approximately 195 kDa which is cleaved by the '3C-like' viral proteinase into at least six non-structural proteins: protein p48, which may play a role in intracellular protein trafficking (Ettayebi and Hardy, 2003); nucleoside triphosphatase (NTPase); protein p22, putatively involved in cellular membrane trafficking and replication complexes; VPg; proteinase and RNA dependent RNA polymerase (Belliot et al., 2003; Hardy, 2005). ORF2 encodes the major capsid protein (VP1) of around 60 kDa which has the following functions: self assembly and capsid formation, recognition of the receptor, host specificity, strain diversity and immunogenicity (Chen et al., 2004). A highly conserved genomic region in GI and GII NoV, including a consensus sequence of 18 nucleotides, extends from the C-terminal part of polymerase gene to the N-terminal part of the capsid coding region. This sequence could be a packaging signal for the NoV genome or a transcription initiation site (Lambden et al., 1995) and could correspond to a hot spot of recombination (Bull et al., 2005; Katayama et al., 2002).

The modular domain organisation of the VP1 subunit consists of a shell (S) and a protruding (P) domain exhibiting distinct differences. Significant structural variations are present especially in the P domain composed of P1 and P2

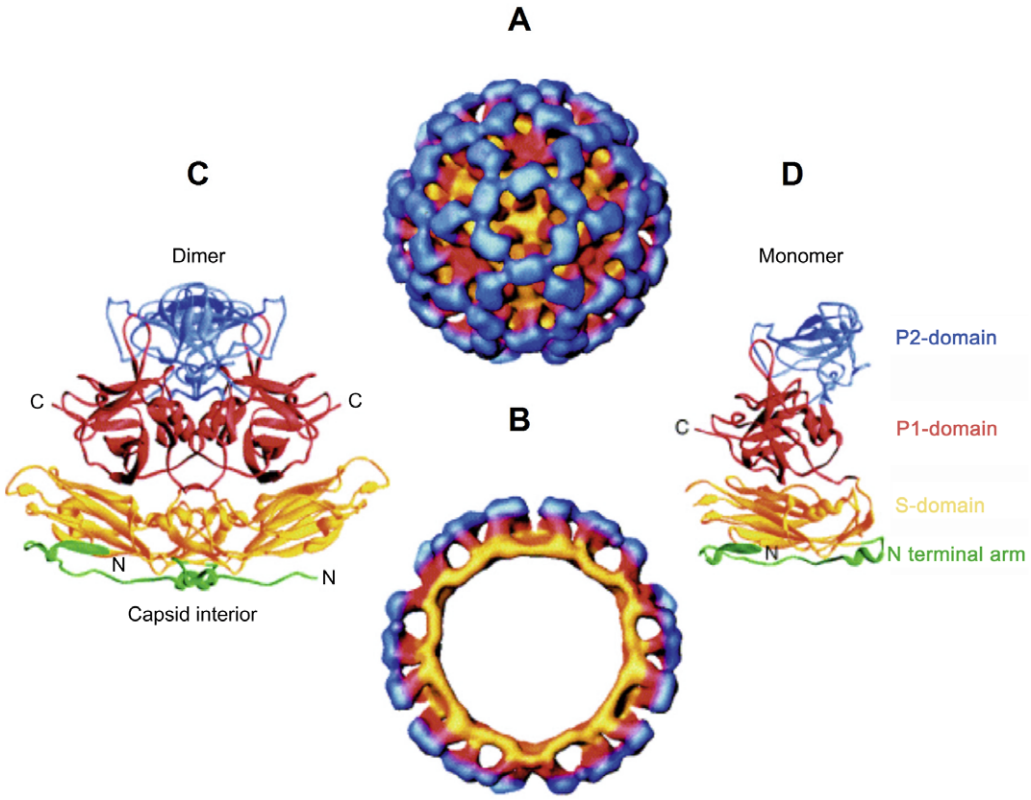

Fig. 2. Capsid structure of the Norwalk virus-like particle solved by cryo-electron microscopic at 22 Å and by X-ray crystallography at 3.4 Å. (A) Surface representation; (B) cross-section; (C) dimer of the capsid protein. Ninety dimers form the entire capsid protein; (D) Each monomeric capsid protein is organised into domains and subdomains. The N-terminal arm region (green) is facing the interior of the VLP, a shell domain (S-domain, yellow) that forms the continuous surface of the VLP and the protruding domain (P-domain) that constitutes the arch at the surface of the VLP. The P-domain is further divided into subdomains P1 (red) and P2 (blue). The latter is implicated in virus–host interactions. Adapted with permission from Hutson et al. (2004).

Table 1
Genome organisation of completely sequenced human and animal norovirus reference strains

Strain	Genogroup	GenBank access number	Genome length (nt)	Nucleotide position		
				ORF1	ORF2	ORF3
Hu/Norwalk	I	M87661	7654	5–5374	5358–6950	6950–7588
Hu/Hawaii	II	U07611	7513	5–5104	5085–6692	6692–7471
Bo/Jena	III	AJ011099	7338	22–5064	5051–6610	6600–7271
Bo/Newbury Agent 2	III	AF097917	7311	22–5076	5063–6631	6423–7271
Mu/MNV1	V	NC_08311	7382	6–5069	5056–6681	6681–7307

nt: nucleotide; ORF: open reading frame.

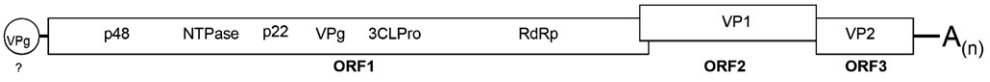

Fig. 3. Genomic organisation of noroviruses. VPg: predicted genome linked viral protein; p48: protein 48; NTPase: nucleotide triphosphatase; 3CLPro: 3C-like protease; RdRp: RNA dependent RNA polymerase; VP1: major structural protein (capsid protein); VP2: minor structural protein; ORF: open reading frame.

subunits (Chen et al., 2004) (Fig. 2C and D). P2 is the hypervariable domain of NoV capsid and its outside localisation is compatible with its function as ligand to cell receptor, found at the surface of intestinal cells (Tan et al., 2004). ORF3 which is located at the 3′-end of the genome encodes a small minor structural protein, VP2, of around 20 kDa, and is involved in expression and stability of VP1 capsid protein (Bertolotti-Ciarlet et al., 2003).

Another trait of NoVs is the accumulation and expression of subgenomic RNAs during replication in infected and cDNA transfected cells, as demonstrated for human and murine NoVs (Asanaka et al., 2005; Wobus et al.,

2004). This subgenomic expression is also used by other positive-strand RNA viruses to regulate and to allow a sufficient synthesis of structural proteins (Miller and Koev, 2000).

Virus–cell interactions

NoV infection is thought to occur in the small intestine, but no studies have identified animal noroviruses in enterocytes. NoV replication may not be restricted to enterocytes. The murine NoV revealed an unexpected tropism for the haematopoietic cell lineages, in particular macrophages and dendritic cells (Wobus et al., 2004). In the human gastrointestinal tract, intestinal dendritic cells can form transepithelial dendrites and directly acquire antigens in the lumen (Niess et al., 2005; Niess and Reinecker, 2005).

Human NoVs recognise carbohydrates linked to the human histo-blood group antigens (HBGAs), ABH and Lewis, as receptors (Hutson et al., 2002; Marionneau et al., 2002). The C-terminal region (P domain) of the capsid protein is involved in this attachment (Hutson et al., 2002; Marionneau et al., 2002; Tan and Jiang, 2005b). These carbohydrates are widely present and most mammal species express such oligosaccharides on their tissues (Marionneau et al., 2001). Receptors for animal NoVs are not yet characterised but it can be hypothesised that such molecules are involved. This hypothesis is supported by findings in other caliciviruses. For example, rabbit haemorrhagic disease virus, a lagovirus, binds to antigens of the ABH histo-blood group family (Ruvoen-Clouet et al., 2000). Interestingly, oysters, often the origin of human food-borne NoV outbreaks, express carbohydrates closely related to some HBGAs in their digestive tissues on which human NoVs could be concentrated by binding, allowing spreading when eaten (Le Guyader et al., 2006).

In vitro, human NoV-like particles were able to bind to swine gastro-intestinal washings coated on plaques (Tian et al., 2007). Furthermore, the binding of human NoVs on swine gut tissues was reported in vivo with some indication of replication (Cheetham et al., 2007). On the another hand, virus-like particles (VLP) from SW918 porcine strain (GII.11, genetically related to human NoV) did not bind to human saliva samples of the major histo-blood group types (Farkas et al., 2005). These data suggest another receptor type for this NoV, with sometimes the opportunity for human NoVs to bind to naturally expressed carbohydrates related to human HBGAs on swine gut tissues (Cheetham et al., 2006, 2007). Another explanation may be the lack of additional factors which could be essential for in vitro and in vivo NoV replication, such as those that could be provided in cell culture in a '3D-conformation' (Straub et al., 2007). Bile acids from the intestinal content are essential for the sapovirus porcine enteric calicivirus (PEC)/Cowden strain replication in cell culture by increasing cAMP concentration and down-regulation of the interferon-mediated phosphorylation of the signal transducer and activator of transcription 1 (STAT1), a key element of innate immunity (Chang et al., 2004). Moreover, recent findings imply that the proteolytic process mediated by trypsin, for example, could be necessary for human NoV replication in the host (Tan et al., 2006).

Like other members of the *Caliciviridae* family and positive-strand RNA viruses, the replication of animal NoVs could occur in association with intracellular membranes and disturb them as much as membrane associated transport (Green et al., 2002; Schwartz et al., 2004; Studdert and O'Shea, 1975). Indeed, cells transfected with a vector plasmid that provides expression of the entire NV N-terminal protein (amino acids 1-398 of the ORF1 polyprotein) showed co-localisation of this protein with cellular proteins of the Golgi apparatus (Fernandez-Vega et al., 2004). In NoV transfected and infected cells, the loss of an intact Golgi apparatus is also clearly obvious (Wobus et al., 2004). Another viral protein, VPg, can inhibit host protein synthesis (Daughenbaugh et al., 2003, 2006). In different studies, animal calicivirus RNA treatment by proteinase K abolished its infectivity suggesting an essential role of VPg (Burroughs and Brown, 1978; Dunham et al., 1998). In addition, the viral proteinase can also inhibit cellular translation by cleavage of the poly-A binding protein (Kuyumcu-Martinez et al., 2004).

Pathogenesis, clinical signs and lesions

The main transmission route is faecal–oral for both animal and human NoVs (Graham et al., 1994; Green et al., 2001; Hall et al., 1984; Hsu et al., 2005). Both epidemiological and experimental observations suggest that another natural route of infection could be the respiratory tract through aerosolised particles in vomitus (Karst et al., 2003; Sawyer et al., 1988). Caliciviruses are characterised by stability in the environment (Rzezutka and Cook, 2004) and relative resistance to inactivation (Duizer et al., 2004a). In the absence of any culture system, stability and resistance of NoVs were studied in correlation with surrogates (VLPs, Feline calicivirus). Murine NoV offers more possibilities to study these fields (Cannon et al., 2006). Low infectious doses (Graham et al., 1994) and large strain diversity (Ando et al., 2000) increase the risk of infection.

Non-hemorrhagic enteritis, mild diarrhoea, transient anorexia and xylose malabsorption were the common clinical signs reported in gnotobiotic calves infected with the bovine NoV Newbury Agent 2. Diarrhoea was more severe in 3-week-old calves than in neonates. The same clinical pattern was observed up to 2 months of age. This virus seemed to be less virulent than the other bovine enteric calicivirus Newbury Agent 1 (Bridger et al., 1984; Hall et al., 1984; Woode and Bridger, 1978). Usually, the viral shedding appeared shortly before or during the first clinical signs. Using EM, viral excretion was noted over a short period (Bridger et al., 1984), a longer faecal excretion period was seen by RT-PCR, which was more sensitive for NoV detection (Han et al., 2005; Rabenau et al., 2003).

Histopathological lesions of calves infected with bovine NoV Newbury Agent 2 and the Jena agent consisted of villous atrophy, crypt hyperplasia and oedema in the submucosa in the proximal small intestine (Bridger et al., 1984; Gunther and Otto, 1987). Gastric and rectal mucosae were not affected (Bridger et al., 1984; Gunther and Otto, 1987; Woode and Bridger, 1978).

Porcine NoVs have been exclusively detected in faecal samples of adult swine without clinical signs (Wang et al., 2005), but in vivo studies have not been carried out. The real impact of porcine NoVs in swine diarrhoea remains to be elucidated.

Murine NoV-1 infection is asymptomatic in wildtype inbred 129 or outbred CD1 mice; on the other hand, mice lacking recombination-activating gene 2 (RAG2) and STAT1 will succumb to infection with this strain. The mice show clinical signs of encephalitis, vasculitis in cerebral vessels, pneumonia and hepatitis. In addition, the agent can be serially passaged by intracerebral inoculation, suggesting a wide NoV tropism and permissivity in immunodeficient individuals (Karst et al., 2003). Murine NoV-1 RNA was detected in spleen, mesenteric lymph nodes and jejunum from mice experimentally infected 5 weeks post-inoculation (Hsu et al., 2005). More recently, mouse lines of different immunodeficient genotypes have been infected with murine NoV-1 demonstrating systemic infections and signs of inflammation in different tissues (lung, liver, peritoneal and pleural cavities) (Ward et al., 2006). It is interesting to note that symptoms in humans are usually mild, self-limiting and of short duration (Rockx et al., 2002), except for immunocompromised, elderly or patients with underlying diseases (Goller et al., 2004; Lopman et al., 2003; Mattner et al., 2006; Okada et al., 2006). Human NoVs cause acute gastroenteritis and/or vomiting with a high secondary attack rate, especially in communities (Caul, 1996), but some human NoV case reports have documented a more severe disease with symptoms like intravascular coagulation disease or encephalitis (Brown et al., 2002; Ito et al., 2006).

In immunocompetent mice, histopathological changes are the only signs of murine NoV-1 infection (Mumphrey et al., 2007). Thus, it is assumed that disease only occurs in mice lacking components of the innate immune system (Karst et al., 2003). However, other murine NoV strains (murine NoV-2, 3 and 4) have been isolated recently in different mouse research colonies in North America (Hsu et al., 2006). These strains exhibited a different pathogenic pattern than murine NoV-1 in experimentally inoculated immunocompetent mice. While a transient infection was observed with murine NoV-1, the three novel strains showed more prolonged faecal shedding (8 weeks compared to 1 week) and signs of chronic tissue infection. This persistence could be associated with continuous replication, commonly observed with feline calicivirus (Wardley and Povey, 1977). Similar features could be suggested with other human or animal NoV strains with the outcome that asymptomatic carriers could contribute to virus dissemination and outbreaks.

Few animal NoVs cause serious clinical signs. In fact, such signs have only been noted in immunocomprised animals. In pigs, signs were only detected in asymptomatic animals. In bovines, NoVs should be viewed as benign pathogens that could facilitate or complicate gastroenteritis particularly in neonates. Only murine NoVs cause severe histopathological changes in their hosts.

Epidemiology

Epidemiological studies have repeatedly shown that NoVs are widespread and that infection is common in the human population as well as in the bovine, porcine and murine species. However, the epidemiology is not well understood and few studies have been carried out on animal NoV infections.

A serological prevalence of 22.1% was found in laboratory mice in North America, making murine NoV the most prevalent virus infecting these animals (Hsu et al., 2005). In The Netherlands, 31.6% of pooled stool specimens from veal calf farms and 4.2% of individual stool specimens from dairy cattle were positive for GIII NoV related to Newbury Agent 2 (van der Poel et al., 2003). In the UK, NoVs were detected in 11% of the cases of bovine diarrhoea tested (Milnes et al., 2007). In the US, different prevalence level of calicivirus shedding were found depending on the state: 72% in veal calves in Ohio (Smiley et al., 2003), 80% in Michigan and 25% in Wisconsin (Wise et al., 2004). In Germany, 9% of diarrhoea stool samples were positive for Jena virus whereas 99% of the serum samples collected from dairy cows were positive for the same GIII virus (Deng et al., 2003). This attests that bovine NoVs are present in cattle at a high rate in different countries.

Genogroup II NoVs were detected in pigs in Japan (Sugieda et al., 1998), The Netherlands (van der Poel et al., 2000), USA (Wang et al., 2005) and, recently, Hungary (Reuter et al., 2007). The detection rate of porcine GII NoV was low: 0.35% in Japan and 2% in The Netherlands (van der Poel et al., 2003). No circulation of porcine NoV was evidenced in Venezuela by RT-PCR screening (Martinez et al., 2006). Seroprevalence of GII NoV in swine was 97% in USA and 36% in Japan (Farkas et al., 2005).

The first putative lion NoV was detected in Pistoia zoo in Italy in a 4-week-old cub that died of severe haemorrhagic enteritis; it has not been demonstrated whether the virus was the causative agent of this enteric disease (Martella et al., 2007).

Enteric caliciviruses have been described in other domestic animal species, including cats and dogs (Herbst et al., 1987; Mochizuki et al., 1993; Schaffer et al., 1985), but until now none has been characterised as NoV.

Immune response

Initial data regarding host immune responses against NoV infection were generated by human challenge with stool filtrate or natural exposure during outbreaks, and

have been complicated by non-immunological host factors. These may be genetic (HBGAs for human strains) and associated with susceptibility to infection (Tan and Jiang, 2005a). Early reports in humans indicated an unusual clinical immunity pattern (Blacklow et al., 1987). Human volunteer studies with NV strain established that short-term immunity, lasting about 6 months, develops against homologous viruses (Johnson et al., 1990). This short-term immunity did not necessarily extend the protection to heterologous NoV infections (Matsui and Greenberg, 2000; Wyatt et al., 1974) and could be followed by renewed susceptibility to infection 1–2 years later.

Thus, a single exposure to the virus does not necessarily confer long-term immunity (Parrino et al., 1977). Moreover, individuals with high titres of pre-challenge antibody levels to NV are not protected against reinfection and disease after a single exposure, but high antibody levels become associated with protection after repeated exposures (Johnson et al., 1990). Calves challenged with the Newbury Agent 2 showed a homologous immunity that developed 3 weeks after first inoculation (Bridger et al., 1984). To our knowledge, the duration of homologous immunity against bovine NoV has not yet been studied.

Innate immunity

Innate immunity plays an important role in the control of the murine NoV-1 infection, while B and T cell-dependent adaptive immune responses are not required for protection and STAT1 is implied (Karst et al., 2003; Wobus et al., 2004). Mice lacking both interferon (IFN)αβ and IFNγ receptors are more susceptible to NoV lethal infection than immunocompetent mice (Karst et al., 2003). In pigs inoculated with human NoV, intestinal IFNα is significantly elevated post-infection (Souza et al., 2007). In addition, self-replicating NV RNAs generated in transfected cells are sensitive to the effects of exogenous IFNα (Chang et al., 2006). The role of innate immunity in controlling infection could explain that immunodeficient subjects can develop a more severe disease and a systemic viral spread following NoV infection.

Adaptive immunity

Essentially limited to the small intestine, NoV infection stimulates the mucosal immune response and, following human experimental inoculation, a specific serum IgA response appears to be a constant feature (Erdman et al., 1989). Salivary IgAs are not cross-reactive between genogroups and could be less cross-reactive than IgG within genogroup (Lindesmith et al., 2005).

Lindesmith et al. (2003) identified two distinct patterns of NV-specific salivary IgA increase after challenge of human volunteers. Some genetically susceptible people that did not succumb to infection after challenge showed an early increase in secretory IgA, suggesting that a memory immune response could be protective. However, it is not known if this protective immunity represents short- or long-term immunity. Immune mechanisms can differ according to the animal species, but it could be assumed that a similar immunity pattern may be observed in animal NoVs. In humans, an IgM peak occurred about 2 weeks after inoculation in association with illness, and a secondary IgM response occurred in the longer term after re-challenge. An IgM response to NoV is consequently not restricted to a primary infection (Cukor et al., 1982) but is rather a marker of recent infection (Brinker et al., 1999).

Also in humans, an IgG response is activated by infection, characterised by a fourfold increase in titres (Graham et al., 1994; Lindesmith et al., 2005), which can remain high for more than 2 years after infection (Iritani et al., 2007). In calves, the antibody response raised after experimental infection is similar to the serological response observed in humans infected with human NoV. Serum IgGs are first detected at 5 days post-infection and maximum titres are reached about 3 weeks after inoculation with a genotype 2 bovine NoV (Han et al., 2005).

A characteristic of these non-enveloped viruses is the relative simplicity of the capsid. The protruding subdomain P2 is the most antigenically variable region of the capsid because it is likely to be influenced by immune pressure (Nilsson et al., 2003). Monoclonal antibodies recognising P2 epitopes block virus–cell interactions. This supports increasing evidence that interactions between NoVs and host cells rely on structures in the P2 domain of VP1 (Lochridge et al., 2005) and that VP1 possesses antigenic determinants involved in protective immunity. Inter-genogroup broadly reactive epitopes are localised in the shell domain (Batten et al., 2006; Yoda et al., 2003). Indeed, although viruses from different genogroups are antigenically distinct, bovine NoVs share a cross-reacting epitope with a human GII.3 norovirus (Oliver et al., 2006b). This epitope is localised in the N-terminal region belonging to the inner shell domain of the capsid protein that is relatively well conserved (Yoda et al., 2003).

In both pigs and humans, infection with a human GII NoV elicits a predominant but not exclusive Th1 response (Lindesmith et al., 2005; Souza et al., 2007). Numerous experiments used NoV VLPs (self assembling of VP1) as a surrogate to study NoV immunity. These VLPs are produced by different protein production systems, in particular the baculovirus system, and are structurally, morphologically and antigenically similar to the infectious virus (Han et al., 2005; Jiang et al., 1992, 1995; Le Guyader et al., 2006). VLPs are immunogenic when they are given to mice orally, intranasally or by the parenteral route (Ball et al., 1998; Guerrero et al., 2001; Jiang et al., 1992), giving rise to a systemic and mucosal immune response. Because infection with NoVs is mainly localised in the small intestine, induction of a local immunity may be important for protection against infection and disease. The conclusion from the many human studies is that immunity against human NoVs is not determined by serum antibodies (Baron et al., 1984) and pre-existing serum antibodies do

not seem to be associated with protective immunity (Johnson et al., 1990).

Diagnosis

Electron microscopy, immunoassays (IA) and RT-PCR are used for NoV diagnosis (Lopman et al., 2002). A major problem for diagnosis using immunological or molecular techniques is the high genetic and antigenic diversity of NoVs. This is well known and described for human NoVs (Zheng et al., 2006). Genetic (Smiley et al., 2003) and antigenic (Oliver et al., 2006b; Wang et al., 2007) diversity is described in animal NoVs but is less than in human NoVs, as is seen with the number of clusters described for each NoV genogroup. This could be explained by detection bias and the development of diagnostic assays able to recognise the expected large diversity of animal noroviruses is required. Moreover, the development of diagnostic methods has been hampered by the lack of a cell culture system for NoVs (Duizer et al., 2004b), other than murine NoVs. Recently, a complex 3D-cell culture system has allowed the growth of GI and GII human NoVs (Straub et al., 2007) and this may be the beginning of a new era in NoV diagnostic tools.

First generation tests such as EM, radio-IA, Western blot or enzyme-IA have used reagents derived from previously infected humans. New generation tests following the successful cloning of NoVs have allowed the production of new reagents (such as VLPs) and new method development (such as RT-PCR) for the diagnosis of NoV infections.

Electron microscopy

Electron microscopy has been a fundamental tool for investigators, and has led to the discovery of the first NoVs, but it is a relatively insensitive method because a high viral load is necessary ($>10^6$ particles per gram of stool) (Atmar and Estes, 2001). Moreover, highly skilled microscopists are required to detect NoVs from prepared stool samples reliably. Some variants of these methods, such as IEM (Kapikian, 2000), or solid phase IEM (Dastjerdi et al., 1999), can also be used and are based on antigen–antibody reaction, visualised by negative staining EM.

ELISA

Expression of the NoV capsid protein in a baculovirus system provides large amounts of VLPs, which are used as antigens in IA. ELISA is the most widely used IA, using hyperimmune sera generated by the immunisation of animals. These assays are highly sensitive compared to EM, but their use in diagnostic laboratories is limited by their narrow specificity (Jiang et al., 2000). In fact, they are based on the detection of NoV antigens and could be hampered by antigenic diversity. ELISAs are useful because of their rapidity and simplicity for screening large number of samples. Antibody detection is more broadly reactive than antigen detection and is more suitable to identify heterotypic NoV infection (Atmar and Estes, 2001). For bovine and porcine NoVs, antibody and antigen ELISAs have been described (Cheetham et al., 2006; Farkas et al., 2005; Han et al., 2005; Oliver et al., 2007). The bovine NoVs (GIII) are divided into two serotypes, corresponding to the two distinct genotypes represented by Jena and Newbury Agent 2 strains (Oliver et al., 2006b). Antibodies against murine NoVs can be detected by ELISA (Mumphrey et al., 2007) or by a fluorescent IA (Hsu et al., 2006).

Three common epitopes shared by NoVs have been identified, one in the same genogroup, GI (Hale et al., 2000), another between GII and GIII (Oliver et al., 2006b), and the a third between GI and GIII (Batten et al., 2006). These discoveries could lead to the development of a broadly reactive antigen detection ELISA.

Reverse transcription polymerase chain reaction (RT-PCR)

Animal NoV strains can be detected by RT-PCR with primers designed for human NoVs. The assay allows the detection of porcine (Sugieda et al., 1998) and bovine (Dastjerdi et al., 1999; Liu et al., 1999; van der Poel et al., 2000) NoVs, but it is less sensitive than assays using animal NoV-specific primers. Therefore, once the presence of NoVs in animal species is proven, specific detection methods can be set up. For example, specific primers for RT-PCR and ELISA for detection of pig (Farkas et al., 2005; Wang et al., 2005) and calf NoVs (Deng et al., 2003; van der Poel et al., 2003) have been developed.

The polymerase gene is highly conserved among NoVs and numerous primer pairs have been published in this region (Le Guyader et al., 1996b; van der Poel et al., 2003; Vinje and Koopmans, 1996; Wang et al., 2006). However, analysis of more than one region is important for the detection of recombinant strains. By DNA sequencing of amplicons, information on viral phylogeny can be obtained and recombinant viruses may be detected.

RT-PCR has been developed after full length sequencing of different human NoV genomes (Jiang et al., 1993; Lambden et al., 1993). The genetic diversity among NoVs makes it impossible to develop a universal primer pair able to detect all NoVs, but some primers have been developed to detect most of circulating strains (Jothikumar et al., 2005; Le Guyader et al., 1996a; Richards et al., 2004; Vinje and Koopmans, 1996). A constant updating of primers is thus necessary.

The sensitivity of RT-PCR may be much lower than expected because of the presence of RT-PCR inhibitors in the sample (Wilson, 1997). The use of an internal control is strongly recommended to validate negative results and a few have been described for animal NoV detection in pigs (Cheetham et al., 2006; Wang et al., 2006) and cattle (Smiley et al., 2003). RT-PCR remains the 'gold standard' for NoV diagnosis because it is the most sensitive routine method used. It is being progressively replaced by real-time

RT-PCR, which is more sensitive and faster. Various methods, such as SYBRGreen and TaqMan, have been already set up for human NoV (Jothikumar et al., 2005; Trujillo et al., 2006). These may also be used for the detection of animal NoVs, and some have recently been published for pig (Cheetham et al., 2006) and cattle NoVs (Wolf et al., 2007). Real-time RT-PCR using a Taqman probe gives the advantage of confirmation in a single assay and the opportunity of quantification if a standard is used (Jothikumar et al., 2005). This last application is of great interest as most NoVs cannot easily be cultivated in routine cell culture for plaque assay quantification.

As there is no harmonisation to compare methods (as a reference assay), the validation parameters reported in the literature are not comparable. However, a conclusion from the published assays is that RT-PCR is more sensitive than EM and ELISA (Burton-MacLeod et al., 2004; de Bruin et al., 2006; Richards et al., 2003) and it is now the mostly used assay to identify animal and human NoV infections.

The hypothesis of zoonotic risk

The detection of NoVs in animal faeces (calves and pigs), with or without clinical signs of gastroenteritis, is frequent (Ando et al., 2000; Deng et al., 2003; van der Poel et al., 2000). Molecular analyses have shown that animal and human strains are closely related, especially porcine NoVs, which are included in the same genogroup (GII) as some human strains (Oliver et al., 2003; Sugieda et al., 1998; Wang et al., 2005). Moreover, replication of a human NoV GII was recently demonstrated in gnotobiotic pigs (Cheetham et al., 2006).

Strengthening the hypothesis that animals may act as a human NoV reservoir, a high prevalence of antibodies against human NoVs was found in pigs in Venezuela. Surprisingly, a higher level of antibody prevalence against GI than GII human NoVs was observed (Farkas et al., 2005), whereas all porcine NoV detected thus far clustered with GII NoVs. These results may be explained by infection of swine with human GI NoVs or by a putative circulation of a yet undiscovered porcine NoV.

Although an animal reservoir and zoonotic transmission could exist, genetic distances (Oliver et al., 2003) and difference between receptors (Farkas et al., 2005; Hutson et al., 2003) do not support this hypothesis. Furthermore, the lack of evidence that the same strains circulate in both the human and bovine species suggests an absence of risk to human health (Oliver et al., 2003). The recent detection of sequences close to GII.4 human NoV in swine and cattle in Canada could however modify this risk evaluation in the future (Mattison et al., 2007).

Although animal NoVs have not yet been isolated from humans, human infection with NoVs related to genogroup III bovine NoV has been suggested by the presence of antibodies against bovine GIII.2 in veterinarians in The Netherlands (Widdowson et al., 2005). The existence of cross-reactive epitopes between human and bovine NoVs (Batten et al., 2006; Oliver et al., 2006b) may explain the detection of antibodies against animal NoVs in humans. Otherwise, bovine strains are unlikely to be a risk to humans because they form a third genogroup genetically distinct from human NoVs (Han et al., 2004; Oliver et al., 2003).

To date, NoV recombinants have been exclusively identified between NoVs belonging to the same genogroup and from the same animal species within bovine (Han et al., 2004; Oliver et al., 2004), porcine (Wang et al., 2005) and human species (Jiang et al., 1999; Katayama et al., 2002; Vinje and Koopmans, 2000). Bivalve molluscs present a problem in that they are filter feeders capable of concentrating viruses present in the surrounding water. Outbreaks associated with seafood are frequent, especially in countries where their consumption is high and also because they are often eaten raw (Lees, 2000). A natural co-infection with GI and GII NoVs has already been described in humans (Chan et al., 2006). Moreover, simultaneous presence of human and animal NoVs has been detected in shellfish (Costantini et al., 2006). These observations raise concern about the risk of co-infection of humans with human and animal NoVs, resulting in possible recombination and emergence of new strains.

Some animal caliciviruses are able to cross the species barrier and potentially use humans as an alternative host (Smith et al., 1998). One serotype of the Snow Mountain sea lion virus was reported to infect humans (Smith et al., 1998) and antibodies against vesivirus were found in cattle and horses (Kurth et al., 2006a; Kurth et al., 2006b).

These data suggest that appropriate conditions could be met to favour the emergence of recombinant viruses and/or an interspecies transmission of genetically compatible noroviruses.

Conclusions

NoVs are the most common cause of outbreaks of non-bacterial gastroenteritis in humans, and are also the most common cause of viral food-borne infection. In animal species, their full impact is not known, but they have already been detected in cattle, pigs and mice in several countries. As animal NoVs are closely related to human NoVs, it can be hypothesised that similar properties are shared by both viruses. Murine NoV, the only easily cultivable NoV, is useful as an animal model to study human NoVs in vitro and in vivo. Also, GII human NoVs replicate in gnotobiotic pigs, which may provide a heterologous model to study the pathogenesis of human infection. Bovine and porcine NoVs are the best candidates to be used as a homologous animal model.

To date, few complete genomes of animal NoVs have been published to better understand relatedness with viruses causing disease in humans. Of great interest for NoV researchers is the possibility of zoonotic transmission. Animal NoVs are genetically close relatives to human strains, especially porcine NoVs, which can be grouped

with GII NoVs which are the viruses that are most frequently associated with outbreaks. The sequence similarity of porcine and bovine strains with human strains suggests that an animal reservoir of NoV infection is plausible. Co-infection and recombination between human and animal strains might occur although they have not yet been detected. Since intra-genogroup recombinants have been characterised in both human and animal species, and human and bovine NoVs have been detected in the same oysters, their co-ingestion by the same person or animal could potentially lead to the emergence of an inter-genogroup recombinant strain.

The emergence of such recombinant has the highest likelihood to occur in countries where high densities of animal and human populations where breeding practices put humans and animals in close contact so increasing the risk for cross species transmission.

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