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Review

Molecular epidemiology and evolution of porcine parvoviruses

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ABSTRACT

Porcine parvovirus (PPV), recently named *Ungulate protoparvovirus 1*, is considered to be one of the most important causes of reproductive failure in swine. Fetal death, mummification, stillbirths and delayed return to estrus are predominant clinical signs commonly associated with PPV infection in a herd. It has recently been shown that certain parvoviruses exhibit a nucleotide substitution rate close to that commonly determined for RNA viruses. However, the PPV vaccines broadly used in the last 30 years have most likely reduced the genetic diversity of the virus and led to the predominance of strains with a capsid profile distinct from that of the original vaccine-based strains. Furthermore, a number of novel porcine parvovirus species with yet-unknown veterinary relevance and characteristics have been described during the last decade. In this review, an overview of PPV molecular evolution is presented, highlighting characteristics of the various genetic elements, their evolutionary rate and the discovery of new capsid profiles driven by the currently used vaccines.

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1. Introduction

Porcine parvovirus (PPV, recently named *Ungulate protoparvovirus 1*) was first isolated in 1965 in Munich, Germany, by Anton Mayr and co-workers as a contaminant of a porcine primary cell culture used for the propagation of classical swine fever virus (Mayr and Mahnel, 1964). In the ensuing years, this virus was found to be associated with reproductive disorders, and a worldwide distribution was observed thereafter (Cartwright and Huck, 1967; Joo et al., 1976; Mengeling and Cutlip, 1976). PPV causes reproductive disorders in sows that can be summarized by the acronym SMEDI (*stillbirth*, *mummification*, *embryonic death* and *infertility*) (Mengeling et al., 2000; Truyen and Streck, 2012). Despite the continuous use of vaccines, several new strains have recently been described, and there is cause for concern because changes in only a few amino acids in the capsid protein can potentially cause marked differences in antigenicity and virulence.

Here, we review the molecular epidemiology and evolution of porcine parvoviruses, focusing on the recent nucleotide changes of PPV and the recognition of novel parvoviruses. We discuss the features of the virus that are thought to influence virulence and summarize the characteristics of its capsid. We also examine the high evolutionary rate of this virus and other parvoviruses and the implications of this evolution, the appearance of new strains, highlighting the genetic elements observed in these new strains and the evolutionary processes that can influence them. Additionally, novel porcine parvoviruses are

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presented and discussed, with a focus on molecular epidemiological roles and clinical importance. Finally, we discuss the possible importance of the wild boar population for the evolution of PPV in domestic pigs and elaborate on possible objectives of future studies to increase our knowledge about parvoviruses.

2. Virus

The genome of parvoviruses represents a single-stranded (*ss*) DNA molecule of approximately 5 kb. Both terminal sequences of the virus form complex palindromic hairpin structures (in a similar "Y" or "T" shape) of approximately 120 to 200 bases (Berns and Hauswirth, 1983). The compact genome of PPV contains only two promoters and encodes seven proteins, and alternative splicing is used to extend the coding capacity of the genome. The two nonstructural proteins NS1 and NS2 are transcribed from the P4 promoter, and these proteins are important for viral replication, particularly DNA replication. A putative non-structural protein, NS3, has also been described (Bergeron et al., 1993). Another two structural proteins (VP1 and VP2) are transcribed from the P40 promoter. VP1 and VP2 are translated from a nested set of coding sequences, and smaller VP2 is produced by splicing from the same RNA template as larger VP1, differing only in their amino-terminus. VP1 has 729 amino acid residues, of which the 120 amino-terminal sites are unique to VP1 and absent in VP2. The third structural protein, VP3, is a post-translational modification product of VP2 (Simpson et al., 2002; Cotmore and Tattersall, 2006). Furthermore, a late non-structural protein (SAT) is expressed from the same VP2 mRNA, initiating seven nucleotides downstream of the VP2 start codon (Zádori et al., 2005).

The capsid of PPV is a spherical shell consisting of 60 copies of either VP1 or VP2 arranged in icosahedral symmetry (Chapman and Rossmann, 1993). Each of the capsid subunits consists of eight antiparallel β-strands, a common structure for viral capsids, together with one α-helix and four loops (Fig. 1) (Chapman and Rossmann, 1993). A projection (spike) at the 3-fold axis, a depression at the 5-fold axis and a dimple at the 2-fold axis of this symmetry are observed on the surface of the closely related canine parvovirus. Amino acids of the subunit loops are primarily located at the 2- and 3-fold axes of symmetry, and these residues are often those that vary among strains and isolates. These regions of PPV are considered to be important for viral infection and immunogenicity (Simpson et al., 2002).

Several neutral amino acids are located on the internal surface of the PPV capsid; this is unusual because most viruses have basic amino acids on their internal virus surface, which supposedly interact with the phosphates of the DNA molecule (Xie and Chapman, 1996). Indeed, the presence of basic residues may result in a high electrostatic enthalpy reaction with DNA molecules (Steitz, 1990), ensuring the efficient packaging of the viral genome into very stable virions.

3. Evolutionary rate among parvoviruses

The originally described conservative character of parvoviruses has most likely contributed to the small amount of interest in monitoring PPV during the 1980s and 1990s. As eukaryotic cells have a cellular polymerase complex that exhibits high confidence in the generation of new DNA copies (due to the efficient repair unit) and thus a low substitution rate (approximately 10^{-9} to 10^{-10} substitutions per nucleotide per year), parvoviruses, which also use the host polymerase for replication, are considered to be stable and to show a substitution rate close to the host (Duffy et al., 2008). In contrast, RNA viruses, which encode their own RNA polymerase (without repair activity), have a substitution rate of approximately 10^{-3} to 10^{-5}/site/year (Drake, 1993).

More recently, however, several studies on mutation dynamics have shown that additional factors may drastically affect the viral mutation rate (Xia and Yuen, 2005; Duffy et al., 2008). Some DNA viruses (mainly *ss*DNA types) evolve very rapidly, whereas some RNA viruses do not (Duffy et al., 2008). The first estimation of a high substitution rate in *ss*DNA viruses came from a study reporting the emergence of canine parvovirus 2 (CPV-2) from the feline panleukopenia virus (FPLV). For both viruses, a substitution rate of 10^{-4}/site/year was estimated, and, in the main branch where CPV-2 emerges, a substitution rate of 7.1×10^{-3}/site/year in the time period between 1968 and 1978 was

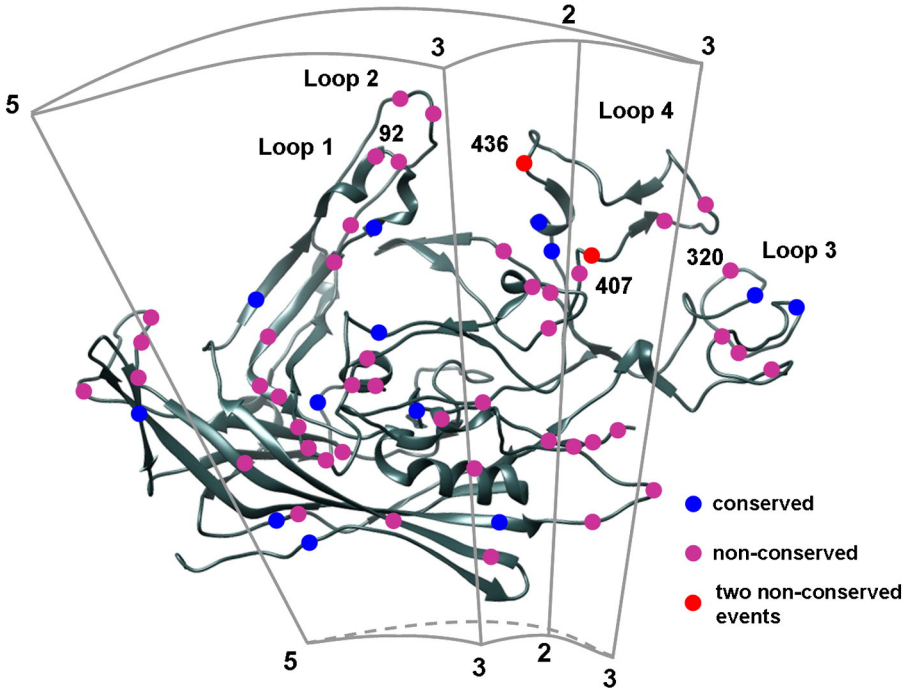

Fig. 1. 3-D model of PPV VP2 with the cartoon technique, with helices (α-helices) and arrows (β-strands) representing the secondary structure. The neighboring 5-, 3- and 2-fold axes of the capsid subunit are shown. The molecular graphics and analyses were performed with the UCSF Chimera package (Pettersen et al., 2004). The coordinates were retrieved from the NCBI Structure database (http://www.ncbi.nlm.nih.gov/Structure/index.shtml); accession number: 1K3V (Simpson et al., 2002). Dots represent conserved/non-conserved amino acid substitutions in the PPV sequences available in GenBank.