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Review

A review of porcine circovirus 2-associated syndromes and diseases

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Abstract

Clinical expression of porcine circovirus 2 (PCV2) infection in swine may result in several distinct syndromes and diseases including post-weaning multisystemic wasting syndrome (PMWS), porcine dermatitis and nephropathy syndrome (PDNS), reproductive failure, porcine respiratory disease complex, granulomatous enteritis, necrotizing lymphadenitis, and possibly exudative epidermitis. Association of PCV2 with congenital tremor in piglets is still controversial. The extent of the involvement of PCV2 in swine disease other than PMWS is currently poorly understood. This review concentrates on PCV-2-associated syndromes and diseases other than PMWS.

Keywords: Porcine circovirus; Porcine dermatitis and nephropathy syndrome; Porcine respiratory disease complex; Post-weaning multisystemic wasting syndrome; Review

1. Introduction

Currently, porcine circovirus 2 (PCV2) is considered to be an important emerging pathogen associated with a number of different syndromes and diseases in pigs. PCV2 was first recognized in 1996, when infection was identified in specific-pathogen-free swine herds in western Canada. It was reported as a new syndrome, termed post-weaning multisystemic wasting syndrome (PMWS) (Clark, 1997; Harding and Clark, 1997).

Since the identification of PCV2 and its association with PMWS, PCV2 has been increasingly isolated from pigs affected with various other clinical manifestations. Overall, clinical syndromes and diseases associated with PCV2 infections are divided into pre- and post-natal manifestations. In the former, PCV2 infection is linked to reproductive failures (Josephson and Charbonneau, 2001; Ladekjaer-Mikkelsen et al., 2001; Kim et al., 2004; O'Connor et al., 2001; West et al., 1999), whereas the post-natal manifestations of the disease in Europe, Asia and North America, are predominantly PMWS and porcine respiratory disease complex (PRDC) (Allan and Ellis, 2000; Harms et al., 2002; Kim et al., 2003b). In parts of England, Ireland and elsewhere, a syndrome known as porcine dermatitis and nephropathy syndrome (PDNS) is more prevalent than PMWS (Allan and Ellis, 2000; Gresham et al., 2001; Meehan et al., 2001; Thomson et al., 2001a). In addition, PCV2 also has been associated with granulomatous enteritis, necrotizing lymphadenitis, and possibly exudative epidermitis. However, the extent of the involvement of PCV2 in swine disease other than PMWS is not clear. Recently, PMWS was reviewed in detail (Chae, 2004) and this review concentrates therefore on PCV-2-associated syndromes and diseases other than PMWS.

2. Characterization of PCV2

The porcine circoviruses (PCV) are members of the genus *Circovirus*, family Circoviridae, which are the smallest non-enveloped, single-stranded, circular DNA viruses that replicate autonomously in mammalian cells (Mankertz et al., 1997; Studdert, 1993; Todd et al., 1991). The virion DNA, encapsulated by a single viral protein, is a single-stranded negative sense circularized molecule of roughly 1,800 bases that has six open

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reading frames (ORFs) (Hamel et al., 1998; Lukert et al., 1995; Mankertz et al., 1997; Meehan et al., 1998). Two types of PCV have been characterized and were subsequently named PCV1 and PCV2 (Meehan et al., 1998). PCV1 is a persistent contaminant of the porcine kidney cell lines, PK-15 (Tischer et al., 1974). It has never been associated with naturally occurring disease and experimental inoculation of pigs did not result in clinical disease (Allan et al., 1995; Krakowka et al., 2000; Tischer et al., 1986). PCV1 is therefore considered to be avirulent. In contrast, PCV2 is identified as virulent porcine pathogen.

PCV2 has been recovered from PMWS tissues in Europe, Asia, and North America (Allan et al., 1998; Ellis et al., 1998; Fenaux et al., 2000), sequenced (Fenaux et al., 2000; Hamel et al., 2000; Larochelle et al., 2002; Mankertz et al., 2000; Meehan et al., 1998) and shown to differ significantly from avirulent PCV1 (Hamel et al., 1998; Tischer et al., 1974, 1986) in the virion nucleotide sequence for the single nucleocapsid protein (Hamel et al., 1998; Meehan et al., 1998). PCV2 isolates from all over the world have since been isolated and sequenced and all are highly homologous (>96%) to each other but not to PCV1 (roughly 62%) suggesting that PCV2 isolates are all members of a single pathogenic virus genotype. Furthermore, all of the characterized isolates of PCV2 associated with PMWS are antigenically similar to each other using monoclonal and polyclonal antibodies (Allan et al., 1999b).

It has recently been hypothesized that different types of PCV2 may be responsible for different disease presentations. Two studies have suggested that PCV2 isolated from reproductive failure and PDNS may be phenotypically or genetically different from PCV2 associated with PMWS (Meehan et al., 2001; O'Connor et al., 2001). However, PCV2 isolates from different clinical disease manifestations have been sequenced and all are highly homologous (overall >90–96%). Most of these studies have found minor differences in the respective PCV genomes (Choi et al., 2002; Farnham et al., 2003; Meehan et al., 2001; O'Connor et al., 2001) but at this time it remains unclear what significance these minor differences may have. Sequence analysis of ORF1 and ORF2 genes has revealed that the extent of nucleotide variation is greater for the ORF2 than ORF1 (Fenaux et al., 2000; Hamel et al., 2000; Mankertz et al., 2000). The alterations in ORF2, which encodes for the major structural capsid protein (Nawagitgul et al., 2000), suggest there may be a link between capsid protein variation and pathogenicity of PCV2. Modification of the major viral capsid may alter determinants involved in tissue tropism or virus-host interactions. One study has suggested that the minor variation in the ORF2 of PCV2 may account for different in tropism with respect to the host organism (Mankertz et al., 2000). In addition, other host factors such as age, route of infection, etc. may affect the pathogenicity and clinical manifestations of PCV2 infection.

3. Post-weaning multisystemic wasting syndrome

PMWS is now well established as a wasting disease associated with PCV2 and is a major economic concern in all pig-producing areas of the world. In Asia and Europe, PMWS occurs in both endemic and epidemic forms. In North America, the sporadic form of the disease predominates. The disease has been reproduced in piglets by either inoculation with PCV2 alone or in PCV2-infected swine co-infected with porcine parvovirus (PPV) or porcine reproductive and respiratory syndrome virus (PRRSV). It also occurs when PCV-2-infected piglets are immuno-stimulated by injections of an immunogen emulsified in an oil-based macrophage-targeted adjuvant (Allan et al., 1999a, 2000; Choi and Chae, 2000; Ellis et al., 1999b; Harms et al., 2001; Kennedy et al., 2000; Kim et al., 2003a; Krakowka et al., 2000, 2001; Kyriakis et al., 2002). PMWS has been comprehensively reviewed by several authors (Allan and Ellis, 2000; Chae, 2004; Segales and Domingo, 2002).

4. Porcine dermatitis and nephropathy syndrome

PDNS is a relatively new and often fatal disease that primarily affects recently weaned and feeder pigs from 1.5 to 4 months of age (Smith et al., 1993; Thibault et al., 1998). The syndrome was first recognized in the UK in 1993 (Smith et al., 1993). Since then, it has been reported in several countries including Korea and North America (Choi and Chae, 2001; Duran et al., 1997; Ramos-Vara et al., 1997; Rosell et al., 2000). PDNS is generally sporadic. In fatal cases, cutaneous lesions consist of severe necrotizing vasculitis affecting the dermis and subcutis, characterized by leukocytoclastic (the presence of neutrophils with nuclear fragments) inflammation involving capillaries, small and medium-sized venules, and arterioles, accompanied by epidermal necrosis and ulceration and dermal haemorrhage (Choi and Chae, 2001; Duran et al., 1997; Smith et al., 1993; Thibault et al., 1998).

Pigs affected with PDNS are older pigs, particularly animals ranging from 12 to 14 weeks of age, but PDNS has also been described in finishing pigs and replacement gilts. The first signs were skin lesions that were multifocal, well circumscribed, slight raised, dark red, circular to irregular and 1–20 mm in diameter. Shortly after the appearance of the skin lesions, pigs may become pyrexic, with rectal temperatures $\geqslant 41$ °C, and display clinical signs of anorexia, severe weight loss, and depression. Pigs with these signs usually die rapidly and mortality in