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Pathogenesis and persistence of PRRS

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Introduction

Porcine Reproductive and Respiratory Syndrome (PRRS) has been perhaps the most economically important disease of swine through the 1990s. Recent studies in our laboratory and by others establish that the PRRS virus (PRRSV) causes both acute and persistent infections (1–7). To study the pathogenesis of both acute and persistent PRRS infections, we have used the 90-day gestational model (2). The benefit of this model is that liveborn pigs experience both an acute PRRS infection that mimics the disease in the field and pigs that survive beyond 21 days postpartum become asymptomatic and persistently infected with PRRSV. In this article we will briefly review the pathogenesis of acute PRRS and provide information on the pathogenesis of persistent infections with PRRSV.

Acute PRRS

What is the pathogenesis of acute PRRS?

Most of you are familiar with the pathogenesis of acute PRRS. Following entry of PRRSV into the host, the virus replicates in resident macrophages at the site of mucosal entry. Virus produced in resident macrophages is then transported either as cell-free or cell-associated PRRSV to regional lymph nodes. Macrophages in lymph nodes may represent a secondary site of PRRSV replication with dissemination of virus via blood and lymph to other organ systems. This multi-systemic distribution of virus results in a variety of clinical responses depending on the age of the pig. Virus is also readily isolated from serum and various other tissues, especially lung (see review in reference 4).

Persistent PRRS

What is the pathogenesis of persistent PRRS?

Replication of PRRSV during persistent infections is more restrictive and it becomes increasingly difficult to demonstrate infectious virus. In our experience, PRRSV replication is restricted to lymphoid tissue (especially lymph nodes or tonsils) during persistent infections or resides in immune-privileged sites such as testes (2,3,5), but it is absent in lung tissue and alveolar macrophages.

What is "persistence" and what does the literature say about persistence of PRRSV in pigs?

Persistent viral infections are characterized by the continuous or intermittent production of infectious virus in the host for an extended period of time. A single stranded RNA virus, such as PRRSV, does not establish latent infections similar to pseudorabies. Rather the virus persists via continuous, but often limited, replication in immune-privileged sites or specific subpopulations of cells, such as macrophages.

Previous reports indicate that PRRSV persists in pigs because virus can be transmitted from PRRSV asymptomatic principals to seronegative sentinel pigs; infectious virus and/or PRRSV RNA can be demonstrated in body fluids (serum, nasopharyngeal washings, and semen) after the cessation of clinical disease and for extended periods of time. Infectious virus has been isolated from tonsil and tonsil scrapings at 132 postpartum and 157 days post-infection, respectively (2,6). Viral RNA has been detected in serum up to 210 days postpartum and in boar semen at 92 days post-infection (2,3). Commingling PRRSV seronegative sentinel pigs with seropositive or convalescent principals indicate that virus is shed to the sentinel pigs up to 22 weeks after infection (1).

What is the site of persistence?

Our results and those of others indicate that PRRSV is most readily isolated from either lymph nodes or tonsils of pigs that are persistently infected (2,6). Testes are also a site of persistence in adult boars (5). The mechanism via which the virus persists in these tissues is unknown.

Which PRRSV infected pigs are most likely to become persistently infected?

In our experiments, 100% of the pigs born live to gilts infected with PRRSV at 90 days gestation and surviving at 21 days of age became persistently infected. Boars appear to have a higher risk of becoming persistently infected than other adult pigs. However, there are few if

any reports that investigate the potential for gilts/sows to become persistently infected.

Do pigs remain persistently infected for "life"?

How you answer this question depends on what you consider the "life of a pig." Infectious PRRSV has been detected in tonsil scrapings up to 157 days after infection (6) and we have detected PRRSV RNA in serum at 210 days postpartum in pigs born from infected sows/gilts. Thus, PRRSV can certainly persist for the "life" of a pig finished for market in 150–160 days.

In one experiment, we retained four persistently infected pigs for a period of 383–421 days postpartum. These animals had intermittent RT-PCR positive results for PRRSV RNA in serum up to 210 days postpartum. Three of these animals were gilts and one was a boar. These four animals had declining S/P ratios on the IDEXX ELISA for several weeks and were considered seronegative (S/P below 0.4) by ELISA at approximately 250 days postpartum. However, each pig still had demonstrable neutralizing antibody titers of 1:4 to 1:8 versus the homologous challenge virus. One seronegative boar was placed in contact with the three gilts from 260 days to 316 days post partum. Two of the three gilts were successfully bred by the this boar, but the boar did not seroconvert during the 56 days of continuous contact. No infectious virus or PRRSV RNA could be detected during this time period in the blood of these pigs. Likewise, the boar, which was previously persistently infected, was placed in contact with two seronegative gilts that also did not seroconvert during the 56-day period of contact.

The two bred gilts farrowed on time with litters of three and eight pigs, respectively. All pigs born to these gilts were healthy and we could not demonstrate either infectious virus, PRRSV RNA, or PRRSV antibody in the pigs, which were euthanized within 7 days after birth. Likewise, the three gilts and the boar were euthanized between postpartum days 383 to 421 and no infectious virus or viral RNA could be demonstrated in several tissues. These, results indicate that PRRSV was essentially eliminated in these animals and that the PRRSV does not necessarily persist for the "life" of the pig.

Do live-attenuated vaccines protect pigs from becoming persistently infected?

While we have no direct evidence to answer this question, one can assume that if fetuses infected *in utero* have a greater risk of surviving to be persistently infected pigs, then prevention of fetal infection via vaccination would reduce the incidence of long term carriers of the PRRSV. However, vaccination does not prevent infection of pigs within the first few weeks of birth and it is our opinion that pigs infected within the first few days of life do not clinically behave much differently than pigs infected *in utero*.

Vaccination of boars does markedly reduce the time of shedding of virulent virus in the semen. Thus, prior vaccination of boars in seropositive boar studs may prevent prolonged shedding of virulent virus in these animals.

Is there a diagnostic procedure that identifies persistently infected pigs?

Quite frankly, the answer is no; however, by using a combination of serologic tests, virus isolation and RT-PCR, one can reach some conclusions. Our results indicate that the best tissue to sample for infectious virus over time is tonsil (2). We could isolate infectious virus from tonsil up to 132 days postpartum (2) and others have isolated infectious virus up to 157 days after infection (6). We were not able to isolate virus or demonstrate virus in the blood by virus isolation or RT-PCR at this time. So tonsil scrapings and tonsil biopsies may be the best tissue source to identify persistently infected pigs.

Young pigs may commonly be viremic for at least 28 to 35 days or longer after infection. The presence of infectious PRRS virus or PRRS RNA in serum or tonsil beyond 35 days after the first appearance of clinical signs is usually indicative of persistence. It is also our opinion that viremia is usually short-lived (1 to 2 weeks) in most adult animals. Adult animals from which infectious virus or PRRS RNA can be demonstrated in serum or tonsil in association with rising or persistent ELISA S/P ratios are good suspects to be persistently infected.

What is the epidemiological significance of PRRSV persistently infected pigs?

Based on limited experimental data, we postulate that subpopulations of persistently infected pigs exist in swine herds experiencing chronic PRRS problems in the farrowing, nursery, and grow/finish units. The presence of subpopulations of persistently infected pigs in herds could explain the failure of early weaning protocols to eliminate PRRSV. Persistently infected pigs are difficult to identify and are an important source of virus when commingled with serologically naive pigs in nurseries, finishing barns and breeding herds.

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