Update on Senecavirus A research: Epidemiology of infection, evolution of the virus and its oncolytic activity

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Summary

Senecavirus A (SVA), formerly known as Seneca valley virus (SVV) (20), is a critical pathogen causing vesicular lesions in pigs and acute death of newborn piglets, resulting in very large economic losses in the pig industry. The aim of this paper was to present the current knowledge about the epidemiology and evolution of Senecavirus A, as well as the role of the virus in oncolytic therapy. From 1988 to 2005, a number of virus isolates were sporadically recovered from pigs in various regions of the United States, but without a detailed description of the clinical signs. After 2014, a sudden increase in SVA outbreaks appeared outside the United States and Canada, and SVA infection was reported in more regions of the United States, in Brazil, China, Colombia, Thailand and Vietnam with extensive distribution. After the expansion of the SVA area, complete and partial SVA genomic sequences were determined from SVA strains in most of these regions. Therefore, advances were also possible in the molecular epidemiology of the virus. A certain genetic distance has been determined between SVA strains isolated in various countries and at different times, suggesting a constant and rapid evolvement of SVA. It was shown that a combination of evolutionary processes, such as multiple mutations at variable sites and purifying selection, drove the genetic diversity and evolution of SVA. Evolutionary changes that accumulated in the SVA genome over the years may have contributed to the increased incidence of the disease. SVA is the first oncolytic picornavirus to be tested in humans and to penetrate solid tumours through the vascular system, unlike many other oncolytic viruses. SVA has a potential cytolytic activity and high selectivity for tumour cell lines with neuroendocrine properties versus adult normal cells

Keywords: Senecavirus A, swine, epidemiology, evolution, oncolytic virotherapy

Senecavirus A (SVA), formerly known as Seneca valley virus (SVV) (20), is a critical pathogen causing vesicular lesions in pigs and acute death of newborn piglets, resulting in very large economic losses in the pig industry. SVA is a non-enveloped, icosahedral virus with a single-stranded positive-sense RNA genome virus that belongs to the genus *Senecavirus*, family *Picornaviridae* (8). Its genome (of approximately 7.3 kb) contains a single open reading frame (ORF) flanked by a long 5' untranslated region (5'UTR; 668 nucleotides) and a short 3'UTR (68 nucleotides) followed by a poly (a) tail. The polyprotein translated from the single ORF is predicted to be post-translationally processed into four structural proteins (VP1 to VP4) and seven non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C, and 3D) (8). SVA was initially incidentally identified in 2002 as a contaminant in PER.

C6 cell cultures (26). From 1988 to 2005, a number of virus isolates were sporadically recovered from pigs in various regions of the United States, but without a detailed description of the clinical signs (8). In 2007, about 30% of 187 pigs from a Canadian market had broken vesicles along the coronary band, and among them approximately 80% were lame. The clinical vesicular lesions were indistinguishable from those of vesicular diseases caused by foot-and-mouth disease virus (FMDV), swine vesicular disease virus (SVDV), vesicular stomatitis virus (VSV), or vesicular exanthema of swine virus (VESV). The PCR results for these viruses were negative, but positive only for SVA (21).

Epidemiology of SVA infection

The first known case of SVA in the United States occurred in Indiana in 2010, in a single 6-month-old

pig with vesicular lesions in the oral cavity, around the nostrils, and on the coronary bands (14). After 2014, a sudden increase in SVA outbreaks occurred outside the United States and Canada, especially in Brazil and China. At the end of 2014 and the beginning of 2015, SVA outbreaks in weaned and adult pigs were reported in different geographical regions of Brazil. SVA infections reported in the United States and Canada occurred only in adult pigs, whereas in Brazil, clinical manifestations were reported for the first time in piglets, and morbidity in neonatal pigs was higher than in adult pigs. Moreover, SVA infection in neonatal piglets could lead to acute death (14). This apparently indicates that there is an evolution of SVA into a more virulent phenotype. In the same year, two cases of SVA were reported in Ontario and Manitoba, Canada (21). The complete coding sequences of SVA from the two clinical cases and nine assembly yard environmental samples were analyzed. A rapid accumulation of genetic variations driven by a high nucleotide substitution rate and purifying selection was observed for these isolates, which suggests that these SVA strains had been evolving constantly (35). In 2015, SVA was detected in China, in newborn piglets in the Guangdong province (22). In 2016, pig herds from Canada and Thailand were also affected by SVA infection (25). From 2015 to 2016, SVA infection in pigs was reported in more regions in Brazil, the United States, China, Canada, Colombia, and Thailand, with extensive distribution (Fig. 1) (9, 15, 25, 29, 30). In view of all of these SVA outbreaks, 2015 can be considered as a turning point for the epidemiology of SVA infection, with many important features of senecaviruses being identified.

In the following years, the number of SVA infection reports significantly increased and the morbidity and mortality rates of senecavirus-induced disease varied widely depending on pig age, geographical region, and herd origin (13). In a herd that is affected for the first time, the morbidity rates range from 4% to 70% depending on the clinical signs and pig age groups (2, 4, 14). SVA outbreaks presented morbidity rates of 0.5% to 30% in weaned pigs and 5% to 30% in finishing pigs and breeders, which varied according to the geographical region and the herd origin (16, 26). Remarkably higher morbidity rates, of 70% to 90% were reported in sows (2). In newborn pigs, especially in one- to four-day-old piglets, morbidity and mortality rates are considerably higher, reaching 70% and 15 to 30%, respectively (4, 14, 26). Clinical manifestations and high mortality rates in piglets last for approximately 2 to 3 weeks in the affected herd. The infection probably becomes endemic when most of the animals are asymptomatic or with subclinical infection and when clinical signs occur in pigs that have not been previously infected, are seronegative, or have low titers of SVA-specific antibodies. Furthermore, declining immunity or the introduction of native gilts in affected herds and the persistence of the virus in the animals and in the environment may induce a new outbreak in previously affected herds (26). SVA shedding was demonstrated in faecal samples from piglets that presented multisystemic clinical signs, including diarrhoea, and from finishing pigs that were naturally infected with the virus and presented vesicular lesions (7, 14, 16). Additionally, immunochemical and RT-PCR assays showed SVA presence in the urinary

Fig. 1. The occurrence of Senecavirus A in the world (modified, according to Sun et al. (29))

epithelium of clinically affected piglets, suggesting that urine may be a SVA dissemination route and a possible contamination source in affected pig herds (16, 26). The SVA genome and viable infective virus particles were isolated in cell cultures from faecal and small intestine samples from mice from clinically affected pig herds, and houseflies collected from affected herds tested positive for the presence of SVA (10). The detection of SVA RNA and the isolation of infective SVA particles in houseflies and mice suggest that these species may play a role in the epidemiology of the infection. The movement of people, primarily on-farm employee entry, and vehicles, especially those used for the disposal of carcasses and feed delivery, farm tools and equipment, including those used for carcass removal, were also implicated as possible means of introduction and indirect transmission routes of SVA in different pig breeding herds (2, 10).

Molecular analysis of SVA strains

After the occurrence and the increasing incidence of SVA-associated vesicular disease in Brazil, China, the United States, Canada, and China, complete and partial SVA genomic sequences were determined from SVA strains in most of these countries. Therefore, advances were also possible in the molecular epidemiology of the virus. The complete genomic sequences of SVA from 2015 to 2016 showed high nucleotide (nt) similarities (95.8 to 99.9%) between each other and lower nt identities (93.8 to 94.6%) with the prototype strain SVV-001 (Tab. 1). The exception was the Canadian SVA strain (KC667560) from 2011, which showed 95% and 96-98.2% nt similarities with the prototype strain SVV-001 (7, 21, 22, 31, 35, 38). The whole SVA genomes have > 93.7% nucleotide identity and 97.71% amino acid identity, with the lowest identities occurring between the prototype strain SVV-001 and the U.S. SVA strains from 2015 on both the nucleotide and amino acid levels. Phylogenetic analysis of the VP1 gene of SVA RNA indicates three clades of SVA (10, 26). Clade I contains the initially identified SVA strains SVV-001, clade II includes the U.S. SVA identified between 1988 and 1997, and clade III contains global SVA strains from Brazil, Canada, China, Thailand, and the United States identified between 2001 and 2016 (10, 26). In

clade III, the sequencing of the VP1 region shows that isolates are generally clustered by country of origin (13). However, the Colombian SVA strain identified in early 2016 is more similar to U.S. isolates than to those found in Brazil (29). In 2017, new cases of SVA were reported in the United States; there were 300 cases of SVA in Wisconsin alone (www.agweb.com/article/be-extra-cautions-with-senecavirus-a/). In the same year, new cases of SVA were also detected in China (18, 30, 37), and 2016 is considered as a turning point for SVA epidemiology in China. Two different subclades of SVA were identified. Viruses that caused outbreaks before 2016 showed higher nucleotide identities with strains isolated in Canada and Brazil, but all SVA strains reported after 2016 were more closely related to SVA strains from the United States. Compared with previous strains, a certain genetic distance was determined for strains isolated in 2017, suggesting a constant and rapid evolvement of SVA (37). All SVA cases reported in China in 2017 were identified in adult pigs, including finishing pigs and sows, but piglets did not show any clinical signs of disease. A phylogenetic analysis based on the complete genome sequence indicated that this virus was closely related to the SVA strain from 2015, indicating that this SVA isolate had emerged in China (34). In November 2018, three new SVA strains were identified in the Henan province of China, and phylogenetic analysis was conducted. The isolates showed 98.1-99.0% genomic identity with each other and the highest similarity, of 98.3-98.7%, to the American strain from 2015 (34). Guo et al. (6) found that the recombination among SVA strains occurred in China beginning from 2016 or earlier; the results of these studies updated the prevalent status of SVA in China. Furthermore, phylogenetic analysis of novel SVA isolated in the Guangxi province in South China was performed (33). The results of these studies and sequence alignment indicated that the SVA CH-GX-01-2018 strain was closely related to the SVA strains from 2017 from the Guangdong province (30), a neighbouring province of Guangxi, with 98.6% identity at the genome nucleotide level. In 2018, SVA was detected for the first time in Vietnam, and the complete sequence of the novel SVA isolate was presented (1). This sequence had 98.5% to 99% homology with iso-

Tab. 1. Nucleotide and amino acid percentage identities of Senecavirus strains

Senecavirus strain	SVV-001 (2002)	U.S. strains (2015)	Brazilian strains (2015)	Canadian strains (2011)	Chinese strains (2015)
SVV-001 (2002)		93.78-93.93 ^a	94.22-94.32 ^a	95.11 ^a	94.39 ^a
U.S. strains (2015)	97.71-97.94 ^b	98.91-99.33 ^a 99.77-99.91 ^b	97.68-97.85 ^a	95.93-96.08 ^a	96.71-96.81 ^a
Brazilian (2015)	97.76 ^b	99.27-99.31 ^b	99.50-100.00 ^a 99.59-100 ^b	96.51-95.55 ^a	97.10-97.14 ^a
Canadian (2011)	98.54 ^b	98.67-98.91 ^b	98.63-98.99 ^b	NA ^a NA ^b	96.70 ^a
Chinese (2015)	98.40 ^b	98.99-99.04 ^b	98.9-98.99 ^b	99.13 ^b	NA ^a NA ^b

Explanations: a – nucleotide; b – amino acid, NA – not applicable

lates from China from 2015 and 2016. The detection of SVA in Vietnam is highly important as a demonstration of further spread of this geographically constrained pathogen. It should also be noted that the cocirculation of FMDV and SVA in Southeast Asia hinders control efforts for both viruses and could potentially lead to emergence of novel viruses through recombination. SVA circulation should be monitored through periodical diagnostic examinations of biological samples from symptomatic and asymptomatic pigs from different sites in the production unit. In addition to serological tests, molecular, immunohistochemical, and in situ hybridization tests can be performed. Depending on the laboratory methodology used, a variety of biological samples can be analysed, such as vesicular and oral fluids and organ/tissue fragments of pigs at different ages, especially tonsils, lymph nodes, spleen, heart, lungs, liver, kidneys, and urinary vesicles (9, 15). The introduction of susceptible pigs into the farm as sentinel animals can also be practiced with great discretion. Suckling animals, especially piglets up to one week of age, should consume adequate or high quantities of high-quality colostrum and be kept in an appropriate environment that provides comfort and welfare to newborns and sows.

Evolution of SVA

It is well known that abundant genetic diversity observed in many RNA viruses has important consequences for viral pathogenesis, host tropism, and evolution (5). Two predominant mechanisms contribute to the variability of RNA viruses: the error-prone RNA-dependent RNA polymerase (RdRp) that lacks proofreading ability, which leads to high mutation rates, and recombination, whereby chimeric viruses can be generated after co-infection of the same cell by two closely related viruses. Recombination is proposed to be a key evolutionary mechanism in RNA viruses that is required to purge the genome of deleterious mutations that accumulate after error-prone replication (27). Recent studies indicate that RdRp fidelity is also associated with the recombination efficiency of SVA (17). The authors developed a SVA-specific cell culture-based recombination assay, which was used to elucidate the role of RdRp in SVA recombination. The results indicate that this polymerase plays a central role in SVA replicative recombination. In addition, the results obtained showed that the two recombination-deficient variants had higher replication fidelity than the wild type (WT) and displayed decreased ribavirin sensitivity compared to the WT. These results have important implications for understanding the crucial role of RdRp in virus recombination and fitness, especially in the molecular mechanism of SVA evolution and pathogenicity (17). Xu et al. (35) have reported the results of the analysis of complete coding sequences of SVA from 2 clinical cases and 9 assembly yard environmental samples collected in 2015 in Canada, along

with previously released complete genomes in the GenBank. With this combined data set, the evolution of SVA over a 12-month period in 2015/2016 was evaluated. These SVA isolates were characterized by a rapid accumulation of genetic variations driven mainly by a high nucleotide substitution rate and purifying selection. In addition, 25 fixed non-synonymous mutations were identified across these strains, compared to the prototype SVA strain (SVV-001). The results suggest that a combination of evolutionary processes, such as multiple mutations at variable sites and purifying selection, drove the genetic diversity observed in the current SVA strains. This study highlights the importance of monitoring SVA mutations for their role in increased virulence and impact on SVA diagnostics (35). The genetic diversity and evolution of SVA has recently been studied by comparing full-genome sequences of historical SVA strains (before 2010) with global contemporary SVA strains (after 2011) (11). The results from the genetic analysis revealed 6.3% genetic divergence between historical and contemporary SVA isolates. Selection pressure analysis revealed that SVA polyprotein is undergoing selection, with four amino acid (aa) residues located in the VP1, 2A, 3C and 3D coding regions being under positive/diversifying selection. Several aa substitutions were observed in the structural capsid proteins VP1, VP2 and VP3 of contemporary SVA isolates when compared to historical SVA strains. Some of these aa substitutions led to changes in the surface electrostatic potential of the structural proteins. This study provides an important insight into the molecular evolution and epidemiology of SVA (11).

Prophylaxis of SVA infection and biosecurity measures

There are no treatments or vaccines available for SVA infection (13). Therefore, sanitary practices should include prophylactic and control measures that include the herd, the animals and the environment. Measures should be taken to avoid the introduction of the virus into pig herds and, in infected herds, to avoid virus dissemination among animals of different pig-producing categories in the same herd. The introduction of SVA can be prevented by adopting strict biosecurity measures. The entry of vehicles, equipment, people, animals, and food into the pig production unit must be strictly controlled (10, 26). Livestock trailers and carcass removal equipment were subjectively assessed as the most likely routes of SVA introduction in a risk-assessment study. Biosecurity measures for people movement events should also be addressed. On-farm employees should shower-in or shower-out of the facility, change clothing and boots prior to entry, and observe a period of downtime after contacting other swine (26). In SVA-positive farms, in addition to the measures previously mentioned, strict cleaning and disinfection of the facilities and equipment have to be

adopted. The effectiveness of disinfectants against SVA is not yet well-known. Since clinical signs caused by SVA infection are very similar to those caused by the FMD virus, control measures should be adopted that consider the possibility of FMDV circulation, including disinfection protocols. This includes the use of 2% sodium hydroxide, 4% sodium carbonate, 0.2% citric acid, 2% acetic acid, 3% sodium hypochlorite and chloride dioxide.

Oncolytic activity of SVA

SVA does not affect humans and it is not pathogenic to normal human cells (12), but it is an oncolytic virus that can propagate in human tumour cells. SVA is the first oncolytic picornavirus to be tested in humans and to penetrate solid tumours through the vascular system, unlike many other oncolytic viruses. SVA has potential cytolytic activity and high selectivity for tumour cell lines with neuroendocrine properties versus adult normal cells (23). *In vitro* cytotoxicity and virus production assays have been performed on several tumour cell lines to determine the relationship between cytotoxicity and virus replication. Viral replication assays proved that SVA was capable of invading and replicating over time in tumour cells, but not in normal cells, such as hepatocytes. Systematically administered SVA resulted in a remarkable decrease in tumour growth (23). A first-in-human, first-in-class Phase I clinical evaluation of SVA in patients with small cell lung cancer with neuroendocrine features was also conducted, which indicated that SVA was safe and had antitumor activity in patients (24). It has also been shown that SVA can kill human retinoblastoma cells *in vitro* (32). Histopathologic analysis of ocular and brain tissues after a single tail vein injection of SVA showed effective treatment of choroid and ocular nerve tumour invasion and prevention of metastasis in the central nervous system (CNS). Liu et al. (19) examined the therapeutic efficacy of SVA and the mechanism of tumour cell infection in pediatric malignant gliomas. SVA was able to directly lyse tumour cells cultured from patient tumours and to infect glioblastoma cells grown as neurospheres. As a result, this virus eliminated about 80% of xenograft tumours after 4 weeks of treatment. The authors conclude that SVA possesses strong antitumor activity against pediatric malignant gliomas and utilizes $\alpha 2,3$ -linked and $\alpha 2,6$ -linked sialic acids as mediators of tumour cell infection (19). Other studies on the oncolytic activity of SVA against 23 pediatric cancer cell lines showed that neuroblastoma and alveolar rhabdomyosarcoma (RMS) were the most sensitive tumour types (20). The results of the abovementioned *in vitro* studies, demonstrating cell killing at very low viral concentrations, identified SVA as a potent oncolytic virus towards neuroendocrine cancer cell lines and a potential therapy for recurrent/resistant tumours expressing neuroendocrine features. In a similar study using tumour-based orthotopic xeno-

graft mouse models, Yu et al. (36) confirmed that SVA killed the primary cultured xenograft cells and eliminated tumour cells capable of forming neurospheres *in vitro* in 5 out of 10 xenograft models. Mice receiving SVA had a significantly greater survival compared to controls, with a median of 141.6 ± 25.2 days in mice with smaller tumours receiving SVA compared to 63.8 ± 4.2 days in their matched controls. Summarizing the potential antitumor activity of Senecavirus in human cancer therapy, it can be stated that SVA appeared to be an ideal oncolytic virus given its ability to penetrate tumours and rapidly replicate, as well as its non-integrating RNA genome, non-pathogenicity, low incidence of pre-existing immunity in humans and selectivity for tumours expressing neuroendocrine features (3).

In conclusion, recent information on the SVA infection in many regions of the world suggests that SVA is not restricted to a specific geographic region and may well be distributed on the global scale in the future. Knowledge about SVA should therefore be widely propagated, and epidemiological investigations should be conducted in countries where the virus has never been detected, especially in those with extensive pig production, where SVA infection may have more economic relevance. Surveillance, epidemiological investigations and genetic characterization of SVA, which is associated with vesicular diseases and neonatal mortality in pigs, are important for controlling SVA and supporting the development of specific and effective diagnostic tests. The quick establishment of the etiological agent of a disease is essential for rapid adoption of control measures, mitigating or preventing the local, regional or international dissemination of the infectious agent. The lack of available commercial vaccines and the fact that SVA is not included in the OIE Terrestrial Animal Health Code, means that the increasing incidence of SVA infection in pigs in different countries will continue to cause unpredictable and substantial outbreaks. Therefore, in response to this threat, animal administration authorities and farm veterinarians must show continued awareness of this disease and remain vigilant in their surveillance, treatment, and provision of effective control measures.

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