Acta virologica **66**: 101 – 109, 2022 doi: 10.4149/av_2022_210

MINIREVIEW

Apoptosis mechanisms induced by parvovirus infections

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Received June 17, 2021; revised November 5, 2021; accepted April 11, 2022

Summary. – Parvoviruses affect both vertebrates and invertebrates, and can be both detrimental and benign to the host. Numerous studies about parvovirus-induced apoptotic cell death have been researched and reported. In most parvovirus infections, cell death heightens the virus dissemination and causes tissue damage, often leading to disease. Cell cycle arrest also induces cytopathic effects in infected cells and is sometimes a prerequisite to apoptotic cell death. Cell death mechanisms caused by parvovirus infections vary depending on the infecting parvovirus strain and the cell lines involved. Apoptosis, however, is a frequent form of cell death induced by parvoviruses. The non-structural protein 1 (NS1) is a major contributor to parvovirus infection-induced cell death. However, other proteins such as the 11 kDa, NP1 and viral genome replication can also induce cell death. Understanding the mechanisms involved in parvovirus cell death, and host response is important in the development of treatment for cytopathic parvoviruses. This review article discusses parvovirus-induced apoptotic cell death and the mechanisms involved.

Keywords: apoptosis; cell cycle arrest; cell death; parvovirus; viral protein

Introduction

Parvoviruses have been in existence for millions of years (Kailasan *et al*., 2015). They are small, icosahedral and non-enveloped viruses. Their genome is made up of 4–6 kb ssDNA molecules, which form hairpin structures responsible for replication (Cotmore *et al*., 2019). They belong to the family of viruses known as *Parvoviridae* and are classified under three subfamilies *Densovirinae*, *Parvovirinae* (Kapgate *et al*., 2018; Cotmore *et al*., 2019; Pénzes *et al*., 2020), and *Hamaparvovirinae* (Pénzes *et al*., 2020). Members of the subfamily *Densovirinae* and *Parvovirinae* are known to infect invertebrates and vertebrates, respectively. *Hamaparvovirinae* is a newly established subfamily based on host association and infects both invertebrates and vertebrates (Pénzes *et al*., 2020). In this article, our focus will be on the *Parvovirinae* subfamily. Cell death can be used as a defense mechanism by the host for halting the viral replication and eliminating infected cells (Upton and Chan, 2014; Jorgensen *et al*., 2017; Orzalli and Kagan, 2017). However, the infecting virus may use cell death as a means of survival, multiplication, and spread, leading to tissue damage and subsequent progression of the infection (Danthi, 2016; Zhou *et al*., 2017). Viruses can trigger different forms of cell death, including apoptosis, necrosis, and pyroptosis (Danthi, 2016; Imre, 2020). The outcome of disease due to parvovirus infections is a result of cytopathic effects such as cell death and cell cycle arrest (Kailasan *et al*., 2015). However, apoptotic cell death is the most dominant form of cell death caused by most parvovirus infections. Apoptosis is the most common and extensively studied noninflammatory form of cell death resulting from viral infections. Unlike other

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Abbreviations: CPV = canine parvovirus; HBoV = human bocavirus; MVM = minute virus of mice; MVMp = minute virus of mice fibrotropic strain; NS-1 = non-structral protein 1; PK-15 cells = porcine kidney-15 cells; PPV = porcine parvovirus; PTC = porcine placental trophoblast cells; ST = swine testis cells

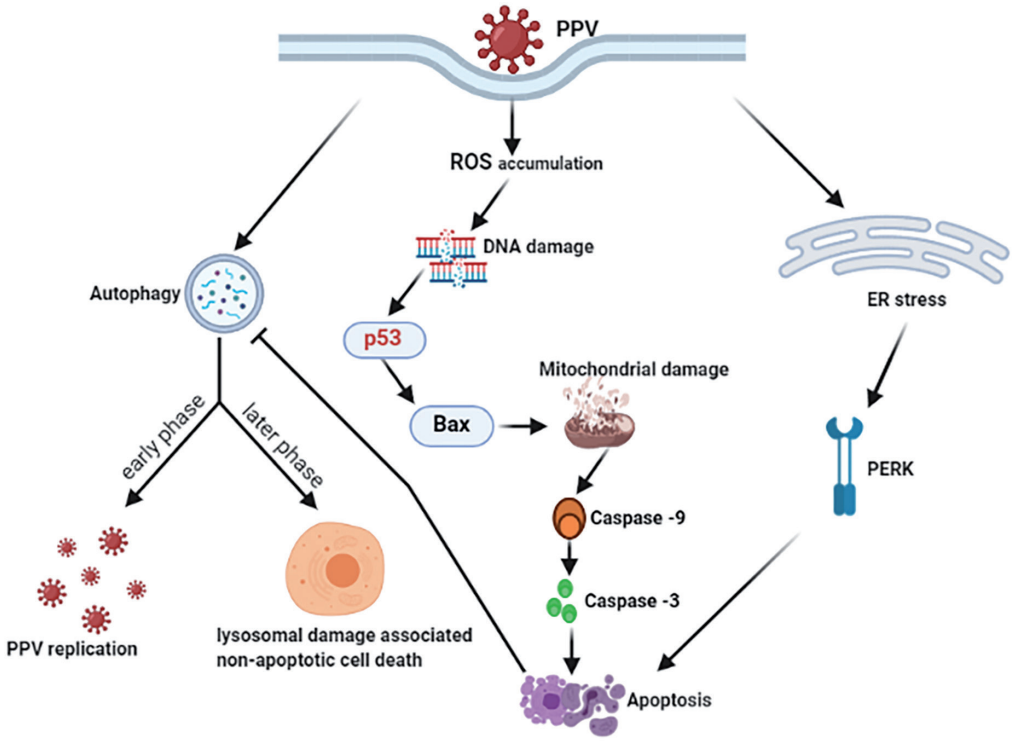

Fig. 1

Mechanism of PPV-induced apoptosis

Pig placenta damage leading to reproductive failure in PPV infected sows is attributed to ER stress and mitochondria-mediated apoptosis. Autophagy supports PPV viral replication, which leads to persistent viral infection and pathogenicity.

forms of passive cell death, apoptosis is an active process and involves the activation, expression, and regulation of genes. Apoptosis resulting from viral infections can have both positive and negative effects on the affected cells. The host organism may use apoptosis to get rid of infected cells. Some viruses, however, use apoptosis as a way of releasing and disseminating new viral particles.

A surge of caspase activation precedes apoptotic events (Tait and Green, 2010; Danthi, 2016). Intrinsic and extrinsic pathways are the two paramount pathways involved in apoptotic cell death. Both pathways bring about similar effector caspases that intensify the initial death signal. The response to stimulation of the tumor necrosis factor receptor (TNFR), TNF-related apoptosis-inducing ligand (TRAIL) receptor, and Fas-ligand receptor (FASL) by extracellular stimuli leads to the induction of the extrinsic apoptotic pathway. As a result of the stimulation, caspase -8 and -10 are activated, followed by the activation of other caspases, which eventually leads to apoptosis. On the other hand, the intrinsic apoptotic pathway results from intracellular stress response such as DNA damage, oxidative stress, ER stress, and cytokine deprivation. Following these events, the mitochondrial membrane becomes permeable and leads to the release of molecules such as cytochrome c into the cytosol, and eventual activation of caspase-9 and subsequent cell death. Reactive oxygen species (ROS) or the Bcl-2 protein family play a key role in controlling the permeability of the mitochondrial membrane (Orzalli and Kagan, 2017; Zhou *et al.*, 2017; D'Arcy, 2019).

Apoptosis may be an essential step in the life cycle of the infecting virus and its pathogenicity by enabling the release of virions (Kvansakul, 2017; Zhou *et al.*, 2017). Pro-apoptotic signaling could be advantageous to the infecting virus by weakening the host cell innate immune response (Rajput *et al.*, 2011).

Porcine parvovirus

Porcine parvovirus (PPV) is a pathogen that affects the reproductive system of porcine, causing reproductive failure in pregnant porcine and the death of fetuses. The virus induces physiopathological and cytopathogenic effects in the host. Pathological effects may include infertility, embryonic death, mummified or stillborn fetuses in affected hosts (Mészáros *et al.*, 2017; Zhang *et al.*, 2018; J. Zhang *et al.*, 2019).

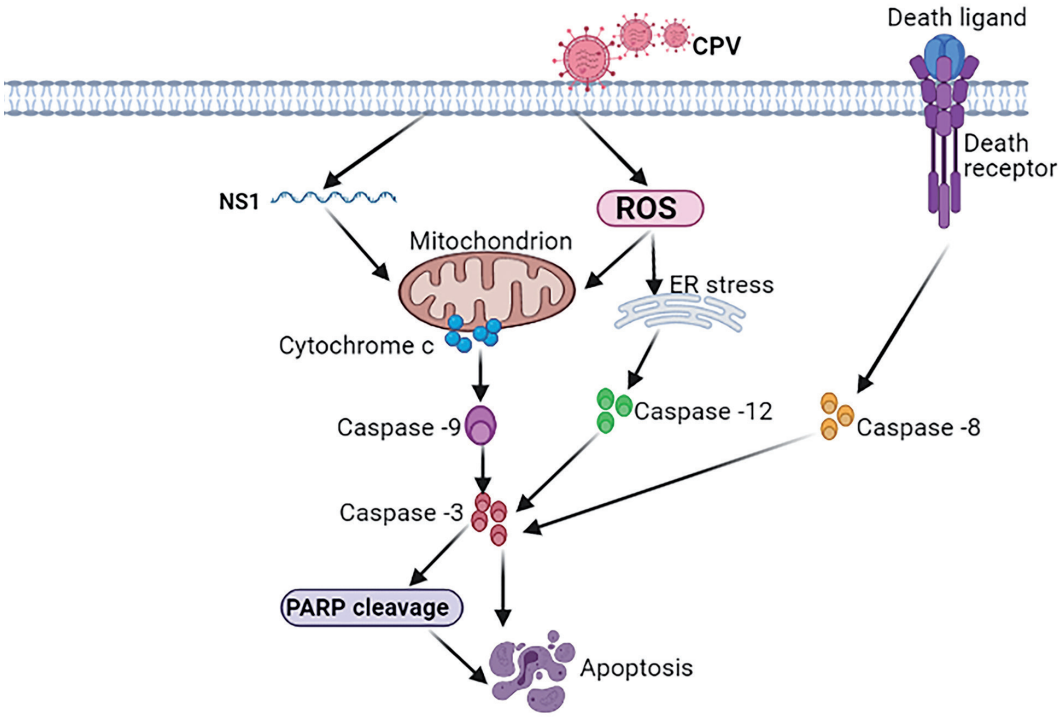

Fig. 2

Schematic representation of CPV-induced apoptosis

Apoptosis occurs via the intrinsic, extrinsic and ER stress-induced apoptotic pathways. The NS1 protein is the main protein that induces intrinsic apoptosis and the p53 gene is not involved in the NS1-induced apoptosis.

Investigation to assess PPV apoptosis mechanisms have been conducted using various cell lines, including Porcine kidney (PK)-15 cells, Swine testis (ST) cells, porcine steroidogenic luteal cells (SLCs), porcine placental trophoblasts (PTCs) (Zhang *et al*., 2015; Zhao *et al*., 2016; Zhang *et al*., 2018; J. Zhang *et al*., 2019). PPV induces apoptosis in infected cells by activating caspases-9 and -3, suggesting that apoptosis induced by PPV occurs via the intrinsic apoptotic pathway. Changes in nuclear morphology consistent with apoptosis were observed; the nucleus and chromosomal DNA were fragmented, and chromatin condensed (Mészáros *et al*., 2017; J. Zhang *et al*., 2019; X. Zhang *et al*., 2019; Cao *et al*., 2020). In PK-15 cells and ST cells, apoptosis occurs through the mitochondrial pathway by inducing the accumulation of reactive oxygen species (ROS) (Zhang *et al*., 2015; Zhao *et al*., 2016; Zhang *et al*., 2018; J. Zhang *et al*., 2019). PPV activates the mitochondria-mediated apoptotic pathway by activating the p53 tumor-suppressing gene. The p53 gene regulates the activation of Bax, a pro-apoptotic protein, hence, making the mitochondria highly permeable and triggering the apoptosis (Zhang *et al*., 2018). When studied in PK-15 cells, the non-structural protein 1 (NS1) of PPV was the principal protein responsible for the induction of mitochondria-mediated apoptosis. NS1 stimulated the accumulation of reactive oxygen species (ROS) within the cells and the mitochondria, resulting in mitochondrial and DNA damage, and cell cycle arrest in phases G1 and G2, which eventually led to apoptosis (J. Zhang *et al*., 2019). Therefore, during PPV infection, the NS1 protein is involved in viral replication, cell cycle inhibition and apoptosis of host cells. NS1 could be targeted at different stages of the viral infection and become a target for possible treatment of PPV infection.

In PK-15 and PT cells, the replication of PPV is repressed by the endoplasmic reticulum (ER) stress-induced apoptotic cell death (Cao *et al*., 2020). The ER-stressed cells stimulate the unfolded protein response (UPR) pathway, which is mediated by signaling pathways such as the protein kinase R-like endoplasmic reticulum kinase (PERK) pathway, and this eventually leads to the apoptosis (Mészáros *et al*., 2017; Cao *et al*., 2020). However, ER stress induced by a small alternatively translated (SAT) protein increases viral spread in PT cells (Mészáros *et al*., 2017). This indicates that the ER stress-induced apoptosis could be used to prevent viral spread by inhibiting the activation of the SAT protein.

Non-apoptotic cell death characterized by lysosomal damage was also observed in PPV-infected PTCs. The

results of the study indicate that non-apoptotic death has a link to autophagy. In the later phase of infection, autophagy suppresses apoptosis and promotes non-apoptotic cell death, which enhances the PPV infection (X. Zhang *et al.*, 2019).

Overall, autophagy, NS1-induced apoptosis and the SAT protein-induced ER stress seem to favor PPV viral spread and infection. Therefore, these mechanisms could be explored as potential targets for anti-PPV therapy.

Canine parvovirus

Canine parvovirus (CPV) causes enteritis and myocarditis in dogs. It is not a localized infection and thus affects several organs of an infected animal. Animals that survive the disease might develop other severe illnesses such as gastroenteritis (Kilian *et al.*, 2018). Due to viral mutation, two new variants, CPV-2a and CPV-2b, have been identified. (Goddard and Leisewitz, 2010; Miranda and Thompson, 2016).

CPV infection induces host cell cycle arrest and DNA damage, along with apoptosis. Cell cycle arrest at the G1 phase was observed in HeLa cells and MDCK cells transfected with CPV (Doley *et al.*, 2014; Gupta *et al.*, 2016). An increase in cyclin kinase inhibitor p27 was observed in transfected cells prior to cell cycle arrest (Dai *et al.*, 2020; Gupta *et al.*, 2016). The upregulation of p27 prevents cells from leaving the G1/S phase and entering the S phase by binding to cyclins D/CDK4 or E/CDK2, hence inhibiting the cyclins activation (Léger *et al.*, 2016). In CPV-infected cells, apoptotic cell death was attributed to ROS accumulation (Gupta *et al.*, 2016) and activation of caspases -3,-8,-9, and -12, indicative of extrinsic, intrinsic, and ER pathways (Doley *et al.*, 2014; Gupta *et al.*, 2016). The NS1 protein of CPV induces apoptosis and cell arrest at the G1 phase. The cells transfected with NS1 were characteristic of DNA fragmentation due to endonuclease activation. Other characteristics include phosphatidylserine translocation, increased hypodiploid cells, chromatin condensation, nuclear condensation, the release of cytochrome c into cytosol, and increased caspase-3 activity (Gupta *et al.*, 2016; Saxena *et al.*, 2013). Inactivity of the p53 gene indicates that NS1-induced apoptosis was p53 independent (Saxena *et al.*, 2013). The activation of caspase -3 by NS1 leads to the cleavage of the PARP protein, the protein responsible for the detection of breaks in DNA strands and the DNA repair (Gupta *et al.*, 2016).

In CPV-infected cells, apoptosis is the primary form of cell death. However, when the infection is prolonged, the cells undergo secondary necrosis. Nykky *et al.* (2010) reported that NFLK cells infected with CPV showed changes characteristic of necrosis; the cells lysed, releasing cell debris, and cell inflammation occurred. The cell plasma was disrupted and became permeable, and nuclear blebbing occurred. Necrosis observed in the study could be attributed to the absence of phagocytes or the inability to eliminate apoptotic cells (Nykky *et al.*, 2010).

Human parvovirus B19

The human parvovirus B19 (B19V) attacks the $CD36^{+}$ erythroid progenitors, the bone marrow, and the liver of a fetus in pregnant women. Destruction of erythroid progenitors and erythroblasts in the bone marrow by the virus leads to the manifestation of symptoms such as decreased red blood cell production, which eventually leads to anemia (Landry, 2016; Servant-Delmas and Morinet, 2016; Qiu *et al.*, 2017; Mende and Sockel, 2018; Sim *et al.*, 2019).

The lack of a permissive cell culture system has hindered *in-vivo* studies of cytopathic effects of BI9V. The virus affects a small number of cells, which include erythroblastoid cell line UT7/Epo-S1 (Wong *et al.*, 2008; Luo *et al.*, 2013; Xu *et al.*, 2017), erythroid progenitor cells (Wong *et al.*, 2008), or circulating angiogenic cells (CACs) (Schmidt-Lucke *et al.*, 2015). The cytopathic effect in B19V-infected cells occurs as a result of cell cycle arrest and apoptosis. Cell cycle arrest occurs early during infection and could be responsible for the cytopathic effect during the early infection phase. In infected cells, cell arrest occurs at the G2/M phase and is primarily induced by the NS1 protein through the ATR-CHK1-CDC25C-CDK1 pathway. NS1 transactivates the C-terminal domain and the signaling from ATR to CDC25C. During normal cell cycle progression, CDC25C dephosphorylates and activates CDK1, a promoter of cell transition to mitosis. However, during B19V infection, CDC25C phosphorylation prevents the dephosphorylation and activation of CDK1, which leads to the formation of an inactive B1-CDK1 complex. After import into the nucleus, the inactive B1-CDK1 complex blocks the cell progression from G2 to M phase, leading to G2/M cell cycle arrest (Xu *et al.*, 2017, 2019; Zou *et al.*, 2018). B19V-induced host cell apoptosis occurs via the intrinsic pathway in non-permissive cells and the extrinsic pathway in permissive cells and involves the activation of caspases. As in most parvoviruses, the NS1 protein plays a critical role in apoptosis, with its NTF binding motif being responsible for inducing apoptosis (Poole *et al.*, 2011; Schmidt-Lucke *et al.*, 2015). Other key players are the VP1 (Schmidt-Lucke *et al.*, 2015) and the small 11 kDa NS protein. Apoptosis induced by the 11 kDa NS protein in erythroid progenitor cells involves the activation of caspase-10. The rate of apoptosis induced by the 11 kDa NS protein is almost 100 times greater than that induced by the NS1 protein (Chen *et al.*, 2010; Schmidt-Lucke *et al.*, 2015; Tzang *et al.*,

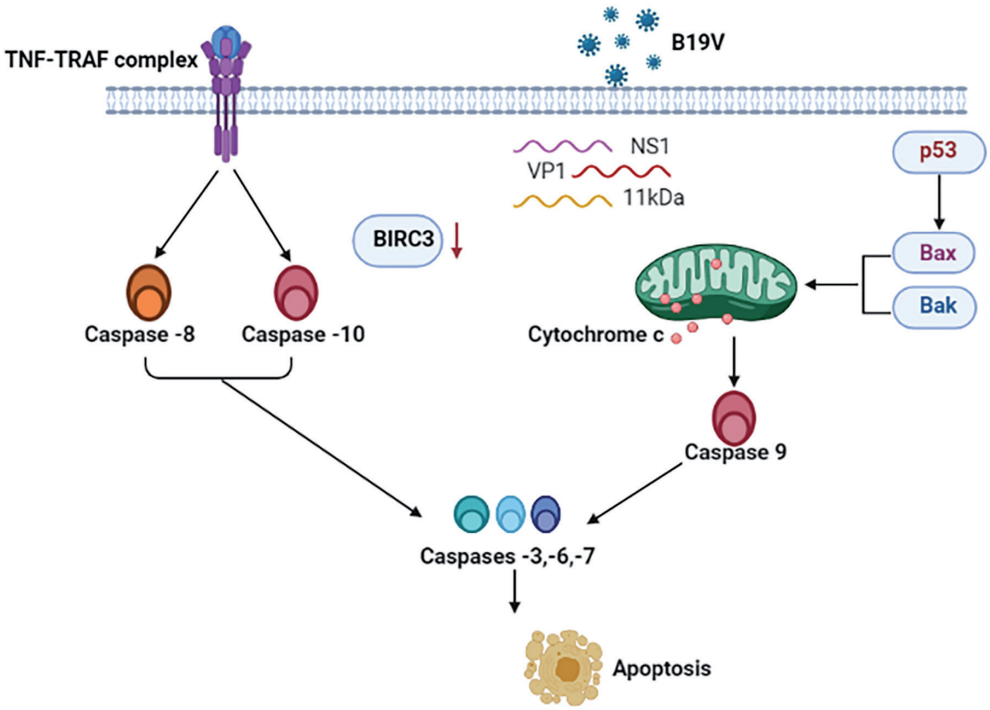

Fig. 3

Mechanism of B19V-induced apoptosis

Apoptosis occurs via both the intrinsic and extrinsic pathway with the NS1, VP1 and 11 kDa proteins playing major roles in the apoptosis induction.

2016; Zobel *et al.*, 2019). During infection, B19V suppresses the mRNA levels of Baculoviral Inhibitor of apoptosis Repeat-Containing protein 3 (BIRC3), an apoptosis inhibitor that impedes apoptosis by hindering the activation of caspases-3, -6, -7, -8, and -9 (Schmidt-Lucke *et al.*, 2015; Zobel *et al.*, 2019). Therefore, in the intrinsic pathway, the suppression of BIRC3 enables cytochrome c activation of caspase-9, leading to the activation of caspases-3, -6, and -7. The expression of the p53 gene and apoptotic signaling proteins Bax and Bad increases. However, in the extrinsic pathway, suppression of BIRC3 enables the formation of a complex with the TNF-receptor associated factor 1 (TRAF1), TRAF2, and TNFα receptor, thus activating caspase-8 and -10. Apoptotic cell damage caused by anti-B19 antibodies may damage the placenta's protective barrier formed by trophoblasts and lead to severe disorders, such as fetal death and anemia during pregnancy.

Human bocavirus

Human bocavirus (HBoV) infection is an infection of both the upper and lower respiratory tract. It affects children and adults with compromised immune systems (Guido *et al.*, 2016; Qiu *et al.*, 2017; Christensen *et al.*, 2019; Lee *et al.*, 2019; Bakir *et al.*, 2020). The viral infection leads to inflammation and injury of human epithelial cells (Qiu *et al.*, 2017; Christensen *et al.*, 2019). However, the viral pathogenicity is yet to be fully understood because the infection usually occurs with other co-infections, which may be viral or bacterial respiratory or gastrointestinal infections. The lack of animal models is another hindrance to overcoming the difficulties experienced in replicating the virus in the in-vitro cell culture (Guido *et al.*, 2016).

In-vitro analysis of HBoV infection in HeLa cells and human bronchial epithelial cells revealed that apoptosis induced by HBoV infection occurred via the mitochondria-mediated pathway and involved the activation of caspases-9 and 3 as well as an increase in the expression levels of pro-apoptotic protein Bax (Sun *et al.*, 2013; Deng *et al.*, 2017). In HeLa cells, the nuclear phosphoprotein (NP1) is the principal protein responsible for the induction of apoptosis, and its N-terminal domain is critical to its nuclear localization. Apoptosis induced by NP1 is not responsible for HBoV replication and protein expression. Before apoptosis, cell cycle arrest at the G2/M phase was observed and rapidly obliterated after the onset of apoptosis (Sun *et al.*, 2013).

Table 1. Summary of cytopathic effects induced during parvovirus infection

Virus	Viral protein involved in CPE	Cell cycle arrest phase	Apoptotic pathway	Cell lines used	References
PPV	NS1	G1 and G2	Intrinsic	Porcine kidney (PK)-15 Swine testis (ST) Porcine placental trophoblasts (PTCs)	Cao *et al*., 2020; Mészáros *et al*., 2017; Zhang *et al*., 2015; J. Zhang *et al*., 2019; X. Zhang *et al*., 2019; Zhao *et al*., 2016
CPV	NS1	G1	Extrinsic Intrinsic ER specific	HeLa MDCK NFLK	Dai *et al*., 2020; Doley *et al*., 2014; Gupta *et al*., 2016; Léger *et al*., 2016; Saxena *et al*., 2013
B19V	11kDa NS1 VP1	G2/M	Extrinsic in permissive cells Intrinsic in non-permissive cells	UT7/Epo-S1 Erythroid progenitor cells	Chen *et al*., 2010; Luo *et al*., 2013; Poole *et al*., 2011; Schmidt-Lucke *et al*., 2015; Tzang *et al*., 2016; Wong *et al*., 2008; Xu *et al*., 2017; Zobel *et al*., 2019
HBoV	NP1	G2/M	Intrinsic	HeLa Human airway epithelial	Deng *et al*., 2017; Sun *et al*., 2013
MVM H-1PV	NS1	S and G2 G2/M	Intrinsic	Fibroblasts	Adeyemi and Pintel, 2012, 2014; Mincberg *et al*., 2011; Op De Beeck *et al*., 2001 Hristov *et al*., 2010; Lacroix *et al*., 2018

However, in human airway epithelial cells, HBoV infection-induced cell death was mediated by pyroptosis and not apoptosis. Pyroptosis is characterized by caspase-1 activation, increased levels of pro-inflammatory cytokines IL-1α and IL-18, and up-regulation of anti-apoptotic genes BIRC5 and IFI6, which suppress apoptosis. Unlike apoptosis, which suppresses the HBoV viral replication, pyroptosis enables the establishment of a persistent airway infection by the virus. The change in response may have developed to confer a replicative advantage, allowing it to establish a persistent infection (Deng *et al*., 2017).

Rodent autonomous parvoviruses

Rodent autonomous parvoviruses include the minute virus of mice (MVM) and H-1PV. Unlike other parvoviruses, these viruses are harmless and naturally possess oncolytic properties (Akladios and Aprahamian, 2016; Angelova and Rommelaere, 2019). Oncolytic viruses preferentially induce cell death in cancerous cells without affecting the healthy cells.

Rodent parvoviruses induce cell cycle arrest during infection. During MVM infection, cell cycle arrest occurs at the S and G2 phases (Adeyemi and Pintel, 2012, 2014), whereas in H-1PV infection, cell arrest is at the G2/M phase (Hristov *et al*., 2010). The S phase cell cycle arrest in MVM-infected cells was p53-dependent but independent of p21. G2 phase cell cycle arrest was dependent on both p53 and p21 (Op De Beeck *et al*., 2001).

Minute virus of mice fibrotropic strain (MVMp)-induced cell death in transformed fibroblast cells was shown to be p53 independent, occurring via the mitochondria-mediated pathway. Post-infection, the mitochondrial membrane was depolarized in a time-dependent manner, and cell death increased. Caspases-3 and -9, BAX, Apafl, and cytochrome c also increased, indicating the activation of the mitochondrial apoptotic pathway by MVMp (Mincberg *et al*., 2011).

H-1PV can induce selective cytotoxicity in cells by targeting tumor cells (Lacroix *et al*., 2010). Cell death in neuroblasts and Ewing sarcoma cell lines infected with H-1PV was caused by apoptosis. Viral replication and release of progeny viruses were linked to cell death. Apoptotic cell death was associated with the activation of caspases-3 and -9, accumulation of ROS, and PARP cleavage (Hristov *et al*., 2010; Lacroix *et al*., 2018). Cells that expressed H-1PV NS1 protein were apoptotic and this showed that expression of NS1 alone is sufficient to elicit cell death. ROS accumulation, DNA damage, mitochondria membrane permeability, and caspase activation were observed in NS1-expressing cells (Hristov *et al*., 2010).

In other cell lines, H-1PV can cause cell death via cathepsin B-dependent cell death (Bretscher and Marchini, 2019). The overexpression of Bcl 2 in glioma cells enables the cells to be resistant to apoptosis inducers and thus prevent apoptosis induced by H-1PV. H-1PV caused cathepsin B-dependent form of cell death by relocating the active cathepsins B and L from the lysosomes into the cytosol and repression of cathepsin inhibitors B and C, enabling the virus to overcome the apoptosis resistance

of glioma cells to cytotoxic agents and soluble ligands such as TRAIL (Di Piazza *et al.*, 2007).

Table 1 summarizes the apoptotic pathways induced by the discussed parvoviruses to elicit cytopathic effects.

Conclusion

Apoptosis is the primary form of cell death induced by most parvovirus infections. Studying the relationship between parvovirus infections and cell apoptosis helps to understand the occurrence, development, and spread of the virus and provides new ideas for virus control. Though small, parvoviruses infect different animals and are highly host-specific. While some viruses do not cause any major changes to infected cells, most viruses use different forms of cell death as a means of disseminating progeny virions. A number of virus-infected cells use apoptotic cell death as a defense mechanism. However, most parvoviruses use apoptotic cell death as a means of survival and viral spread by taking advantage of the host cell defense system. Parvoviruses have the ability to activate pro-apoptotic proteins or suppress anti-apoptotic proteins within the infected cells, hence triggering apoptosis and causing tissue damage and disease progression.

Human bocaviruses (HBoV, HBoV 2, HBoV 3) and B19V are the only parvoviruses known to infect humans, and B19V is the most pathogenic. Studying the interaction between the B19V and host cells has been limited due to the lack of a permissive cell culture system. However, the development of $CD36^{+}$ erythroid progenitor cell clones will enable more research on the virus pathogenicity. The association of human bocaviruses with disease is still unclear as it usually occurs as a co-infection with other pathogens. Dieninghoff *et al.* (2017) have reported a clinical case of fatal HBoV infection in a cystic-fibrosis patient, and therefore, more research into the virus pathogenicity should be considered. Rodent parvoviruses are important parvoviruses due to their non-pathogenic and oncolytic properties. Studies have been and are still being conducted to analyze and assess the possibilities of using rodent parvoviruses in the human cancer treatment (Lacroix *et al.*, 2018; Bretscher and Marchini, 2019; Grueso *et al.*, 2019; Ferreira *et al.*, 2020; Hartley *et al.*, 2020) and this could be a major break-through.

Parvoviruses are good experimental subjects in the study of cellular mechanisms such as cell death and DNA damage response due to their short genome and simple gene-expression profile. In addition to our current knowledge of parvoviruses, more studies should be carried out to further understand virus-induced apoptosis and the stages, at which the apoptotic pathways occur in the replication cycle of the virus. This will enable future research on the control of innate apoptotic defense mechanisms that curb viral infection and replication.

Acknowledgments. This study was financially supported by the National Key R&D Program of China (grant No. 2017YFD0500802042), the "13th Five-Year Plan" of the Science and Technology Research and Planning Project of the Education Department of Jilin Province (JJKH20190944KJ). The funders had no role in the study design.

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