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Apoptotic signaling cascades operating in poliovirus-infected cells

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1. ABSTRACT

The flaccid paralyses characteristic of poliomyelitis are a direct consequence of the infection of motor neurons with poliovirus (PV). In PV-infected mice, motor neurons die by apoptosis. However, the mechanisms by which PV induces cell death in neurons remain unclear. Analyses of the apoptotic pathways induced by PV infection in several cell lines have demonstrated that mitochondria play a key role in PV-induced apoptosis. Furthermore, mitochondrial dysfunction results from an imbalance between pro- and anti-apoptotic pathways. We present here an overview of the many studies of PV-induced apoptosis carried out in recent years and discuss the contribution of these studies to our understanding of poliomyelitis.

2. INTRODUCTION

Poliovirus (PV) is the etiological agent of acute paralytic poliomyelitis. It has three serotypes (PV-1 to -3) and belongs to the genus *Enterovirus* of the *Picornaviridae* family (1). This family contains many human and animal pathogens, including human hepatitis A virus, human rhinoviruses — the agents of the common cold — and foot-and-mouth disease virus.

Despite the success of the World Health Organization's global poliomyelitis eradication program, PV remains a public health issue in several developing countries, notably in Africa and Asia (2). This is partly due to the spread of PV in insufficiently immunized populations

and to the emergence of epidemics associated with oral polio vaccine (OPV)-derived strains (3).

Paralytic poliomyelitis involves the destruction of motor neurons associated with PV replication. In PV-infected mice, motor neurons die through apoptosis (4). However, the mechanisms by which PV induces cell death in neurons remain unclear.

Apoptosis is an active cell death process triggered by various stimuli, including viral infections (5). It is mediated by caspases, a family of cysteine proteases with specificity for aspartic acid residues. In many models, mitochondria are key regulators of apoptosis (6). Mitochondrial outer membrane permeabilization (MOMP) leads to a loss of mitochondrial transmembrane potential and the release of proapoptotic molecules, including cytochrome *c*, from mitochondria into the cytosol. In the cytosol, cytochrome *c* forms a caspase-activating complex by interacting with Apaf-1 (apoptosis protease-activating factor-1) and procaspase-9. This event triggers the activation of caspase-9, which processes caspase-3, thereby initiating the apoptotic cascade. MOMP may also result in commitment to cell death in the absence of caspase activation, through the mitochondrial release of caspase-independent death effectors, including apoptosis-inducing factor (AIF) and endonuclease G (Endo G), among others (7).

Mitochondrial apoptotic function is tightly regulated by the Bcl-2 family of proteins. Some, including Bcl-2 and Bcl-X_L, maintain mitochondrial integrity, preventing the release of cytochrome c, whereas others, such as Bax and the so-called "BH-3 only" proteins, including Bid and Bim, promote the release of cytochrome *c*.

In this review, we will provide an overview of recent findings concerning the signaling pathways leading to apoptosis in PV-infected cells and will discuss their involvement in central nervous system (CNS) injury during poliomyelitis pathogenesis.

3. POLIOVIRUS

3.1. Structure of the virion

PV consists of a single-stranded RNA genome of positive polarity surrounded by a non enveloped icosahedral protein capsid. The capsid of the mature virion is approximately 30 nm in diameter and consists of 60 copies of each of the four viral structural proteins, VP1 to VP4 (Figure 1A). A deep surface depression, the "canyon", surrounds each five-fold axis of symmetry and contains the binding site of the cell receptor (8) (Figure 1B).

The PV RNA genome is about 7,500 nucleotides long (Figure 1C). It is polyadenylated at its 3'-terminus and covalently linked to a small viral protein, VPg (3B), at its 5'-terminus (9). It contains a long 5' non coding region (NCR) followed by a single large open reading frame (ORF) and a short 3' NCR including the poly (A) tail. The ORF is translated to produce a 247 kDa polyprotein, which is processed to generate the three large precursors of the structural (P1) and non structural (P2 and P3) proteins.

3.2. Poliovirus receptor

The human PV receptor, CD155, and its simian counterparts belong to the immunoglobulin superfamily (10, 11). The members of this family are related to the nectin family of adhesion molecules found at intercellular junctions. CD155 contains three extracellular Ig-like domains (D1 to D3), followed by a transmembrane region and a short cytoplasmic tail (Figure 1B). The binding site for PV has been mapped to the N-terminal extracellular Ig domain (D1). In humans, two allelic forms of CD155 have been found, one with an Ala residue and the other with a Thr residue in D1, at amino-acid position 67 (10-13).

Despite the large body of data on CD155 accumulated in recent years, the role of this molecule in the cell remains unclear. CD155 may play a role in cell adhesion, as the ectodomain of CD155 interacts specifically with vitronectin, a constituent of the extracellular matrix (14).

In the CNS, CD155 expression is activated by the secreted morphogen sonic hedgehog protein (15), which, like vitronectin, is associated with regions of the CNS involved in the differentiation of motor neurons during embryonic development (16). The short cytoplasmic domain of CD155 has also been shown to interact with Tctex-1, a light chain subunit of the dynein motor complex (17, 18). This interaction is thought to mediate the retrograde axonal transport of endocytic vesicles containing CD155 and may therefore be responsible for the rapid retrograde axonal transport of PV-CD155 complexes.

CD155 has also been described as a tumor antigen, as it is strongly expressed in certain human tumors, including colorectal carcinoma (19) and malignant gliomas (16). CD155 may also play a key role in cell motility during tumor cell invasion and migration (20).

Finally, CD155 specifically induces NK cell activation by interacting with DNAM-1 (the leukocyte adhesion molecule DNAX accessory molecule-1), also known as CD226 (21), and with CD96, also known as tactile (T cell-activated increased late expression) (22).

3.3. Viral cycle

In vitro, PV multiplies exclusively in primate cell lines (human or simian). The viral cycle of PV proceeds entirely in the cytoplasm of the host cell and lasts approximately 8 hours at 37°C in cell culture (9).

The initial event in the viral cycle is attachment of the virion to the receptor, CD155. PV binding to CD155 destabilizes the virion and induces the conformational modifications required for RNA release (23). Two recent studies have shown that the early steps of PV infection depend on tyrosine kinase, tyrosine phosphatase SHP2 and the RhoA GTPase according to the cell model used for PV infection (24, 25). Once PV RNA has been released into the cytoplasm of infected cells, its translation is initiated by the binding of ribosomes to a highly structured region in the 5' NCR, the internal ribosomal entry site (IRES) (9). The efficient IRES-dependent translation of PV RNA requires IRES-specific cellular factors. Translation produces a large

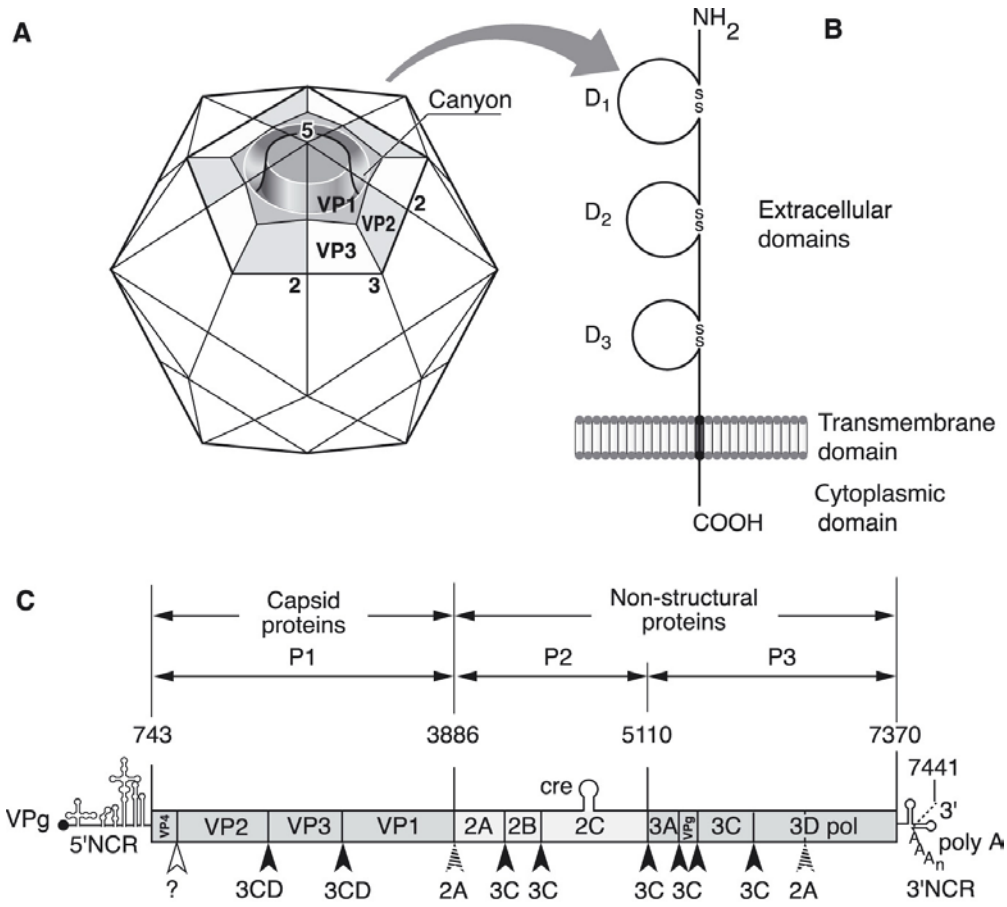

Figure 1. (A) Schematic diagram of the structure of the poliovirus capsid. The two-, three- and five-fold axes of symmetry and the positions of capsid proteins VP1, VP2 and VP3 are indicated for one protomer. Five molecules of VP1 surround the five-fold axis of symmetry, whereas VP2 and VP3 alternate around the three-fold axis of symmetry; VP4 is exclusively internal. The depression surrounding the five-fold axis, known as the canyon, is formed by residues of VP1, VP2 and VP3, and contains the site for cell receptor binding (Adapted from (8))**.** (B) Schematic diagram of the structure of CD155. The poliovirus receptor has three extracellular domains (D1 to D3), a transmembrane domain and an intracytoplasmic domain. (C). Organization of PV-1/Mahoney genome. The 5' and 3' non coding regions, labeled 5'NCR and 3'NCR, respectively, flank the single open-reading frame, encoding the polyprotein, which is shown as an elongated rectangle. The protein precursors P1, P2 and P3, are indicated by arrows above the genome. The viral proteins are indicated in the rectangles. The small viral protein VPg (also named 3B) is covalently linked to the 5' end of the RNA genome. Proteolytic cleavages occur between the amino acid pairs Asn-Ser, Gln-Gly and Tyr-Gly, as indicated by open, solid, and cross-hatched arrowheads, respectively. The cleavage sites of proteases 2A, 3CD and 3C are shown. The mechanism of cleavage of the precursor, VP0, to give VP4 and VP2, is unknown (adapted from (100)).

polyprotein, which is processed co- and post-translationally by the viral proteases 2A, 3C, and its precursor 3CD (Figure 1C). This releases the structural and non structural proteins responsible for the proteolytic activities, RNA synthesis and biochemical and structural changes occurring in the infected cell.

Viral RNA replicates on the surface of membranous vesicles budding from various host cell organelles, such as the endoplasmic reticulum and Golgi apparatus (26). These vesicles are induced by two viral proteins, 2BC and 3A, in a process related to autophagy (27, 28). In this way, PV increases the availability of cellular and viral components for its own replication. PV RNA is replicated by the viral RNA-dependent RNA polymerase 3Dpol, with most of the other non structural PV proteins and cellular factors also involved in viral RNA synthesis. RNA replication starts with the formation of a complementary negative-stranded RNA molecule, which serves as the template for the synthesis of progeny positive-stranded viral RNAs (9).

The formation of viral particles seems to be coupled to RNA replication. Once assembled, the virions accumulate in the cytoplasm of infected cells in the form of crystalline inclusions, which are released by the bursting of vacuoles at the cell surface (29). Vectorial release has been described in polarized human intestinal epithelial cells (30, 31). The massive release of new progeny virions occurs during cell lysis.

3.4. Effect of poliovirus replication on the host cell

As PV infection progresses *in vitro*, the host cell undergoes substantial metabolic and morphological changes, commonly referred to as cytopathic effects (9).

Early in the infectious cycle, PV proteases (2A and 3C) mediate the shutoff of both transcription and cap-dependent translation (9). Non structural proteins also have a large effect on host intracellular membrane structure and function. The 2BC and 3A proteins induce the formation of vesicles from the membrane, and inhibit protein trafficking through the host secretory pathway (32-36). PV may therefore evade host anti-viral responses by interfering with the expression and transport of immune system mediators.

Recent studies have also shown that PV infection may inhibit trafficking between the cytoplasm and the nucleus, resulting in the accumulation of nuclear proteins in the cytoplasm (37, 38).

PV infection may also trigger the development of apoptosis, as described below.

4. PATHOGENESIS OF POLIOMYELITIS AND POST-POLIO SYNDROME

The term poliomyelitis is derived from the Greek words "polios", meaning gray, and "myelos", meaning marrow, relating to the destruction of neurons in the gray matter of the anterior horn of the spinal cord in this disease.

Humans are the only natural host of PV, and PV infection results in poliomyelitis in only 1 to 2% of cases. The virus is mostly transmitted via the fecal-oral route. Following oral ingestion, it first infects the oropharynx and the gut, where it causes few, if any, symptoms; it then spreads to the CNS (for a review see (39-41)). The main target cells of PV in the CNS are the motor neurons of the spinal cord and brainstem. The destruction of motor neurons, as a consequence of PV replication, results in paralysis. Studies with mice transgenic for the PV receptor molecule CD155 (Tg-CD155 mice) have shown that the specific tropism of PV for motor neurons is due to the expression of CD155 on these cells. However other factors, such as the alpha/beta interferon response (42) and IRES-dependent translation, are also involved (43).

Many patients develop a disease called post polio syndrome, involving progressive muscle weakness, after decades of clinical stability following acute paralytic poliomyelitis (44). The presence of PV RNA sequences or PV-related RNA and of anti-PV IgM antibodies in the spinal fluid of these patients suggests that this syndrome may result from PV persistence (45, 46). Consistent with this hypothesis, PV can establish persistent infections in cultures of human cells of neuronal origin (47-49) and in the mouse CNS (50).

5. POLIOVIRUS AND APOPTOSIS

Cell damage in the CNS in response to virus infection may involve apoptosis (for exhaustive review see (5, 51)). This has been illustrated *in vivo* with a number of human and murine neurotropic RNA viruses, including HIV (52), HTLV-1 **(**53), reovirus (54), rabies virus (55, 56), measles virus (57, 58), dengue virus (59), Sindbis virus (60, 61), and Theiler murine encephalomyelitis virus (62), a member of the Picornaviridae family. Three other picornaviruses, Coxsackievirus B3 (63), HAV (64), and enterovirus 71 (65, 66) induce apoptosis in cell cultures.

5.1. Poliovirus-induced apoptosis in nerve cells *in vivo* and *ex vivo*

As stated above, PV-induced paralysis results from the destruction of motor neurons, but little was known about the process leading to the death of neurons until recently.

Work with mouse models has shown that PV-infected motor neurons in the spinal cord die by apoptosis: the extent of apoptosis is correlated with viral load and its onset coincides with that of paralysis (4). Moreover, CNS injury may be aggravated by apoptosis in uninfected non neuronal cells — probably glial or inflammatory cells — contiguous to the PV-infected neurons (4). PV-induced apoptosis is therefore an important element of the tissue injury in the CNS leading to paralysis in infected mice.

PV-induced apoptosis in nerve cells has been investigated in cultures of mixed mouse primary nerve cells from the cerebral cortex of Tg-CD155 mice (67). These cultures contain all three main CNS cell types: neurons, astrocytes and oligodendrocytes. All these cell types are susceptible to PV infection, and viral replication leads to the DNA fragmentation characteristic of apoptosis (67). Furthermore, PV-induced apoptosis is mediated by caspases in this model. Mixed primary nerve cell cultures harbor PV-infected glial cells in addition to PV-infected neurons, by contrast to what is observed *in vivo*. This finding is consistent with data for primary cultures of human fetal brain cells (49), and the discrepancy may be due to a difference in the expression patterns of CD155 *ex vivo* and *in vivo*. Indeed, glial and ependymal cells expressing CD155 in a new Tg-CD155 mouse model were recently shown to be susceptible to PV infection (68). Cultures of mixed mouse primary nerve cells could serve as a model for investigations of the molecular mechanisms of PV-induced apoptosis in nerve cells.

5.2. Poliovirus-induced apoptosis in non neuronal cells *in vitro*

PV can trigger apoptosis in cultures of human colon carcinoma cells (CaCo-2) (69), promonocytic cells (U937) (70) and dendritic cells (71).

In a human epithelial cell subline (HeLa), Tolskaya *et al.* (72) showed an absence of apoptosis following productive PV infection. By contrast, apoptosis may develop following non permissive infection with various PV mutants (guanidine-sensitive, guanidine-dependent, or temperature-sensitive mutants). In permissive conditions, apoptosis induced by apoptotic inducers, such as metabolic inhibitors, is suppressed by PV infection (72, 73). PV therefore appears to encode proteins with two opposite

functions, one triggering and the other suppressing apoptosis. Agol *et al.* (74) proposed a model in which there is a switch of cell commitment in the middle of the viral cycle, from apoptosis to an anti-apoptotic state and cytopathic effect during productive PV infection. Analyses of specific apoptotic pathways in this model have suggested that early PV-induced apoptosis results in the translocation of cytochrome *c* from the mitochondria to the cytosol, thereby activating caspase-9 and caspase-3 (75). The subsequent abolition of apoptosis in this subline of HeLa cells may be due, at least in part, to the aberrant processing and degradation of procaspase-9 (75).

Several studies have investigated the viral factors involved in the induction of apoptosis in PV-infected cells. It has been shown that the production of each of the PV proteases, 2A or 3C, is sufficient to trigger apoptosis (76, 77), suggesting that PV proteases activate an endogenous cell suicide program. Similarly, the 2A and 3C proteases encoded by another neurotropic enterovirus, enterovirus 71, induce cell apoptosis (65, 66). When elucidating the exact molecular mechanism by which 3C triggers apoptosis, it should be borne in mind that this protease cleaves various host proteins, including transcription factors (26, 78, 79) and the cytoskeletal protein MAP4 (80). The cleavage of these proteins may therefore trigger apoptosis via a transcriptional inhibition mechanism or cytoskeletal changes. Protease 2A is involved in the cleavage of eIF4GI, eIF4GII, and the poly (A)-binding protein (PABP), all of which are involved in cellular protein synthesis (81, 82). Thus, the PV protease 2A may induce apoptosis by preventing the cap-dependent translation of particular cellular mRNAs encoding proteins required for the maintenance of cellular viability. Alternatively, 2A may induce apoptosis by allowing the preferential cap-independent translation of cellular mRNAs encoding apoptosis-inducing proteins. Proteases 2A and 3C may also trigger apoptosis via the cleavage of other unidentified cellular substrates.

Another PV non structural protein, 2B, has also been shown to play a role in PV-induced apoptosis. This protein is associated with the replication complex and virus-induced membranes and has viroporin activity (83). This protein has recently been shown to localize to mitochondria, inducing cytochrome *c* release and apoptosis (83).

The double-stranded PV RNAs generated during viral replication may also trigger apoptosis in HeLa cells, under conditions of permissive PV infection, through the activation of interferon, 2'-5' oligoadenylate synthetase (OAS) and RNase L (84).

PV/CD155 interaction may also be involved in the induction of apoptosis by PV (see below, paragraph 5.2).

As described above, PV may also suppress apoptosis. This feature may involve other mechanisms, in addition to the procaspase 9 degradation described above. The host secretory pathway is specifically suppressed by 3A, due to the loss from the cell surface of tumor necrosis factor (TNF) receptor and receptors for various other cytokines (34, 36, 85). This results in a decrease in the sensitivity of cells to these cytokines and may be therefore indirectly prevent apoptosis. Furthermore, the PV protease 3C induces apoptosis (76), but may also be able to delay or prevent apoptosis, as it mediates degradation of the transcriptional activator and tumor suppressor p53 (86).

5.3. CD155 and apoptosis

PV can establish persistent infections in cells of neural origin (neuroblastoma cells) and in human fetal brain cell cultures (47-49). During persistent infection in human neuroblastoma IMR-32 cells, specific mutations are selected in CD155 affecting domain 1, the binding site for PV (87). These mutations include the Ala 67 -> Thr substitution, corresponding to a switch from one allelic form of the PV receptor to the other. This form of CD155 ($CD155_{Thr67}$) is not expressed in parental IMR-32 cells. A role for CD155 in cell cytopathic effects has been suggested from studies of mutated forms of CD155 generated by site-directed mutagenesis affecting residues in domain 1 (88). The effect of the mutations selected during persistent infection on the susceptibility of cells to PV-induced cytopathic effects has been investigated by expressing the two forms of PV receptor ($CD155_{Thr67}$ and $CD155_{Ala67}$) independently in mouse LM cells lacking the CD155 gene. Virus adsorption and growth were identical in the two cell lines, but PV-induced cytopathic effects occurred later in cells expressing $CD155_{Thr67}$ (LM-$CD155_{Thr67}$), than in cells expressing $CD155_{Ala67}$ (LM-$CD155_{Ala67}$) (87). An analysis of PV-induced death in these two cell lines showed that the extent of DNA fragmentation, mitochondrial dysfunction, and caspase activation were lower in LM-$CD155_{Thr67}$ cells than in LM-$CD155_{Ala67}$ cells (89). Thus, the level of apoptosis was lower in cells expressing the $CD155_{Thr67}$ form selected during persistent PV infection than in cells expressing the other allelic form of the receptor. The $CD155_{Thr67}$ form may thus favor persistent PV infection in neuronal cells (89). Other unidentified factors may also be involved in decreasing apoptosis levels during persistent PV infections, as recently shown in human intestinal cells (Caco-2) cured of persistent poliovirus infection (90).

5.4. Poliovirus simultaneously induces JNK-mediated cell death and the PI3K/Akt survival pathways in neuroblastoma cells

5.4.1. Poliovirus induces Bax-dependent cell death mediated by the c-Jun NH_2-terminal kinase

Analyses of the apoptotic pathways induced following PV infection in several cell lines have shown MOMP, as demonstrated by the release of cytochrome c from the mitochondria into the cytosol, to be important (75, 89). However, the detailed mechanisms of mitochondrial deregulation following PV infection of neural cells remained unknown until recently. We investigated the PV-induced signaling cascade leading to activation of the mitochondrial pathway in a neuroblastoma cell line, IMR5 cells (91). We found that PV infection activates Bax, a pro-apoptotic member of the Bcl-2 family (Figure 2). This activation involves a change in the conformation of Bax and its redistribution from the cytosol to mitochondria. Furthermore, specific neutralization of Bax by the cytomegalovirus-encoded cell death suppressor protein,

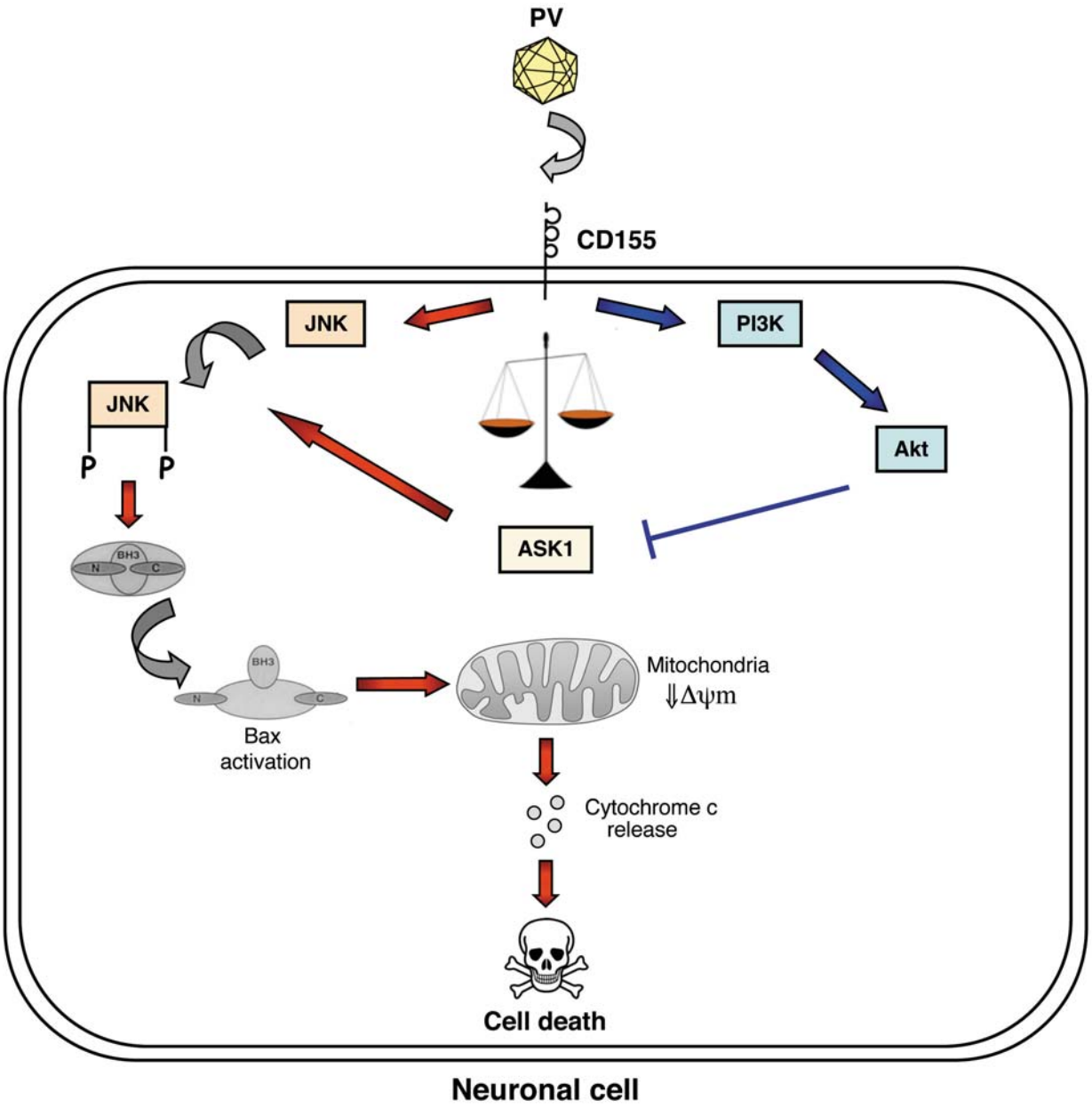

Figure 2. Induction of pro- (in red) and anti- (in blue) apoptotic signaling pathways in neuroblastoma cells following PV infection**.**

vMIA (92), prevents cytochrome *c* release, consistent with a role for PV-induced Bax activation in MOMP (91). The requirement for the pro-apoptotic Bax protein in this model is particularly interesting, because Bax is widely distributed in the central nervous system and is thought to be a major sensor of neuronal death (93, 94)**.**

We also found that c-Jun NH2-terminal kinase (JNK) was activated soon after PV infection (Figure 2). Moreover, the pharmacological inhibition of JNK with SP600125 inhibited Bax activation, cytochrome *c* release into the cytosol and the release of extracellular virus, without affecting the total amount of virus produced.

These results indicate that activation of the apoptotic mitochondrial pathway in PV-infected neuronal IMR5 cells is Bax-dependent and mediated by early JNK activation. A role for JNK activation has also been described in the cell death induced by certain other viruses, including reovirus (95), swine influenza virus (96), and Coxsackievirus B3 (97), another member of the *Picornaviridae* family. Moreover, it has recently been shown that the treatment of reovirus-infected mice with a specific JNK inhibitor significantly prolongs the survival of mice after intracerebral infection and that this increase in survival is correlated with lower levels of neuronal apoptosis (98).

We then investigated whether PV adsorption onto IMR5 cells induced JNK activation in the absence of PV replication, by assessing JNK phosphorylation after adding UV-inactivated PV to IMR5 cells. Interestingly, the PV-cell interaction alone was sufficient to induce JNK activation, but PV replication was required for PV-induced apoptosis in IMR5 cells. It has been suggested that PV/CD155 interaction may play a role in cell death (88), consistent with the findings of Agol's group following non permissive infection (72). Furthermore, as previously stated, PV-induced apoptosis may be modulated as a function of the allelic form of CD155 expressed at the cell surface (89).

As stated above, JNK activation is not sufficient to trigger complete PV-induced apoptosis, with PV replication required in our model. Indeed, in addition to the PV/CD155 interaction, several non structural viral proteins have been implicated in the pro-apoptotic process in PV-infected cells, whereas others have been shown to delay or prevent apoptosis. Thus, PV-induced apoptosis is complex and involves a delicate balance between several viral and cellular proteins, determining the fate of the cell.

5.4.2. Early activation of the PI3K/Akt survival pathways limits poliovirus-induced JNK-mediated cell death in neuroblastoma cells

We found that JNK activation occurred early after PV infection, (30 min post-infection), with apoptotic features first observed several hours later in PV-infected cells (6 h post-infection). As previously reported by Agol's group (74), several events concerning the balance between pro- and anti-apoptotic signals, may occur in PV-infected cells between 30 min and 6 h post-infection.

We searched for a putative anti-apoptotic pathway in IMR5 neuroblastoma cells and found that PV also activated phosphatidylinositol 3-kinase (PI3K)/Akt survival signaling, limiting the extent of JNK activation and cell death (99). We showed that JNK inhibition was associated with PI3K-dependent negative regulation of the apoptosis signal-regulating kinase 1 (ASK1), acting upstream from JNK in PV-infected IMR5 cells (Figure 2). As for JNK activation, PV/CD155 interaction alone is sufficient to induce Akt phosphorylation in the absence of viral replication. Thus, the early PI3K/Akt survival pathway seems to act upstream from the interplay between cellular and viral proteins potentially influencing apoptosis in PV-infected cells.

6. CONCLUSION

In the CNS, PV-induced apoptosis seems to be a significant factor in the pathogenesis of poliomyelitis, as illustrated by mice models. *In vitro* studies in various cellular models have shown that PV may trigger or prevent the development of apoptosis, depending on the infection conditions and host cell type. In neuroblastoma cells, PV simultaneously induces the JNK-mediated cell death and PI3K/Akt survival pathways. The PI3K/Akt survival pathways may delay PV-induced apoptosis and virus externalization, thereby limiting the spread of PV-induced damage in the central nervous system during poliomyelitis.

Some non-structural viral proteins are good candidates for involvement in the pro- and anti-apoptotic processes in PV-infected cells. However, most of these data were obtained with individual protein production systems and the situation is more complex in the context of cellular infection. CD155 may also be involved in modulating PV-induced apoptosis, as a function of the allelic form expressed at the cell surface. PV-induced apoptosis is less extensive in cells expressing mutated $CD155_{Thr67}$ selected during persistent PV infection than in cells expressing the other allelic form, $CD155_{Ala67}$. The activation of the JNK and PI3k/Akt pathways can be induced by PV/CD155 interaction alone. It would be interesting to investigate whether JNK activation is less efficient in cells expressing $CD155_{Thr67}$ than in cells expressing $CD155_{Ala67}$ and whether, conversely, the level of PI3k/Akt activation is higher in $CD155_{Thr67}$ cells. This modulation would be beneficial to the virus and possibly to host cells: if apoptosis is not induced correctly or at all, the virus may be able to establish persistent infection in surviving cells. It would therefore also be interesting to determine which allelic form of CD155 is expressed in patients developing poliomyelitis and post-polio syndrome. It has recently been shown that the frequency of $CD155_{Thr67}$ is significantly higher in patients with amyotrophic lateral sclerosis or progressive muscular atrophy than in controls (13), indicating the possible involvement of CD155 in diseases of the CNS.

Despite these recent data, several molecular details of the apoptotic pathways leading to cell death following PV infection remain to be determined. Indeed, even if PV/CD155 interaction alone is sufficient to induce pro- and anti-apoptotic signaling, PV-induced apoptosis does not occur without PV replication and viral protein synthesis. The nature of the crosstalk between cell and viral proteins in the delicate balance underlying this process of cell death in PV-infected cells remains to be investigated.

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Abbreviations: AIF: apoptosis-inducing factor; Apaf-1: apoptosis protease-activating factor-1; ASK1: apoptosis signal-regulating kinase 1; CNS : central nervous system; DNAM-1: leukocyte adhesion molecule; DNAX accessory molecule-1; Endo G: IRES: internal ribosomal entry site; JNK: Jun N-terminal kinase; MOMP: Mitochondrial outer membrane permeabilization; NCR: non coding region; OAS: 2'-5' oligoadenylate synthetase; OPV: oral polio vaccine; ORF: open reading frame; PABP: poly (A)-binding protein; PV: poliovirus; tactile: T cell-activated increased late expression; Tg-CD155: transgenic for the PV receptor molecule CD155; TNF: tumor necrosis factor

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