Host-pathogen interactions during apoptosis

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Host pathogen interaction results in a variety of responses, which include phagocytosis of the pathogen, release of cytokines, secretion of toxins, as well as production of reactive oxygen species (ROS). Recent studies have shown that many pathogens exert control on the processes that regulate apoptosis in the host. The induction of apoptosis upon infection results from a complex interaction of parasite proteins with cellular host proteins. Abrogation of host cell apoptosis is often beneficial for the pathogen and results in a successful host invasion. However, in some cases, it has been shown that induction of apoptosis in the infected cells significantly imparts protection to the host from the pathogen. There is a strong correlation between apoptosis and the host protein translation machinery: the pathogen makes all possible efforts to modify this process so as to inhibit cell suicide and ensure that it can survive and, in some cases, establish latent infection. This review discusses the significance of various pathways/steps during virus-mediated modulation of host cell apoptosis.

[Hasnain S E, Begum R, Ramaiah K V A, Sahdev S, Shajil E M, Taneja T K, Mohan M, Athar M, Sah N K and Krishnaveni M 2003 Host-pathogen interactions during apoptosis; *J. Biosci*. **28** 349–358]

1. Introduction

Apoptosis is a genetically controlled, morphologically and biochemically distinct form of programmed cell death that occurs during development, immune cell proliferation, maintenance and perpetuation of cellular integrity and tissue homeostasis in multicellular organisms (Vaux and Strasser 1996). Apoptosis characteristically occurs in isolated single cells. Inappropriate apoptosis is linked to a number of parasitic infections as well as the cause and progression of diseases such as neurodegenerative disorders, aging and cancer. Apoptosis therefore has distinct clinical implications (Katoch *et al* 2002), and understanding its regulation will result in new drugs and molecules that will target specific steps in the apoptosis pathway. It is an energy-consuming, proteolytic, autodestructive process and is a consequence of the activation of specific genes and proteins which are phylogenetically highly conserved. Unlike apoptosis, necrosis or non-apoptotic cell death, a prototype of which is cell death due to ischemia (oncosis), is characterized by depletion of intracellular ATP stores, swelling of the cell with disruption of organelles and rupture of the plasma membrane. Necrosis results from physical injury and is not

Keywords. Antioxidant; baculovirus; host-pathogen; eIF2*a*-kinase; P35; PKR

Abbreviations used: *Ac*NPV *Autographa californica* nuclear polyhydrosis virus; EMCV, encephalomyocarditis virus; FADD, Fas-associated death domain protein; Wt, wild-type.

genetically controlled. While the pathways for apoptosis and necrosis are distinct, they nonetheless overlap and cross talk *in vivo*. An event that produces necrosis may trigger apoptosis in surrounding tissues or conversely, induction of apoptosis, under certain circumstances, could indirectly result in necrosis. The morphologic characteristics of apoptosis include, nuclear condensation and fragmentation, and condensation of the cell with preservation of organelles. The process is followed by formation of membrane-bound apoptotic bodies, which subsequently undergo phagocytosis by nearby cells without associated inflammation.

In higher vertebrates, apoptosis is pivotal for the normal development and function of the immune system. Both self-reactive maturing immunocompetent cells and hyper-reactive mature cells are eliminated by apoptosis. In addition, apoptosis has been recognized as an important defense mechanism against viral, bacterial and parasitic pathogens during innate and adaptive immunity (Williams 1994; Liles 1997). Apoptosis of infected host cells facilitates the survival of the host by diminishing the production of pathogens. Also, apoptosis in specific cells contributes to the regulation of pathogen-induced immune responses (Liles 1997). Viral, bacterial and protozoan pathogens have evolved different strategies to modulate host cell apoptosis (Liles 1997; Barry and McFadden 1998; Gao and Kwaik 2000).

Direct as well as indirect effects of parasites and their products (Luder *et al* 2001) modulate host cell death by inhibiting or modulating host immune responses or facilitating the intracellular survival of the pathogen. Host virus interaction is a dynamic process wherein viruses have evolved various means to co-exist by reducing their visibility, while the host immune system attempts to suppress and eliminate infection without damage to itself. Many cells undergo apoptosis in response to viral infection, with a consequent reduction in the release of progeny viruses. Viruses have therefore, evolved multiple mechanisms for modulating host cell apoptosis. Viruses may interfere with either the highly conserved 'effector' mechanisms of programmed cell death or regulatory mechanisms specific to mammalian cells. In addition to conferring a selective advantage to the virus, the capacity to prevent apoptosis is the key to the transformation of the host cell by oncogenic viruses. Successful viral replication requires not only the efficient production and spread of its progenies, but also evasion of host defense mechanisms that limit replication by killing infected cells.

2. Regulation of apoptotic cell death

Apoptosis is initiated by the binding of death ligands to their specific cell surface receptors (such as Fas) or tumour necrosis factor receptors (TNFRI and TNFRII), or by other stimuli such as chemotherapeutic agents, irradiation, reactive oxygen species (ROS), growth factor withdrawal etc. (Vaux and Strasser 1996; Yuan 1997; Begum *et al* 1999). Also the release of perforin and granzymes by natural killer (NK) cells or antigen specific cytotoxic T lymphocytes (CTL) induces apoptosis in target cells (Trapani *et al* 2000). Transduction of these proapoptotic stimuli via different signalling pathways results in either direct activation of caspases (figure 1) or the release of cytochrome c from the mitochondria into the cytosol resulting in the formation of apoptosome and consequent caspase activation (Thornberry and Lazebnik 1998). Thus, activation of the caspase cascade finally results in death of the cells (figure 1). A recent report (Mohan *et al* 2000) shows modulation of TNFα-induced apoptosis in corneal fibroblasts by transcription factor NF-κB, thereby contradicting the earlier reported up-regulation of apoptosis by TNF-α receptor system.

3. Apoptosis and viral pathogenesis

Viruses after infecting target cells replicate to produce large number of progeny virions, and spread the progeny to initiate the next round of infection. Some viruses encode specific proteins to optimize their replication. Infection by viruses, however, triggers apoptosis of the infected cell to restrict virus infection. This is done by reprogramming of the host cell apoptotic pathway to effect death of the infected host cell before the release of progeny viruses. In order to ablate host defense mechanisms, viruses have evolved proteins that are able to inhibit or delay the host protective actions by targeting strategic points in the apoptotic pathways (Granville *et al* 1998). There is a growing awareness that viral proteins such as Op-IAP (Hawkins *et al* 1996) from the *Orgyia pseudotsugata* nuclear polyhedrosis virus (*Op*NPV), FLICE inhibitory proteins (FLIPs) from several herpes viruses (Ploegh 1998), CrmA from Cowpox virus and p35 from *Autographa californica* nuclear polyhedrosis virus (*Ac*NPV) have antiapoptotic potential (Chang and Yang 2000; Shi 2002). CrmA protein is a caspase as well as granzyme-B inhibitor and blocks apoptosis induced by CTL, TNF or Fas (Ploegh 1998).

Certain pathogenic DNA viruses actively inhibit apoptosis of their host cells, while measles virus induces apoptosis in dendritic and T cells of the immune system. The adenovirus E3-14·7 K protein, expressed early in the life cycle of human adenoviruses to protect the virus from the antiviral response of host cells, inhibits cell death mediated by TNF-α and FasL receptors. Specific induction of apoptosis in immune cells is seen in HIV infections (Pantaleo and Fauci 1995). HIV kills $CD4^+$ T

cells and disables the capacity of the immune system to respond to antigens. Several viruses, including herpes and pox viruses, have acquired genes that specifically inhibit the apoptotic machinery (Spriggs 1996). HTLV-I infection interferes with the autonomous suicide program of T cells, not just Fas/FasL but also TNFR/TNF-*a* pathways, to prolong the life of the infected cells (Yang *et al* 2002) (table 1). This may contribute to viral persistence and favour survival and subsequent expansion of dysregulated infected T cells with the potential to produce HTLV-I-associated autoimmune-like diseases or malignancies. Puumala viral (pathogenic RNA viruses) nucleocapsid protein (PUUV-N) interacts with Daxx, a Fas-mediated apoptotic enhancer, and this PUUV-N: Daxx interaction could be important for host defence (Li *et al* 2002). The apoptotic function of Daxx could be mediated either by nuclear Daxx as a transcriptional regulator or by cytoplasmic Daxx as a Fas receptor-associated protein that mediates the activation of JNK and host cell apoptosis possibly by enhancing degradation of Bcl-2.

4. Baculovirus P35

Baculovirus such as *Ac*NPV, possesses at least two different classes of anti-apoptotic genes, which allow them to block apoptosis of the infected cells, thereby, promoting viral replication and dissemination to neighbouring cells and tissues. The IAP genes, also present in higher eukaryotes, have a more restricted role and appear to function at an early point in the pathway(s) leading to apoptosis. The other class of genes include p35 (a 35 kDa protein), which functions as a suicide inhibitor of the caspase family (caspase 1, – 2, – 3, – 4, – 6, – 7, – 8 and – 10) of cysteine proteases (Zhou *et al* 1998) involved in the induction and execution of apoptotic cell death. The

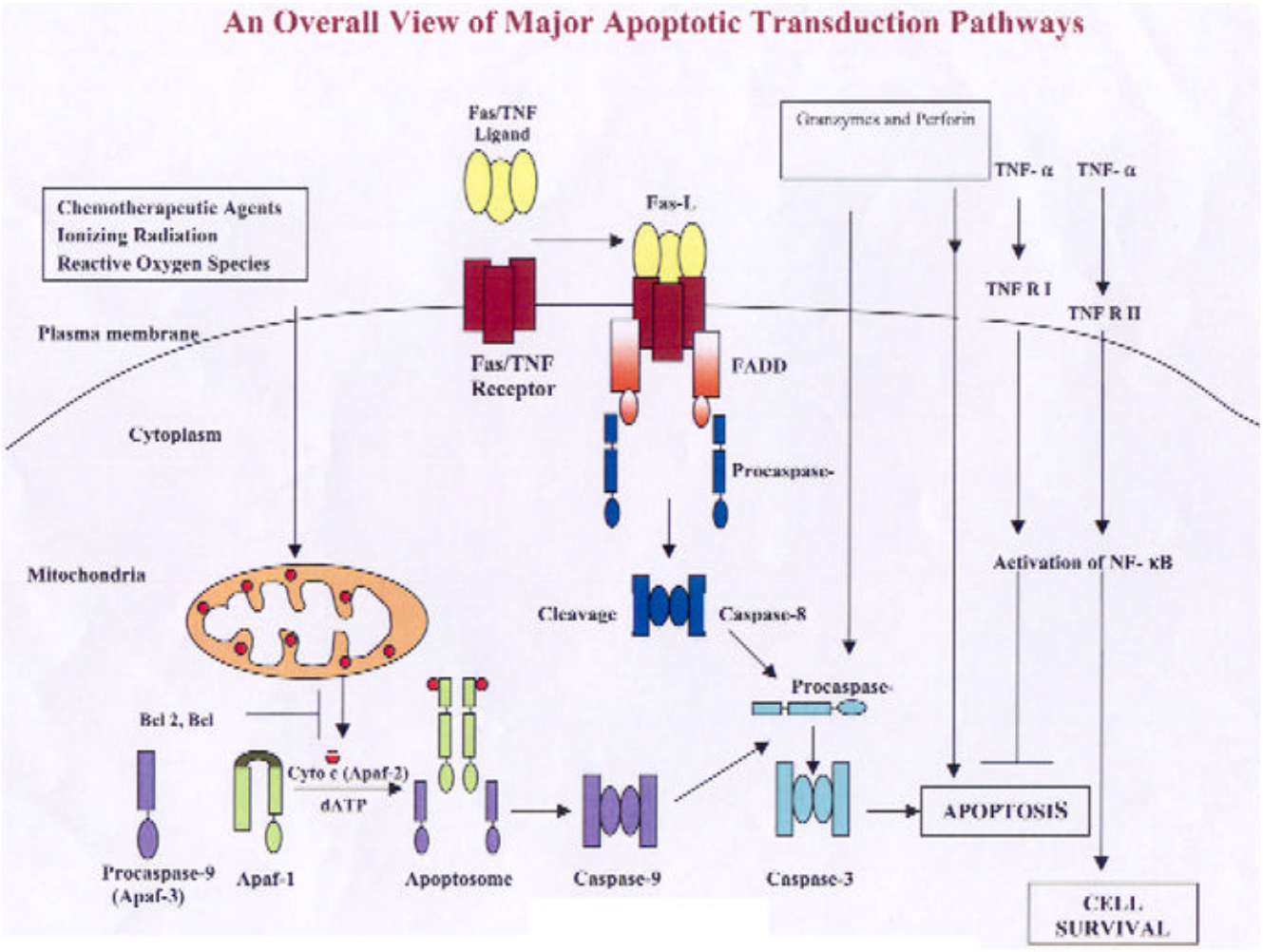

Figure 1. A simplified view of the major apoptosis transduction pathway.

P35 protein prevents apoptosis induced by a variety of apoptotic agents in different systems. It acts as a substrate for caspases and gets cleaved at the Asp87 residue into a 10 kDa and 25 kDa fragment: the larger 25 kDa fragment binds to the active site of initiator caspases and prevents them from activating downstream caspases, thereby inhibiting apoptosis (Bertin *et al* 1996; Xue and Horvitz 1995; Green and Reed 1998; Bump *et al* 1995). In addition to human caspases, p35 also inhibits CED protein from *Caenorhabditis elegans* as well as, *Sf*-caspase-1 from the insect *Spodoptera frugiperda* (Miller 1997). Recently, a 2·2 Å resolution crystal structure of the p35 monomer showed that cleavage alone is insufficient for caspase inhibition and a reactive site loop at p35 protein's main *b*-sheet core determines post cleavage association and stoichiometric inhibition of target caspases (Fisher *et al* 1999). P35 protein has recently been described to exhibit a dual mode of action. Studies conducted *in vitro* and *in vivo* (Hasnain *et al* 1999) demonstrated that p35 also functions directly as an antioxidant by mopping out free radicals and consequently prevents cell death by acting at an upstream step in the reactive oxygen species-mediated cell death pathway (Sah *et al* 1999). *In vitro* cultured *Sf*9 cells when treated with apoptotic dose of H_2O_2 post *Ac*NPV infection, failed to undergo apoptosis (figure 2). However, when infected with a mutant *Ac*NPV carrying a deletion of the p35 gene, apoptosis in *Sf*9 could not be rescued (Sah *et al* 1999) thereby demonstrating the involvement of the P35 protein in preventing H_2O_2-induced apoptosis. Direct proof of the role of P35 as a 'sink' to absorb oxidative stress comes from *in vitro* and *in vivo* ESR free radical-trapping experiments (figure 3). The specific ESR spectrum corresponding to the free radicals generated *in vitro* or *in vivo* were abolished in the presence of recombinant p35 pointing to the ability of p35 to sequester reactive oxygen species and thereby inhibit ROS-mediated apoptosis (Sah *et al* 1999). The oxidant-antioxidant involvement in apoptosis in insect cells has recently been found to be regulated at the level of mitochondrial cytochrome *c* release (Mohan *et al* 2003).

Table 1. Summary of the different pathways involved during interactions of viruses with their respective hosts.

Name of the virus	Host components targeted in the apoptosis-pathway	Mechanism used by virus to inhibit apoptosis
Autographa californica nuclear polyhedrosis virus (*Ac*NPV)	Caspases, SOD, catalase, GSH	P35 functions as a suicide inhibitor of the caspase family as well as an antioxidant by mopping out free radicals by acting at an upstream step in the ROS-mediated cell death pathway. IAPs, function at an early point in the pathway(s) leading to apoptosis by binding and inhibiting caspase proteases.
Cowpox virus	Caspases, CTL, TNF or Fas	CrmA protein is a caspase as well as granzyme-B inhibitor and blocks apoptosis induced by CTL, TNF or Fas.
Herpes viruses	FLICE	FLICE inhibitory proteins (FLIPs) have anti-apoptotic potential.
Human adenoviruses	TNF-*a* and FasL receptors	E3-14·7 K protein protects the virus from the antiviral response of host cells and inhibits cell death mediated by TNF-*a* and FasL receptors.
Pathogenic RNA viruses	Fas-mediated apoptotic enhancer	Puumala viral nucleocapsid protein (PUUV-N) interacts with Daxx, a Fas-mediated apoptotic enhancer mediating the activation of JNK and host cell apoptosis.
Poliovirus	The double stranded RNA-dependent kinase (PKR), janus kinase (JAK), the STATs (signal transducers and activators of transcription)	PKR is an important cellular target that viruses inactivate to prevent apoptosis. Poliovirus infection proteolyses PKR and reduces the total PKR levels.
HIV-1 (human immunodeficiency virus-1)	PKR, interferon gene transcription through IRF-1 and NF-*k*B	TAT protein of HIV reduces PKR levels by an unknown mechanism.
Epstein-Barr virus, Hepatitis delta virus,	dsRNA-mediated activation of PKR	These viruses interfere with the dsRNA- mediated activation of PKR by binding to the conserved dsRNA-binding domains of PKR or sequestering the RNA activators or by interference of PKR dimerization.
HTLV-I (human T lymphotrophic virus-I)	Fas/FasL, TNFR/ TNF-*a*	Interferes with the autonomous suicide program of T cells, Fas/FasL as well as TNFR/TNF-*a* pathways, to prolong the life of the infected cells.

Reactive oxidative damage to cellular macromolecules, such as nuclear and mitochondrial DNA and proteins, caused by ROS is considered to be of key importance in the aging process (Yan *et al* 1997). The chain of oxidative reactions initiated by ROS eventually knocks down the crucial biomolecules driving the cellular machinery, thereby activating caspases to ultimately bring about the execution of cell death. The fact that the presence of p35 protein is required well before the initiation of apoptosis by oxidative stress implies that p35 intercepts the oxidative stress-induced pathway at an upstream step besides the execution step of PCD. The anti-oxidant property of p35 resembling Bcl2 is significant in the sense that it may save cells from being committed to die and thus enhancing their functional life span. Therefore, the ability of p35 to inhibit ICE proteases coupled with our demonstration of its anti-oxidant property additionally points to its 'Swiss army knife' like action similar to Bcl-2 (Hengartner 1998).

5. Host-pathogen interactions in apoptosis: the translation connection

One of the most crucial requirements for the propagation of virus and for persistent infection is to maintain the competency of the host cell protein translational machinery. Virus infection often leads to a shut down of host protein synthesis to facilitate the selective translation of viral mRNAs. Decline in host cell protein synthesis and metabolic repression induces cellular apoptosis, thereby pointing to the importance of translational control programs in mounting an antiviral response. Viruses have devised fascinating tricks to modify the translational machinery (Kaufman 1999) to suit their requirements and to inhibit host apoptosis (Shen and Shenk 1995) and many such mechanisms are vital for viruses to establish their latent states. These anti-death mechanisms include (i) modulation of the anti-apoptotic members of the Bcl-2 family, resulting in inhibition of formation of 'apoptosome', (ii) inactivation of the tumour suppressor p53, and (iii) caspase inhibition.

Virus-infected cells produce interferons (multifunctional effectors), which inhibit viral replication and cell growth. While type I interferons are responsible for antiviral response, type II interferons are made by natural killer cells and activated T cells in response to antigenic stimulation. These interferons trigger the activation of several genes via the janus kinase (JAK) which in turn

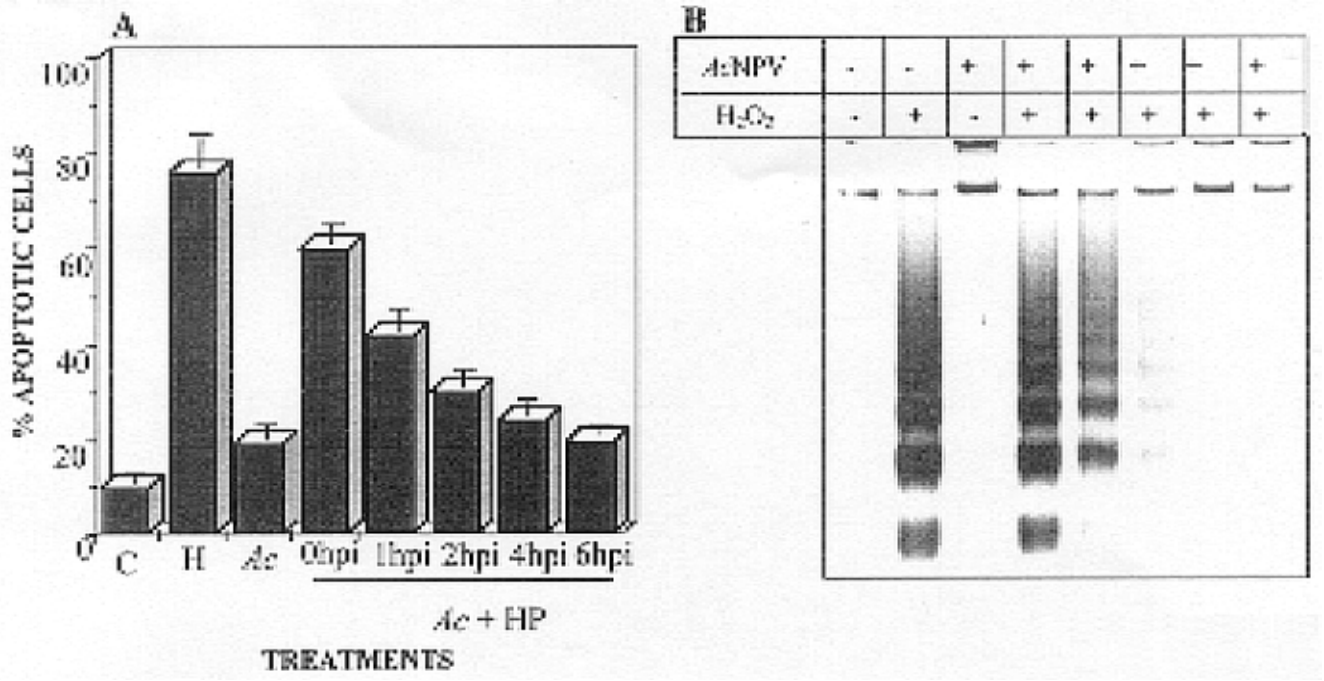

Figure 2. (**A**) The *Ac*NPV *p35* gene inhibits H_2O_2 (HP)-induced apoptosis. *Sf*9 cells infected with wild-type baculovirus at 10 moi and then exposed to 1 mM concentration of HP at different time periods after infection (0–6 h). Percentage cells undergoing apoptosis was scored. (**B**) Nucleosomal ladder assay for the cells infected with wild-type virus before HP-exposure at different time periods after infection. Lane 1, uninfected cells; lanes 2, 3, cells treated with HP and *Ac*NPV (Ac) alone; lanes 4, 5, 6, 7, 8, cells treated with HP at different h post infection (0, 1, 2, 4, 6, respectively). Note the disappearance of the DNA ladder, a characteristic of apoptosis, in *Ac*NPV-infected cells exposed to H_2O_2. (Reproduced from Sah *et al* 1999, With the permission from the National Academy of Sciences, USA.)

activates the signal transducers and activators of transcription (STAT). The double stranded RNA-dependent kinase (PKR) and 2′, 5′ oligoadenylate synthetase (2′–5′A synthetase) have been found to be important in defending the cell against viral infection (Wong *et al* 1997). PKR is an important cellular target that viruses inactivate to prevent apoptosis. PKR activation occurs by dsRNA that is produced by viral replication. PKR mounts anti-viral response through several different mechanisms which include (i) induction of interferon gene transcription through IRF-1 and NF-*k*B (Chu *et al* 1999), (ii) inhibition of viral protein synthesis at the level of initiation and (iii) induction of apoptosis with subsequent autodigestion of the cell.

PKR is one of the four well-characterized eukaryotic translational initiation factor 2 (eIF2α) kinases in eukaryotic systems. Like PKR, 2′–5′ A synthetase is also activated by dsRNA although it lacks the double-stranded RNA-binding motifs. Active 2′–5′ A synthetase yields a series of 2′–5′ linked oligonucleotides, which in turn activate RNAaseL that degrades RNA. Translational inhibition, whether caused by viral infection or by chemical inhibitors, can be the cause of the origin or enhancement of apoptosis. Both PKR and RNAseL have been implicated as mediators of apoptosis (Lee and Esteban 1994; Zhou *et al* 1997). Both these enzymes are present in the cell's arsenal to fight against the virus infection. However, in their uninduced state, they cannot offer full protection. They are induced and fully mobilized in response to interferon treatment, and activated in response to virus infection or physiological dsRNA. In addition to dsRNA, PKR is activated by cellular proteins that contain double stranded RNA-binding motifs (PACT and RAX) (Patel and Sen 1998; Ito *et al* 1999) and also by heparin

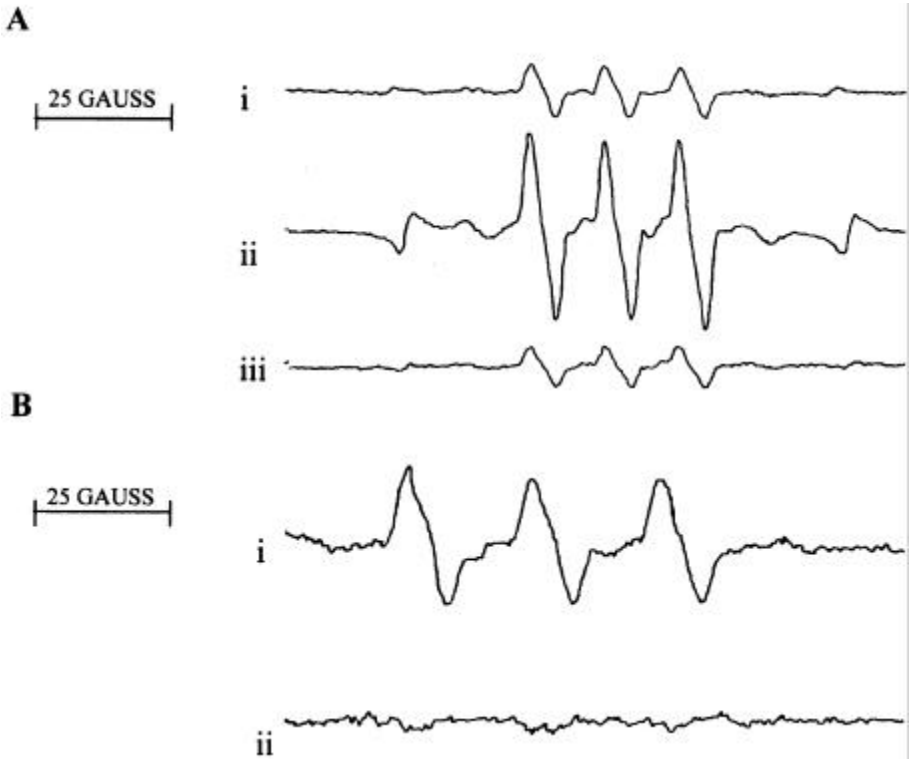

Figure 3. Mechanism of action of P35. (**A**) P35 acts to sequester ROS. ESR spectrum of the superoxides generated by using *in vitro* xanthine/xanthine oxidase system. The basal level of the spectra generated by the xanthine oxidase (i) or those by the superoxides generated by the xanthine/xanthine oxidase system in the absence (ii) and the presence (iii) of the P35 protein are displayed. (**B**) ESR spectrum of ROS generated *in vivo* through the Fenton reaction in *Sf*9 cells. pNN1 transfected cells were subjected to intracellular ROS generation through Fenton reaction and monitored for the peaks generated by ESR spectrum. The spectra generated by hydroxyl radical in the absence of P35 (i) or after heat shock induction of pNN1 transfected cells (ii) are presented. PNN1 is a plasmid that expresses recombinant p35 protein upon transfection of *Sf*9 cells. Note the absence of ESR spectra once the p35 protein is expressed in the cells. (Reproduced from Sah *et al* 1999, with the permission from the National Academy of Sciences, USA.)

(Hovanesian and Galabru 1987). The importance of PKR or other eIF2α kinase involvement in apoptosis has become more evident from the fact that PKR and perhaps other eIF2α kinases can also be activated by caspases (Saelens *et al* 2001; Gunda *et al* 2002).

Phosphorylation of eIF2α by PKR has assumed significance in finding a relationship between translation control, viral infection and apoptosis. List of viral products which inhibit different steps of PKR activation in host cells is still growing. In the presence of dsRNA, PKR is dimerized and autophosphorylated, which then phosphorylates the substrate eIF2α. Viral encoded products interfere in one or the other step of the activation of PKR as mentioned above. Poliovirus infection proteolyses PKR and reduces the total PKR levels, whereas, expression of tat protein of HIV-1 also reduces PKR levels by an unknown mechanism. Some of the viruses produce small structured RNAs such as adenovirus VA RNAI (Reichel *et al* 1985), TAR RNA of HIV-1 (Gunnery *et al* 1992), Epstein-Barr virus RNA (EBER) (Swaminathan *et al* 1992), hepatitis delta virus (HDV), RNA (Robertson *et al* 1996), etc. All of these interfere with the dsRNA-mediated activation of PKR, usually by binding to the conserved dsRNA-binding domains of PKR or sequestering the RNA activators. In addition to RNA products, viral encoded proteins such as vaccinia E3L (Chang *et al* 1992; Rivas *et al* 1998), s3 protein of reovirus S4 gene (Beattie *et al* 1995), influenza NS1 (Cassady *et al* 1998), and Us11 protein of herpes simplex virus (HSV1) (Mulvey *et al* 1999) bind and remove dsRNA required for PKR activation. Interference of PKR dimerization is yet another strategy adopted by many viruses (Lee and Esteban 1994; Lee *et al* 1997; Melville 1997, 1999; Gale *et al* 1998).

Inhibition of PKR function during viral infection appears to be an important strategy to shut down the host apoptotic response in order to achieve persistent viral infection. Infection with encephalomyocarditis virus (EMCV) and with other viruses exemplifies this phenomenon. EMCV is an interferon-sensitive cytolytic virus that induces massive apoptosis in infected murine cells (Meurs *et al* 1992). This may be due to its inability to counter the cellular PKR activity. In contrast, PKR-deficiency confers persistent infection to this cytolytic virus (Yeung *et al* 1999). Influenza virus infection-induced cellular apoptosis (Fesq *et al* 1994) can be overcome by inhibition of endogenous PKR function (Takizawa 1996). Consistent with these observations, increased PKR levels have been shown to sensitize cells to apoptosis-mediated by influenza virus (Balachandran *et al* 2000). Constitutive expression of NS5 5A protein produced by HCV, that is known to inhibit PKR-mediated eIF2α phosphorylation, makes the cells refractory to PKR-dependent apoptosis (Gale *et al* 1999).

The baculovirus insect cell system (Sah *et al* 1999; Gunda *et al* 2002) is an interesting host-virus system to study the relationship between host eIF2α phosphorylation and apoptosis. *Ac*NPV infects *Spodoptera frugiperda* (*Sf*9 and *Sf*21) insect cells and is used to express heterologous recombinant proteins (Chatterji *et al* 1996; Hasnain *et al* 1997; Ramachandran *et al* 2001). Baculovirus encoded PK2 protein has been shown to inhibit both human and yeast eIF2α kinases as well as PKR activity (Dever *et al* 1998). Extracts of insect cells infected with wild type (wt) baculovirus inhibit the phosphorylation of recombinant rabbit eIF2 under *in vitro* conditions (Sudhakar *et al* 1999). Wt virus infection resists apoptosis that is mediated by various agents, where as a virus carrying a deletion of p35 gene readily induces apoptosis and stimulates eIF2α phosphorylation in the absence of any other apoptotic stimuli (Gunda *et al* 2002). Furthermore, apoptotic extracts were found to cleave purified PKR *in vitro*. These findings suggest a novel mechanism for PKR or eIF2α kinase activation in virus-infected cells and complement the recent observations (Saelens *et al* 2001), demonstrating that caspase-cleaved PKR is active in cellular apoptosis. Both PKR-mediated and RNAseL expression–induced cell death can be blocked by Bcl-2 expression, thereby suggesting that PKR acts upstream of the Bcl-2 protein and is part of the mitochondria-dependent pathway (Lee *et al* 1997; Diaz-Guerra *et al* 1997).

It is suggested that PKR and perhaps, other eIF2α kinases like PERK act via eIF2α phosphorylation. This is substantiated by the fact that TNFα-induced cellular apoptosis is partially prevented by the over expression of S51A, a non-phosphorylatable form of human eIF2α, or stimulated by the overexpression of S51D (a phosphomimetic form of eIF2α in Cos-1 cells) (Srivastava *et al* 1998). It was observed that over-expression of S51D was sufficient to induce apoptosis in these cells. In contrast, our recent observations (Gunda *et al* 2002) have shown that expression of recombinant human phosphomimetic form of eIF2α using baculovirus does not stimulate apoptosis in *Sf*9 insect cells presumably due to the expression of baculovirus p35 anti-apoptotic protein. However, apoptosis induced by UV exposure in uninfected cells was stimulated by over-expression of phosphomimetic form of human eIF2α, whereas, expression of S51A (the non-phosphorylatable form of eIF2α) was able to mitigate the UV-induced apoptosis. These findings together with other observations support that apoptosis in *Sf*9 cells is characterized by increased eIF2α phosphorylation, and is a consequence of caspase activation. Consistent with this notion, p35 deletion virus was shown to stimulate apoptosis and eIF2α phosphorylation, whereas caspase inhibitors blocked apoptosis and eIF2α phosphorylation. These recent observations suggest that

baculovirus produces proteins, such as PK2, which inhibit directly PKR or cellular eIF2α kinase activity, and thereby eIF2α phosphorylation. In addition, the anti apoptotic p35 protein can modulate eIF2α phosphorylation indirectly by maintaining caspase in an inactive form. An active caspase can activate eIF2α kinases, like PKR, *in vitro* upon cleavage (Saleans *et al* 2001) or as shown by our results in apoptotic *Sf*9 cells (Gunda *et al* 2002). In addition, PKR-dependent cellular apoptosis has been shown to require the activity of Fas-associated death domain protein (FADD) and has been suggested that this eIF2α kinase may promote death inducing signalling complex (DISC) formation (Balachandran *et al* 1998). Further, PKR-mediated apoptosis may also signal through NF-κB and p53 (Gil *et al* 1999).

6. Conclusions

Apoptosis, a genetically controlled cellular suicide process is essential for development, maintenance of cellular homeostasis and defense against environmental insults including pathogen attack. Protection of the host from opportunistic infections and subversion of the host defense response by viruses, and other pathogens is a consequence of the host-pathogen interaction(s). As the host and pathogen are likely to be linked in a dynamic equilibrium where apoptosis plays a pivotal role in viral pathogenesis, future research on pathogen-induced apoptosis will not only provide new insights into the apoptotic pathway but will also uncover new therapeutic avenues. The therapeutic potential resulting from the controlled manipulation of the apoptotic process, has raised great expectations in the biomedical community. Pharmacological and immunological manipulation of the host pathogen interactions during apoptosis could lead to new modalities of intervention in the disease process.

Acknowledgements

KVAR and SEH thank the Department of Biotechnology (New Delhi) while RB thanks the Council of Scientific and Industrial Research (CSIR, New Delhi) for research support. MK thanks the CSIR for JRF.

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