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Mitochondria as a Favourite Organelle for Invading Viruses

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Abstract

The self-destruction of cells infected with viruses undergoes the process of apoptosis generally to restrict infection and the spread of viral progeny. To avoid infection host has evolved interconnected complex defence network that comprises innate and acquired immune response. Mitochondria being considered as powerhouse of a cell is not limited to only energy production, but mitochondria perform various other functions in (disease, apoptosis and host innate immune system) which make them absolutely indispensable to the cell. This makes them a target of almost all the invading pathogens including viruses. Therefore being a multifunctional organelle, the viruses choose mitochondria as a favourite organelle as they can easily take control of the whole cell and make it to promote or block apoptosis as per their need.

Introduction

Mitochondria besides acting as a power house of a cell are multifunctional organelles but it is also true that mitochondria are the most suitable target of cells under attack from microorganisms like viruses or ROS produced upon different viral infections although there are also various other targets. Mitochondria perform various other functions which make them absolutely indispensable to the cell, therefore by hijacking the mitochondrial functions upon different viral infection make them easy to take control of the whole cell. Mitochondria has been found to be involved in different signal transduction pathways, play role in process of aging, regulation of different biochemical pathways involved in cellular metabolism programmed cell death, in development, diseases immune response and cell cycle control [1-15]. The mitochondrion contains a single 16 kb circular DNA genome which encodes 13 polypeptides, 2 ribosomal 12 RNA, 22 tRNA. All of these by-products of mtDNA are essential in electron transport chain for the generation of ATP by the process called oxidative phosphorylation [16]. The ATP generation requires some proteins from both the nuclear genome as well as from mitochondrial Genome. Thus any injury to mitochondria DNA results in serious cell damage. The mtDNA being more suitable to damage is due to lack of protective histones and also it lies in close to electron transport chain which is the main centre of ATP production in mitochondria. Mitochondria possess two well defined compartments: the matrix, surrounded by the inner membrane (IM), and the inter-membrane space, surrounded by the outer membrane (OM). The inner membrane is folded into special structures called as cristae carrying special protein complexes required for electron transport chain and allows free transport of CO_2, O_2 and water only. The outer membrane and inner membrane encloses a space called as inter membrane space (IMS) which is fully loaded with apoptotic factors like cyt-c, SMAC/Diablo, endonuclease G which are released when an apoptotic signal is received by mitochondria ($\Delta\psi$m). The matrix contains different proteins and recyclable molecules required for energy production to be used to perform different functions.

Higher vertebrates have evolved two major mechanisms to control virus infection. One is based on the host's immune response against the virus infection, and the other is biased on cell autonomy, in which cells undergo certain physiological changes upon the onset of infection such as unscheduled activation of the cell cycle by viral proteins. The self-destruction of virally infected cells through the process of apoptosis generally serves to limit infection and the spread of viral progeny, and

therefore accords some degree of protection against infection. Many virus-encoded gene products (proteins) interfere with both the intrinsic and extrinsic apoptotic pathways by interacting directly or indirectly with components of the highly conserved biochemical pathways that regulate PCD or even necrosis (Figure 1). Viruses present a biological puzzle. On the one hand, they block apoptosis by interacting with Bcl-2 anti-apoptotic sensor proteins to prevent premature death of the host cell and so maximize virus progeny from a lytic infection or facilitate a persistent infection. On the other hand, a growing number of viruses appear to actively promote apoptosis by interacting closely with the pro-apoptotic Bcl-2 family sensor proteins upon the completion of a lytic infection and by serving to spread virus progeny to neighbouring cells while evading the host's inflammatory responses. Viruses may perform both functions depending on their need. Recent studies have shown that it is not just the majority of viruses, but also most other plant viruses, that force the cell to undergo the process of apoptosis. However, why the virus forces the host cells to undergo apoptosis is not fully understood and is presently being characterized. Therefore, additional intensive, detailed studies will serve to further elucidate the mechanisms of lytic infection and may provide new drug targets for the treatment of important virus infections.

Apoptosis major form of controlled cell death has a key role in the pathogenesis of many diseases including viral, cancer, inflammation, and neurodegenerative diseases. The process of programmed cell death (PCD) is controlled by a different range of cell signalling pathways originating either from the external environment of a cell (extrinsic) or from within the cell itself (intrinsic) [17]. The common event at the end-point of both the intrinsic and extrinsic pathways is the activation of a set of cysteine proteases (caspase). The extrinsic pathway originates at the plasma membrane following the engagement of a family of cytokine receptors, such as tumour necrosis factor receptor-1 (TNF-R1)
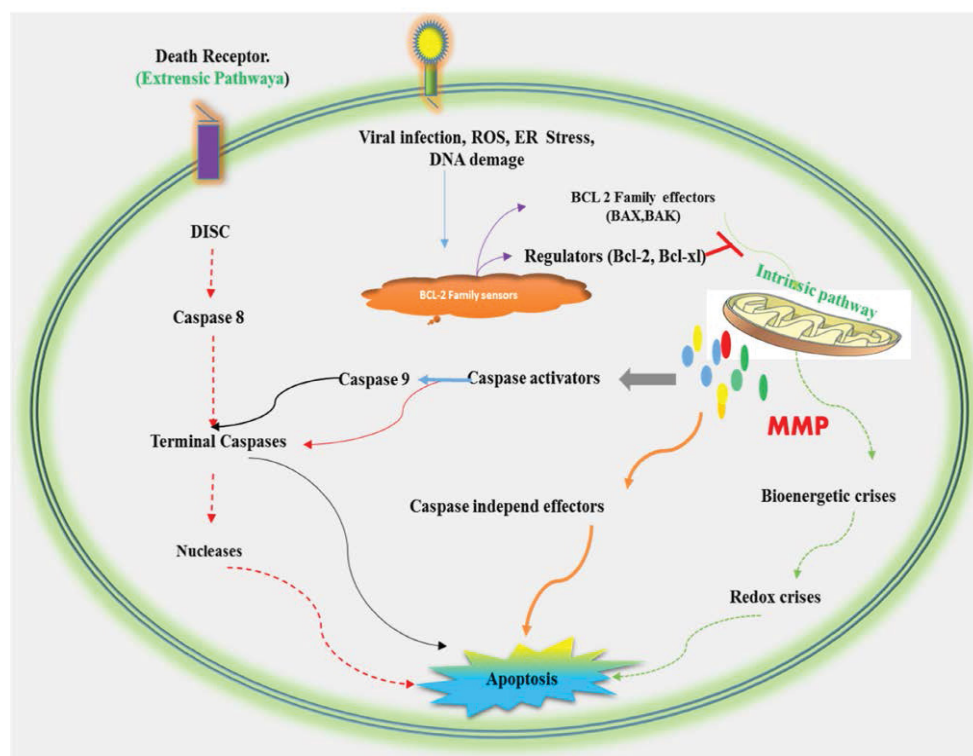
Figure 1: Represents the schematic diagram of extrinsic and intrinsic apoptotic pathways induced by different viruses. The extrinsic pathway originates at the plasma membrane by ligand/receptor binding results in the recruitment of several adapter proteins and proenzymes, which in turn activate caspases (caspase-8 and -10), and finally results in apoptosis and cell death. The intrinsic pathway is triggered by different extracellular or intracellular signals, such as viral proteins oxidative stress, that results in MMP (Δψm) loss and activation of the initiator caspase-9. Caspase-9, in turn, activates caspase-3, a major effector caspase responsible for the degradation of cellular substrates. The common event at the end-point of both the intrinsic and extrinsic pathways is the activation of a set of cysteine proteases (caspases). ROS-reactive oxygen species, ER-endoplasmic reticulum, DISC- death inducing silencing complex.

by their cognate ligands (TNF-α). Ligand/receptor binding induces the recruitment of several adapter proteins and proenzymes, which in turn activate caspase (caspase-8 and -10), and finally results in apoptosis and cell death [18]. The intrinsic pathway is triggered by different extracellular or intracellular signals, such as oxidative stress, that results in activation of the initiator caspase-9. Caspase-9, in turn, activates caspase-3, a major effector caspase responsible for the degradation of cellular substrates [19]. Apoptosis may be used by the host both to limit the production of viruses and to disseminate them [20-23]. However, viruses use the apoptosis process to produce sufficient virus progeny or facilitate virus release [24,25]. The PCD induced by virus infection has often been defined as typical apoptosis [26-28]. However, recent studies disclosed that non-apoptotic forms of PCD are important for the pathogenesis of certain RNA viruses, including the JC virus, hepatitis C virus, coxsackievirus B3, Enterovirus and dengue virus [21,29]. The mechanism of DNA virus-induced non-apoptotic cell death is not well known. Although not all signals initiating the apoptosis pathway are understood, in many but not all, cases, the tumor suppressor protein p53 is required to propagate the signal to commit suicide [30,31]. The fate of the cell to undergo apoptosis mainly depends on the dynamic balance between the Bcl-2 family sensor proteins, which both promote and inhibit apoptosis (Figure 1) [32]. Members of the Bcl-2 family sensor proteins represent a major key point in the apoptotic pathways. They appear to sit at a node in the apoptotic pathway at a point of integration for stimuli that provoke apoptosis and, in many but not all cases, they appear to influence the activation of caspase family members (proteases), which perform the "execution" phase of apoptosis, by

cleaving a number of cellular proteins to bring about the destruction of cellular structures [33].

Mitochondria in normal and apoptotic cells

Mitochondria are multifunctional organelles covered by outer membrane (OM), and inner membrane and in between lies the inter membrane space. The IM is folded into special structures called as Christie with increases the surface area of inner membrane. The Christie is in turn equipped with protein complexes required for electron transport chain (ETC), ANT and ATP synthase. To function properly, the IM is almost impermeable in physiological conditions there by allowing the respiratory chain to create an electrochemical gradient. The electric potential created is important for maintaining MMP (Δψm) of IM. The pumping of proton by electron transport chain out of the inner membrane in necessary for activation of ATP synthase which phosphorylates ADP to ATP. The ATP generated on the matrix side of IM is in turn exported by ANT in exchange of ADP. The outer membrane is highly rich in voltage dependent channels (VDAC), which in normal physiological conditions is permeable to solutes of size up to 5000 Da. The IMS is chemically equivalent to cytosol in terms of low molecular weight solutes and is rich in special set of proteins. Only 13 subunits of the respiratory chain in the IM are encoded by the small (about 16,500 bp) mitochondrial genome, which resides in the matrix. However rest of almost more than 99% proteins are encoded by nuclear genome and selectively imported into either of the mitochondrial compartments. The protein composition of the OM, IM, inter membrane space and matrix thus is very unique.

The MMP (Δψm) loss results by the imbalance in the membrane potential of both inner as well as outer membranes, which results in arrest of biosynthetic functions as well as bioenergetics crises in a cell. The MMP (Δψm) loss results in the release of different proapoptotic proteins from IMS like cytochrome c (Cyt c) and Smac/DIABLO, as well as caspase independent death effectors such as apoptosis-inducing factor (AIF) and endonuclease G (EndoG) [34-36].This results in the induction of both caspase independent and caspase dependent cell death [37]. Accidentally induced MMP (Δψm) contributes to the development of diseases characterized by an excess of cell death, such as ischemia/reperfusion injuries, trauma, toxic/metabolic syndromes as well as chronic neurodegenerative conditions like amyotrophic lateral sclerosis or Alzheimer, Parkinson, and Huntington diseases [38,39]. MMP (Δψm) is highly regulated process controlled by a different complex network of signaling pathways that involves both endogenous (e.g. pro- and anti-apoptotic Bcl-2 family proteins, p53, kinases, phosphatases, lipid second messengers [40-46], ROS, Ca^{2+} overload as well as exogenous factors (e.g. viral proteins, toxins, pro-oxidants [29,47-50]. As MMP (Δψm) loss results serious damage to cell and were from the cell has no chances to heal. Therefore in the intrinsic apoptotic cascade, any viral factor that influences MMP (Δψm) must have a major impact on cell fate, either by inducing or blocking cell death [29].

From the last few years, major efforts and also success have been made to understand of the mechanisms underlying MMP (Δψm) in disease and health. Recently different models have been proposed and worked in both in vivo and in vitro studies explaining the possible mechanisms underlying the MMP. MMP loss in whatever way results lead to both functional as well as structural collapse of mitochondria that commits the cell to death [51,52]. The question still remains unanswered how these structural modifications of mitochondria might impact on viral infection.

Different models explaining MMP (Δψm) loss

The loss of MMP (Δψm) associated with apoptosis have different effects on both the outer as well as inner membrane which further may or may not result in matrix swelling. The presence of large number of VDAC on OM makes it highly selective and freely preamble to solutes and small metabolites (5 kDa). This cut-off maintains not to lose the matrix from the IMS. The apoptosis associated loss of MMP (Δψm) has been explained by presenting different models. Usually 4 models have been put forward while carrying the in vitro studies on purified mitochondria.

1st model: The first model explains the permeabilization of IM, when some viral proteins or chemical substances interact with the ANT located on IM which results in osmatic matrix swelling and OM rupture (Figure 3). The OM rapture because the surface area of the IM with its folded cristae exceeds that of the OM (Figure 3). Many well-known MMP (Δψm) regulators, like Bak, Bax, Bcl-xl, Bcl-2 and cyclophilin D (mitochondrial target of cyclosporine A,), interact with the ANT located on mitochondrial inner membrane [53-55]. Recent studies has discovered various viral proteins with apoptosis inducing and apoptosis-inhibitory (pUL37x from cytomegalovirus) (Vpr from
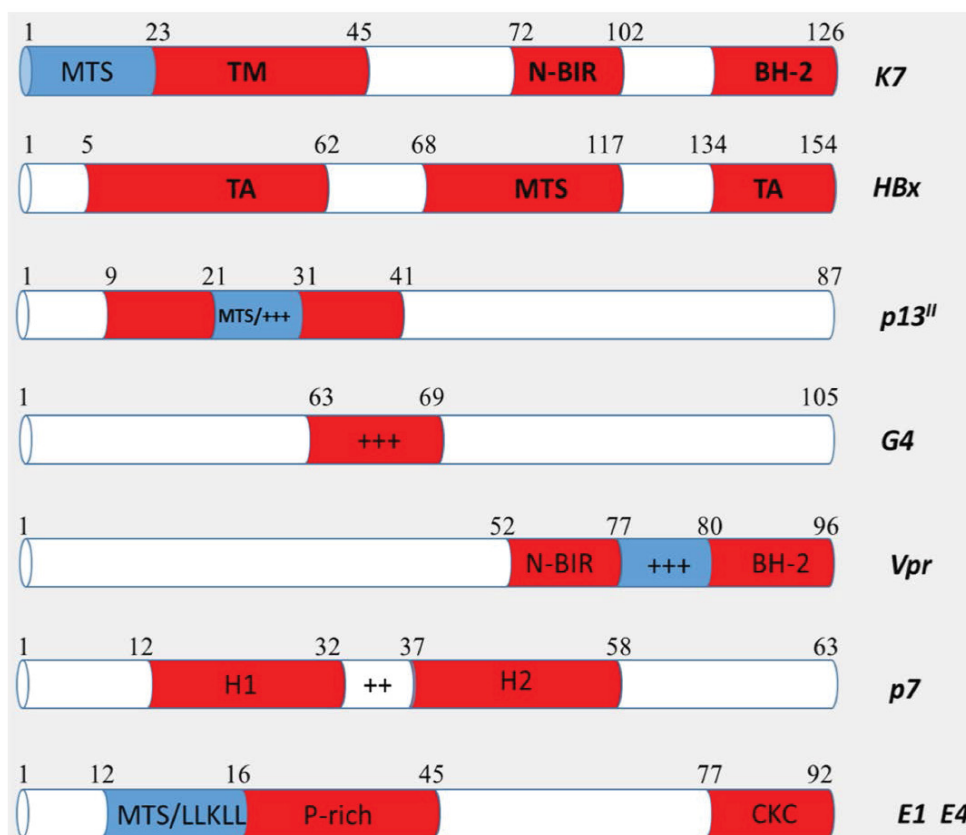
Figure 2: Showing the functional domains identifies in different viral proteins acting through mechanisms different from that of vBcl-2. *TM*, transmembrane domain; *MTS*, mitochondrial targeting signal; *LLKLL*, cut leucine-rich region; *TA*, transactivation domain; *BH2*, BCL-2 homology region; *N-BIR*, baculovirus internal repeat-like domain; *CKC*, domain required to collapse the keratin network, which also contains sequences directing multimerization. +++, positively charged amphipathic -helix; *H1, H2,* -helical regions; The MTS/LLKLL sequence of HPV E1∧E4 protein serves both for keratin binding and mitochondrial targeting .

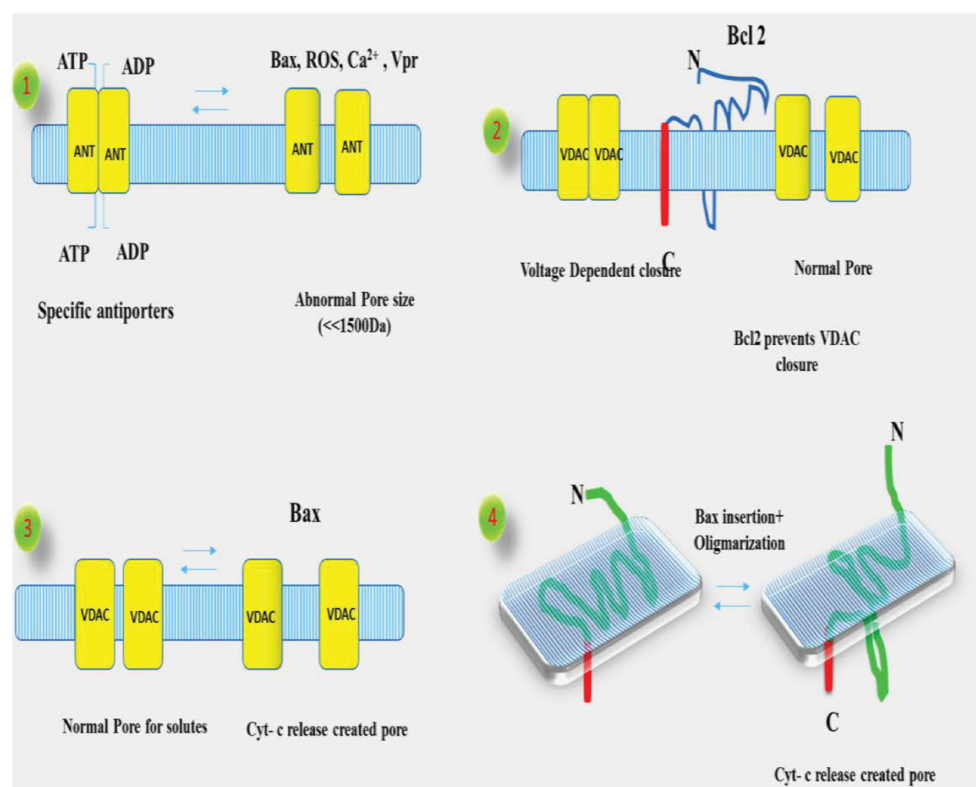**Figure 3:** Schatemic diagram explaining the different possible mechanisms of MMP (Δψm) loss due to permebilization of both outer as well as inner membrane. *1*, Normal adenine nucleotide translocator (ANT) functions as a vital ATP/ADP-specific antiporter or in case of MMP (Δψm) loss can act as a lethal nonspecific pore. Pore formation is aided by interaction with cyclophilin D (CypD). *2*, The inhibition of voltage dependent closure of VDAC is carried by anti-apoptotic protein Bcl-2 which otherwise will be destructive. *3*, The voltage-dependent anion channel (VDAC) may be converted into a cytochrome-*c*-release permanent pore. *4*, Oligemerization of Bax can form a nonspecific pore without requiring interactions with different mitochondrial membrane proteins.

HIV-1) activity that also interact particularly with VDAC and ANT [56,57].

2nd model: The second model explains the pore formation by VDAC on OM without affecting the inner membrane (Table 1,2). This MMP (Δψm) loss has further been found to be enhanced by Bax and inhibited by Bcl-2 *in vitro*. The formation of pore on the outer membrane by the interaction of Bax with VDAC when inhibited by Koenig's polyanion, (VDAC inhibitor), results that it is VDAC, not Bax, which plays the actual role of MMP (Δψm) loss on the outer mitochondrial membrane.

3rd model: The third model explains that the oligomerization of Bax on mitochondrial membrane when Bax is translocating from cytosol to mitochondrial membrane results in the formation protein translocation channel which is independent of VDAC. Thus the Bax and VDAC act independently depends upon the apoptotic inducing signal (Figure 3,4) [58,59].

4th model: In the fourth model, the VDAC regulates MMP (Δψm) through yet another mechanism related to its functional and physical contact with the ANT (Figures 3 and 4). An apoptosis-related increase in DYm (IM) would transfer charges to the OM, thereby resulting in closure of the VDAC (which closes when voltage increases) [60]. The Bcl-2 may play its role by acting as an ionophore (Ion permeable and protein impermeable) to maintain the electrical mitochondrial membrane potential across the outer membrane. Therefore Bcl-2 indirectly plays its role by exchange of ATP/ADP (VDAC- and ANT-dependent continuous exchange of ATP/ADP)across mitochondrial membrane which results in avoiding the interspace matrix swelling which results as a consequence of instability in VDAC/ANT [60,61].

Role of mitochondria in host immune response

The viral entry into the host cell activates signaling pathways, leading to the production of IFN's, inflammatory cytokines and chemokine's which limit or eliminate the invading virus. The host cell uses pattern recognition receptors (PRR's) to detect viral foreign nucleic acids. There are three types of PPR's-TLR's, RIG 1 and nucleotide oligomerization like receptor(NOD) TLR-3 are present in all immune cells and recognize dsRNA. The RIG-1 is special receptors with c terminal domain having helicase activity which is ATP dependent, whereas the N terminal domain of RIG-1 has two caspase activation and recruitment domains (CARDs). The conformational changes of RIG 1 expose its CARD domains to bind and activate downstream effectors leading to the formation of enhance some triggering NF-κB production [62].

Recently another protein which functions downstream of RIG-1 with CARD domain have been identified. This proteins are known by different names like mitochondrial anti-viral signaling protein (MAVS), virus-induced signaling adaptor (VISA), IFN- promoter stimulator 1 (IPS-1) and CARD adaptor inducing IFN- (CARDIF) [63-66]. Research indicates that the MAVS has an important role in raising the antiviral defences in the cell. The in vivo knockout studies with MAVS -/- deficient mice has shown compromised immune response against viruses, though they don't show any developmental abnormality
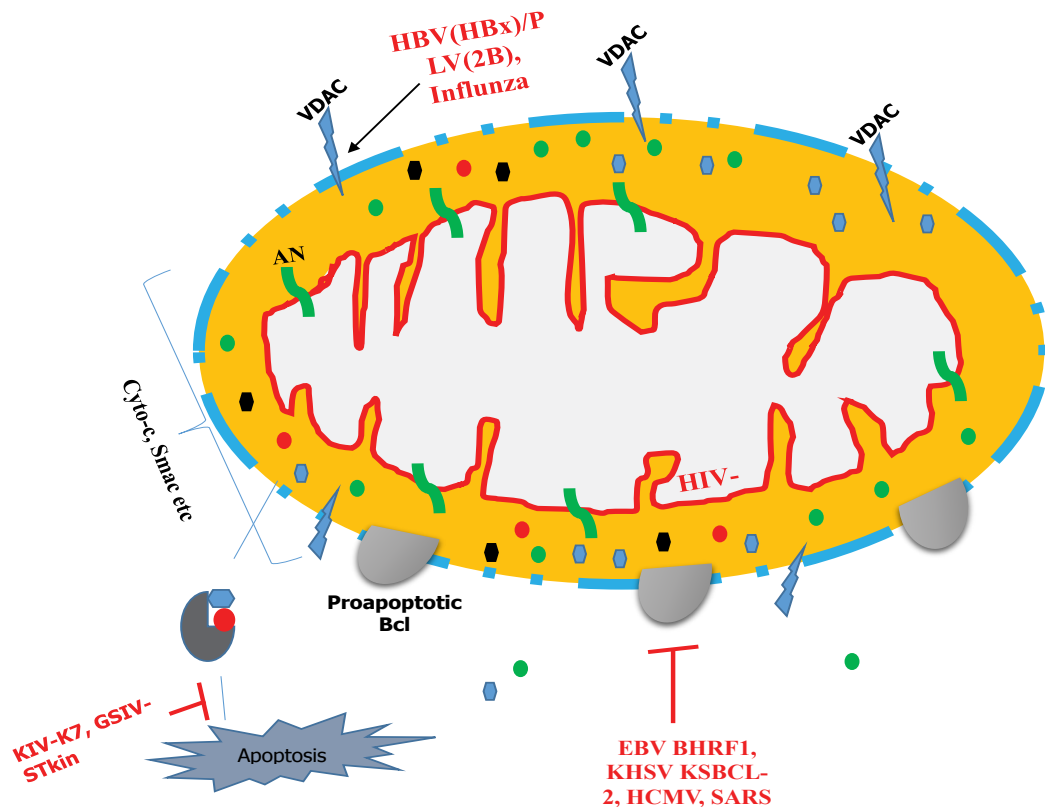
Figure 4: Showing interaction of different viral proteins with mitochondria. The apoptotic signal received by mitochondria results in MMP (Δψm) loss by imbalance in BCL-2 family protein which ultimately activates downstream apoptotic signals.
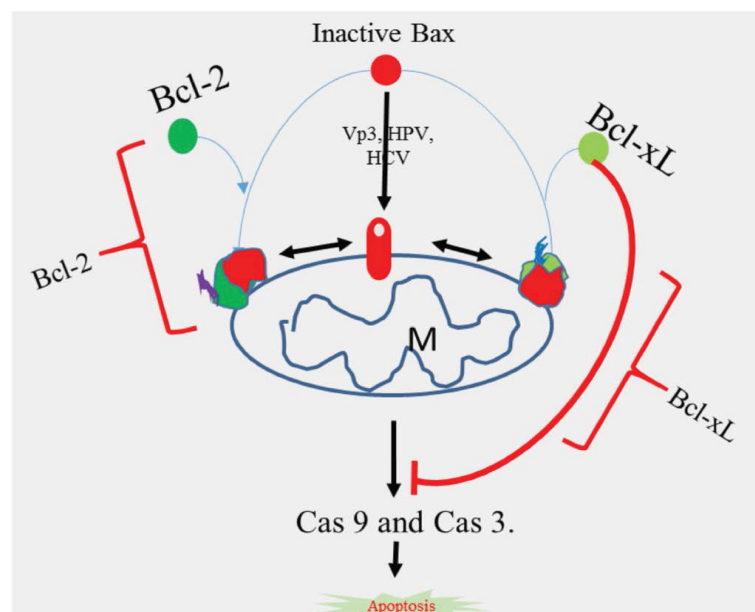
Figure 5: Inactivation of Bax can be directly converted into active form by interacting with proteins with BH3 domains. The activated Bax undergoes oligomerization on mitochondrial membrane and results in pore formation that ultimately leads to MMP (Δψm) loss. However the interaction of Bax with anti-apoptotic proteins Bcl-2 and Bcl-xl drives the relocalization of Bax exposing the N terminal domain that unable its insertion into mitochondrial outer membrane. Recent studies have shown that Bax can be activated by different viral proteins other than containing BH3 domains. However the complete mechanisms are not well understood. Example like (GSIV -ST-kinase)

Figure 6: GSIV ST-kinase induced MMP loss by JC1 lyophilic dye in grouper fish GF-1 cells at 24 hpt, upon transfection by ST kinase (g-i) and control vectors (d-f). Hydrogen peroxide treatment (a-c) is as a positive control. The red color indicates the healthy mitochondria whereas the increase in green fluorescence indicates the MMP loss.

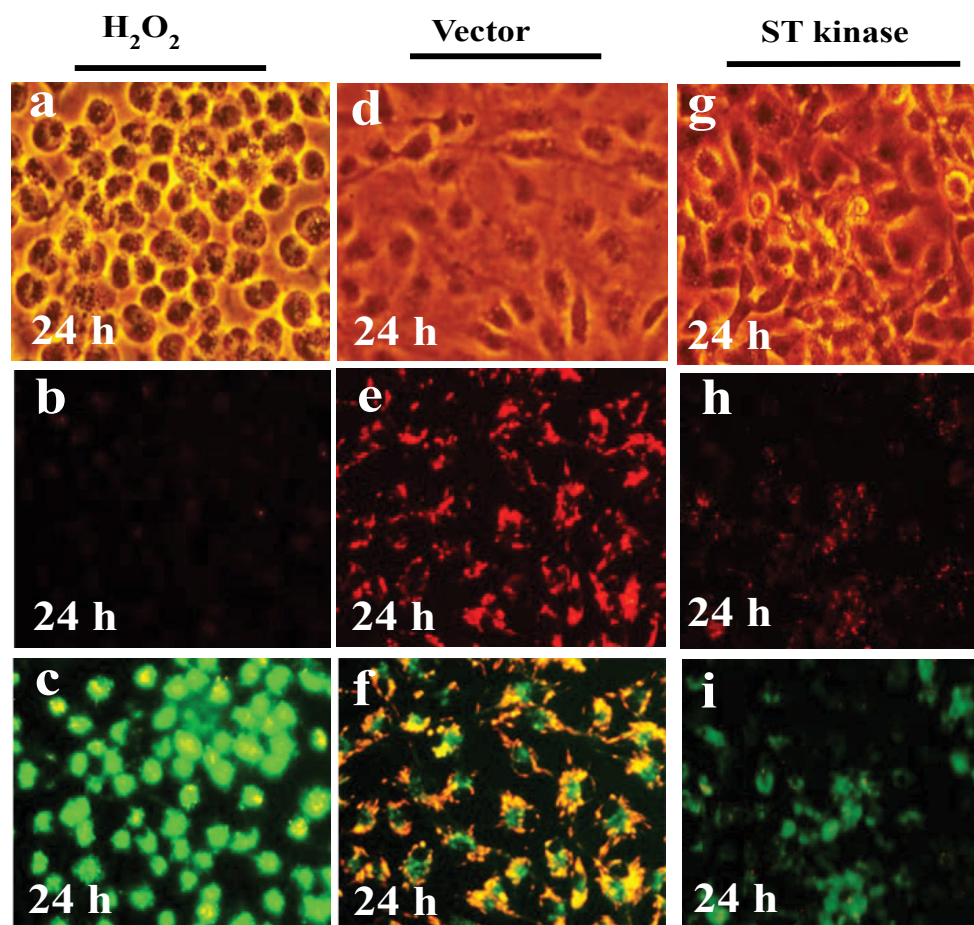[67]. Overexpression of MAVS leads to activation of NF-κB and IRF-3, leading to the induction of type I interferon response. In the absence of MAVS, this effect is abrogated [68] indicating the specific role of MAVS in inducing antiviral response. Although the present studies about the proteins acting downstream of MAVS to induce interferon production has not yet given any solid clue. The C-terminal Trans membrane domain of MAVS has been found vital in targeting the proteins to the mitochondrial outer membrane instead of protein rich region [68]. Further domain studies have revealed that the C terminal Trans membrane domain of MAVS share similarity with the c terminal tails of various proteins located on the mitochondrial outer membrane like Bcl-xl and Bcl-2. Therefore the ability of viruses to hijack the localization of MAVS to different cellular organelles instead of their target organelles or affecting their cleavage from mitochondria ultimately effects the interferon production which viruses use to protect from host immune response.

Viral proteins targeting mitochondria

Many virus-encoded gene products (proteins) interfere with both the intrinsic and extrinsic apoptotic pathways by interacting directly or indirectly with components of the highly conserved biochemical pathways that regulate apoptosis or even necrosis [32]. Viruses present a biological puzzle. On the one hand, they block apoptosis by interacting with Bcl-2 anti-apoptotic sensor proteins to prevent premature death of the host cell and so maximize virus progeny from a lytic infection or facilitate a persistent infection. On the other hand, a growing number of viruses appear to actively promote apoptosis by interacting closely with the pro-apoptotic Bcl-2 family sensor proteins upon the completion of a lytic infection and by serving to spread virus progeny to neighbouring cells while evading the host's inflammatory responses. Viruses may perform both functions depending on their need. Recent studies have shown that it is not just the majority of aquatic viruses, but also most other viruses, that force the cell to undergo the process of apoptosis. Obviously, viruses target the central parts of the proapoptotic signal transduction and execution machineries. Examples of proteins that subvert pro-apoptotic signals include viral proteins that block tumour necrosis factor (TNF) and its signals [69] viral proteins that inhibit ds-PKR, a protein kinase that is activated by ds-RNA (and which can initiate apoptosis in virus-infected cells) [70] viral proteins that inhibit p53 (a transcription factor that is often rate-limiting for DNA damage-induced apoptosis) [71,72] and viral proteins that inhibit caspase [73,74]. In addition, viral proteins are often acting on mitochondrial receptors and membranes to inhibit or induce MMP ($\Delta\psi m$) and this is the focus of the present paper (Tables 1 and 2).

Many viral proteins that alter mitochondrial ion permeability and/or membrane potential have been identified. Most prominent of these are discussed below:

1. Poliovirus (PLV) infection causes acute disease called as paralytic poliomyelitis which results in flaccid paralysis due

Virus	Protein	Intracellular Localization	Effect on mitochondrial morphology	References
HBV	X	M,N	Yes	98-101
HIV	Vpr	M,N	Yes	39
IAV	PB1-F2	M,N	Yes	93
HTLV-1	P13 II	M,N	Yes	40
BLV	G4	……	Yes	124
AVE	VP3. 2C	M	Yes	112,113
WDSV	Orf C	M,C	Yes	76
HPV type 16	E1^E4	M		79,81
NNV	B2	M,C	Yes	123
GSIV	ST-Kinase	C	Yes	122

Table 1: Proapoptotic viral proteins acting on the mitochondria.

Virus	Protein	Intracellular Localization	Protects Cell from	References
KSHV	K7 or vIAP	M, ER, PM	TG, TNF-a, anti Fas	110-111.
HCV	NS2	ER (M with CIDE-B)	CIDE-B	117-121.
Myxoma	M11L	M	STS, anti-Fas, PPIX	112-124
Vaccinia	FIL	M	STS, anti-Fas	71
CMV	vMIA	M	Oxidants, anti-Fas, Bax, tBid, TN,TG, STS, BFA, NFX, CPX, HCQ	102

Table 2: Antiapoptotic viral proteins acting on the mitochondria.

to caspase dependent apoptosis of motor neurons [75]. The polio virus encoded viroprotein 2B induces a perinuclear redistribution of mitochondria and ultimately alters their morphology resulting in MMP ($\Delta\psi$m) loss [76] in a similar fashion as by HBx protein of hepatitis B virus.

2. The overexpression of Orf C of WDSV, a retrovirus causing benign tumors in fish characterized by seasonal regression [77,78]. Cause similar perinuclear clustering of mitochondria and MMP ($\Delta\psi$m) loss followed by cytochrome c release and other apoptosis inducing factors.

3. The E1 and E4 are two early genes encoded by spliced mRNAs of HPV virus genome. The *in vitro* studies carried on mature human keratinocytes have shown that E1 E4 binds and collapses cytokeratin network of cells [79]. Then makes a way towards mitochondria by special N terminal Lucien rich mitochondrial localization signal were it detaches mitochondria and get them aggregated around the nucleus. The detached mitochondria undergo morphological change and results in MMP ($\Delta\psi$m) loss and apoptosis. Several other proteins like E6 and E7 play a role in prevention of p53 induced apoptosis [80-83].

4. The anti-apoptotic core protein of HCV inhibits the DCA induced mitochondrial apoptosis. The core protein inhibits DCA induced mitochondrial apoptosis by inhibiting Bcl-2 family proteins. The viral core protein decreases the expression of Bax and increases the expression of Bcl-xl anti-apoptotic protein but there occurs no overall change in Bax in between cytosol and mitochondria. The increase in Bcl-xL expression suppress the cytochrome c release from mitochondria and inhibits DCA induced apoptosis. Another research has shown TNF alpha induced apoptosis is blocked by HCV core protein but sensitizes cells to Fas mediated apoptosis [84,85].

5. The *in vitro* studies of protein M and protein P of VSV rhabdovirus causes mitochondrial apoptotic pathways. The virus usually causes apoptosis of neurons [86]. The M protein causes the modulation of the BCL-2 family proteins whereas the exact mitochondrial apoptotic pathway in case of protein P is still unknown [87-90].

6. The protein PB1-F2 encoded by the genome of Influenza A virus is a death inducing gene. It mainly induces mitochondrial mediated cell death [91]. It has a C-terminal mitochondria localization signal, which is conserved in the influenza family [92,93]. PB1-F2 while localizing to mitochondria usually interacts directly with VDAC1 and ANT3 figure 4 [94]. This interaction involves both OM and IM of mitchondria and ultimately leads the release of apoptotic protein from IMS thereby causing cell death Therefore protein PB1-F2 distorts the mitochondrial morphology leading to MML loss and cell death.

7. Viruses altering intracellular distribution of mitochondria so that the host cell mitochondria is subservient to the needs of the virus by HBV

Hepatitis B virus x protein (HBx) is a protein essential for viral replication and shows oncogenic properties in animal models [95]. The overexpression HBx sensitizes hepatocytes to apoptosis induced by different stimuli such TNF-α and TRAIL [95]. The overexpression studies of protein HB x has shown that protein causes apoptosis by perinuclear mitochondrial distribution coupled with MMP ($\Delta\psi$m) loss. Mutant Studies of HBx has revealed that hydrophobic residues (MTS) are important for mitochondrial localization, MMP ($\Delta\psi$m) loss and cell death [96,97]. Moreover, PT inhibitors, antioxidants and the anti-apoptotic proteins Bcl-2 and Bcl-xL are able to protect HBx expressing cells from death. HBx reportedly interacts with at least two mitochondrial proteins, namely heat shock protein 60(HSP60) [98] and theVDACisoformVDAC3 [97] but still the exact mechanism of interaction is not clearly understood. It is unknown whether these interactions occur simultaneously. The apoptosis induced by HBx protein Viz. mitochondrial dysfunction and changes in mitochondrial morphology has been found to play a major role in chronic liver disease and carcinogenesis [99-102].

8. The vMIA (Viral mitochondrial inhibitor of apoptosis) protein of cytomegalovirus (HCMV) is an anti-apoptotic protein which blocks the mitochondrial mediated cell death [103] .The protein has N terminal mitochondrial localization signal and C terminal

anti-apoptotic domain which recruits Bax to mitochondria and inhibits apoptotic process induced by MMP ($\Delta\psi$m) loss [104]. It localizes to mitochondria and interacts with ANT and Bax [105,106]. It protects the cells against CD95 ligation [36], over expression of Bid [106], staurosporine [105] and oxidative stress induced cell death [107,108]. In overall the vMIA protein maintains the morphology of mitochondria without MMP ($\Delta\psi$m) loss [109]. In *in vitro* studied, the overexpression of vMIA in cells lacking Bax results in mitochondrial alteration which indicates the Bax is not involved in vMIA mediated mitochondrial cell death. The exact mechanism of how vMIA works is not fully understood but it do protects the cells from downstream events of apoptosis but not upstream of mitochondrial by blocking Cyt c release, caspase 9 activation and ATP generation.

9. KHSV encoded K15 protein possess a special putative repeat at its c terminus region. The localization of k15 protein into mitochondria binds to pro apoptotic protein Nip3 and anti-apoptotic protein Hax-1 with sequence similarity to Bcl-2 [110]. This makes the infected cells unable to undergo the process of apoptosis. Therefore k15 plays a key role in tumorigenesis and is usually expressed during latency in infection tumors [111].

10. The *in vitro* transient study carried upon two AEV virus encoded genes Vp3 (structural protein) and protein 2C (nonstructural) protein has revealed that both the proteins localizes to mitochondria. Vp3 induces Cas-3 mediated cell death pathway whereas 2c induces the release of cytochrome c by loss of MMP ($\Delta\psi$m) and ultimately activates downstream Cas 9 and Cas 3 leading to apoptosis [112,113]. The 2c protein has been found highly conserved among the picornaviruses but the exact role played by 2c in viral replication is still not clearly understood.

11. The protein 7A encoded by SARS-Cov genome is a viral apoptosis inducing gene by inhabiting the host anti apoptotic gene Bcl-xL [114,115]. Further *in vitro* studies has shown NSP15 protein encoded by SARS virus has been unable to block apoptosis induced by staurosporin whereas it blocks apoptosis in a dose dependent manner upon overexpression of MAVS in cultured cells [116].

12. Viruses using the mitochondrial machinery to modulate the host interferon response (HCV virus reducing host beta-interferon production through the RIG1 pathway):

The protein NS3/4A encoded by the genome of HCV usually persists in its host by effecting the interferon production involving RIG-I pathway [117,118]. The protein is a serine protease which cleaves MAVS at cys-508, which is located near its mitochondrial targeting domain. The protease activity makes MAVS inactivated by detaches MAVS from mitochondria as they are nonfunctional in free form. Further studies [119,120] have revealed that the NS3/4A can co-localize to mitochondria directly, however a mutation by arginine at cys-508 has shown can prevent the cleavage of MAVS from mitochondria [120]. Therefore this indicates that HCV hijacks the MAVS of the mitochondria to suppress the host immune response.

13. Cleavage of mitochondrial MAVS (mitochondrial anti-viral proteins) to paralyze the host immune response by GB virus. Similarly the GB virus B belonging to family Flaviviradie cleaves MAVS from mitochondria in a similar fashion as does

by HCV viruses which weakens the host immune response be decreasing the interferon production [121]. However the mutation studies carried in the HCV has shown the importance of cysteine residue in cleaving the MAVS from mitochondria.

14. The GSIV fish virus serine/theroine kinase gene induces apoptotic cell death via p53 mediated up regulation of Bax and down regulation of Bcl-2 which causes MMP ($\Delta\psi$m) loss [122]. This loss of MMP ($\Delta\psi$m) then mediates cell death signaling, which in turn results in an activation of the caspase mediated cell death pathways at the mid to late stage of viral replication.

15. The fish Betanodavirus non-structural protein B2 is a proapoptotic gene. The B2 protein results in mitochondria mediated necrotic cell death in grouper liver cells (GL-av). The transiently expressed B2 upregulates expression of the proapoptotic gene Bax and loss of MMP ($\Delta\psi$m) but not cytochrome C- release [123,124]. Taken together, results suggest that B2 upregulates *Bax* and triggers mitochondria-mediated necrotic cell death independent of cytochrome *c* release.

16. The sub major capsid protein, VP3 of aquatic birnavirus upregulates the proapoptotic protein Bad in fish and Mouse cells. The sub major capsid Vp3 induced up regulation of Bad expression alters mitochondrial function including MMP ($\Delta\psi$m) loss and activation of initiator caspase 9 and caspase 3 [125,126].

17. Viruses appropriating the host mitochondrial protein p32 to self-replicate (Rubella virus: The capsid protein encoded by the genome of Rubella virus hijacks the function of p32 mitochondrial matrix protein. Studies have shown that the capsid protein possess two clusters of arginine residues which are required for its interaction with P32 protein. The expression of the capsid protein alone in cell culture studies has shown to induce perinuclear clustering of mitochondria and the formation of electron-dense intermitochondrial plaques, which are both observed in RV-infected cells [127]. Mutagenic studies in which recombinant virus encoded arginine to alanine mutation in the p32 binding region of capsid protein resulted in decreased mitochondrial clustering, indicating that interactions with this cellular protein are required for capsid-dependent reorganization of mitochondria and replicated to lower titers. Therefore disruption of stable interactions between capsid and p32 was found to be associated with decreased production of sub genomic RNA which in turn lowers virus replication and ultimately leads to less virus progeny [127].

Use of molecular mimicry by viruses to invade mitochondria

During the process of coevolution some viruses have evolved to encode proteins that mimic the activity of their host proteins to successfully complete their life cycle without the hindrance of host immune response. For example Mimivirus, a member of the newly created virus family Mimiviridae, encodes a eukaryotic mitochondria carrier protein (VMC-I) [128], this protein mimics the function of the host cell's mitochondrial carrier protein which controls the mitochondrial transport machinery in infected cells. Therefore taking control of host cells transport of ADP, dADP, TTP, dTTP and UTP in exchange for dATP across membrane, for energy production which virus uses for replication of its genome to produce new progeny [128]. In addition several other proteins encoded by the same virus (L359, L572, R776, R596, R740, R824 L81, R151, R900 and L908) with

mitochondria localization signals, which suggest that mimivirus has evolved a strategy to take over the control of host energy production units (mitochondria) for its use to replicate [128].

Viruses deplete the host mitochondrial DNA (mtDNA) to evade from the mitochondria evoked antiviral host responses

Mitochondria play an important role in host cell survival. In addition to respiratory functions, plays a crucial role in cellular antiviral defenses including apoptosis and the type 1 interferon response. Therefore performing various other functions which make them absolutely indispensable to the cell, different viruses appear to have adopted the strategy of damaging the host cell mitochondrial DNA to take control of the whole cell. Thus the ability of viruses to interfere with Herpes simplex virus (HSV) causes both productive and latent infections in its human host. The HSV-1UL12 gene encodes two distinct proteins: UL12 and UL12.5. The UL12 is an alkaline nuclease, and the UL12.5 is an N terminally truncated 500-aa polypeptide that lacks the first 126 residues of UL12 [129]. Mostly UL12 is known to play a crucial role in viral genome replication and processing [130]. UL12.5 does not accumulate in nucleus but also nuclease and strand-exchange activities [131]. UL12.5 localizes predominantly to mitochondria, where it triggers massive degradation of mitochondrial DNA early during HSV replication [132]. In addition to that UL12.5 has been found to acts directly within the mitochondrial matrix to degrade mitochondrial DNA by its nuclease activities [133].

In case of HCV infection, the generation of reactive oxygen species causes damage to host mitochondrial DNA. The Zta protein of EBV interferes with the mitochondrial single strand DNA binding protein to reduce the mitochondrial DNA replication and increase in viral DNA replication [134]. Interestingly, depletion of mtDNA has also been observed in HIV/HCV coinfected humans. However, the fully understood biological importance of mitochondrial DNA damage during the whole infection cycle still remains confusing.

Conclusion

Mitochondria are now known as being vital in the regulation of cell survival and death. Therefore, an ever-expanding number of signal-transducing molecules, like viral effectors have been identified to act on mitochondria and to influence MMP ($\Delta\psi$m). Recent studies have shown that many viruses encode protein that are targeted into mitochondria and control a number of functions, including apoptosis, cell growth, ionic haemostasis and signalling pathways. Many virus genomes (HIV, HCV, KHSV and CMV) encode various proteins in their hosts having both pro and anti-apoptotic activity and activate them depending on their need. This highlights the mechanisms by which these viruses regulate the dynamic balance between the anti and pro- apoptotic Bcl-2 family proteins to increase their chances of survival inside the host cell. The overall data summarized in the review have shown that mitochondria act as a one of the cherished organelle for invading viruses and many virus encoded mitochondrial targeted proteins play a significant role in the pathogenesis of the disease they cause. Therefore exploring the exact roles of viral genes as well as whole viruses in apoptosis at molecular level could lead to the discovery of novel therapeutic strategies and pathogenic insights into different viral diseases. Essential and important questions, however still remains unanswered concerning the molecular mechanisms of MMP ($\Delta\psi$m) induced by viral proteins/viruses. Therefore answering these queries may result in identification of key MMP ($\Delta\psi$m) regulatory process involved in MMP ($\Delta\psi$m) loss and viral host protein protein interactions. The prevention and treatment of viral infection is quite challenging task but studying virus/host/protein interactions at molecular level will help in providing various opportunities for both identifying as well as rationally designing new cytotoxic or cytoprotective drugs.

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