We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 17

Modulation of Mitochondria During Viral Infections

Latif Reshi, Hao-Ven Wang and Jiann-Ruey Hong

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73036

Abstract

Mitochondria are organelles critical for cell survival because they produce ATP and modulate programmed cell death (PCD) pathways. PCD pathways are important in many clinical disorders, such as ischemia/reperfusion injuries, trauma, and toxic/metabolic syndromes, as well as in chronic neurodegenerative conditions, such as amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease. Moreover, many viruses and other pathogens target the mitochondria. Viruses induce the production of various proteins in their hosts that have proapoptotic and anti-apoptotic activities, depending on the cellular environment. More specifically, many viruses that target mitochondria regulate the balance between the anti- and proapoptotic Bcl-2 family proteins and thereby increase their own survival within the host cell. Recent studies indicated that mitochondria centralize several critical innate immune responses based on the presence of several important signaling proteins within the mitochondria: mitochondrial antiviral signaling (MAVS), stimulation of interferon genes (STING), and NLR family member X1. Therefore, mitochondria are not only vital because they regulate cell survival and death but also they have broad roles in the control of cell functions following pathogen invasion. This chapter highlights the tight interplay between viral infection and mitochondria.

Keywords: virus, apoptosis, mitochondria, mitochondrial membrane potential (MMP), diseases, Bcl-2 family, viral death genes

1. Introduction

1.1. Viruses and hosts

Viral diseases are becoming increasingly common worldwide, so it is important to identify the causative species and examine the underlying pathogenesis to prevent future epidemics and reduce the spread of new diseases. Although many host responses can contribute to the pathogenesis of viral diseases, little is known about the role of mitochondria in viral pathogenesis.

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

Mitochondria are suitable targets for infectious microorganisms, such as viruses, because they act as powerhouses of the cell and have various other important functions. Therefore, "hijacking" the mitochondria disrupts overall cell function and makes it easy for a virus to control the cell and propagate. The host, in turn, has several responses that it uses to protect itself from viral invasions. One defense mechanism is based on the immune system, and another is based on cell autonomy, in which cells undergo certain physiological changes upon the onset of infection, such as unscheduled activation of the cell cycle following induction by certain viral proteins. When an infected cell undergoes programmed cell death (PCD), which includes apoptosis, autophagy, and necroptosis, this can prevent the spread of the virus infection to neighboring cells. A further complication is that viruses often promote apoptosis, but they can also block apoptosis by interacting with different signaling molecules of the host cell. Many viruses, especially human viruses, can perform either function, depending on the underlying conditions. Recent studies have shown that most viruses force cells to undergo apoptosis. However, from the perspective of the virus, apoptosis of the host seems to provide no benefit, so this is a topic of the current research. Therefore, additional studies that elucidate the mechanisms underlying the induction of the virus-induced PCD and cell lysis may help to identify new drug targets for the treatment of viral infections.

1.2. Intrinsic and extrinsic pathways of apoptosis in viral infections

Programmed cell death has a key role in the pathogenesis of many conditions including viral diseases, cancer, inflammation, and neurodegenerative diseases. Apoptosis is a highly complex process that is controlled by numerous cell signaling pathways [1]. The common event at the end point is activation of a set of cysteine-aspartic proteases (caspases) [2, 3]. Apoptosis may benefit host cells by limiting the production and dissemination of viruses [4]. However, apoptosis may benefit viruses if it allows them to increase production and dissemination of progeny [5, 6]. The PCD induced by a virus infection is often described as "typical apoptosis" [7]. However, recent studies reported that nonapoptotic forms of PCD are important for the pathogenesis of certain RNA viruses, including the JC virus, hepatitis C virus (HCV), coxsackievirus B3, enterovirus, and dengue virus [8]. The mechanism of DNA virus-induced nonapoptotic cell death is not well understood. Although not all signaling pathways that induce apoptosis are fully understood, the fate of a cell undergoing apoptosis mainly depends on the balance between the Bcl-2 family sensor proteins, which can promote and inhibit apoptosis (**Figure 1**) [9–11]. Recent studies have shown viral pathogenesis that involves oxidative damage and apoptosis.

1.3. Role of ROS in viral diseases

Recent studies have shown that mitochondria are the targets of the reactive oxygen species (ROS) that are produced inside a cell during viral infections, and that mtDNA is a major target of these ROS [11]. Mitochondrial ATP generation requires proteins from the nuclear and mitochondrial genomes. ROS disrupt the oxidative production of ATP, which is required for normal cellular function, because damage of mtDNA disrupts the normal synthesis of proteins needed for mitochondria function and making them suitable targets for attack by ROS produced during infections by viruses and other microorganisms, although ROS also have other

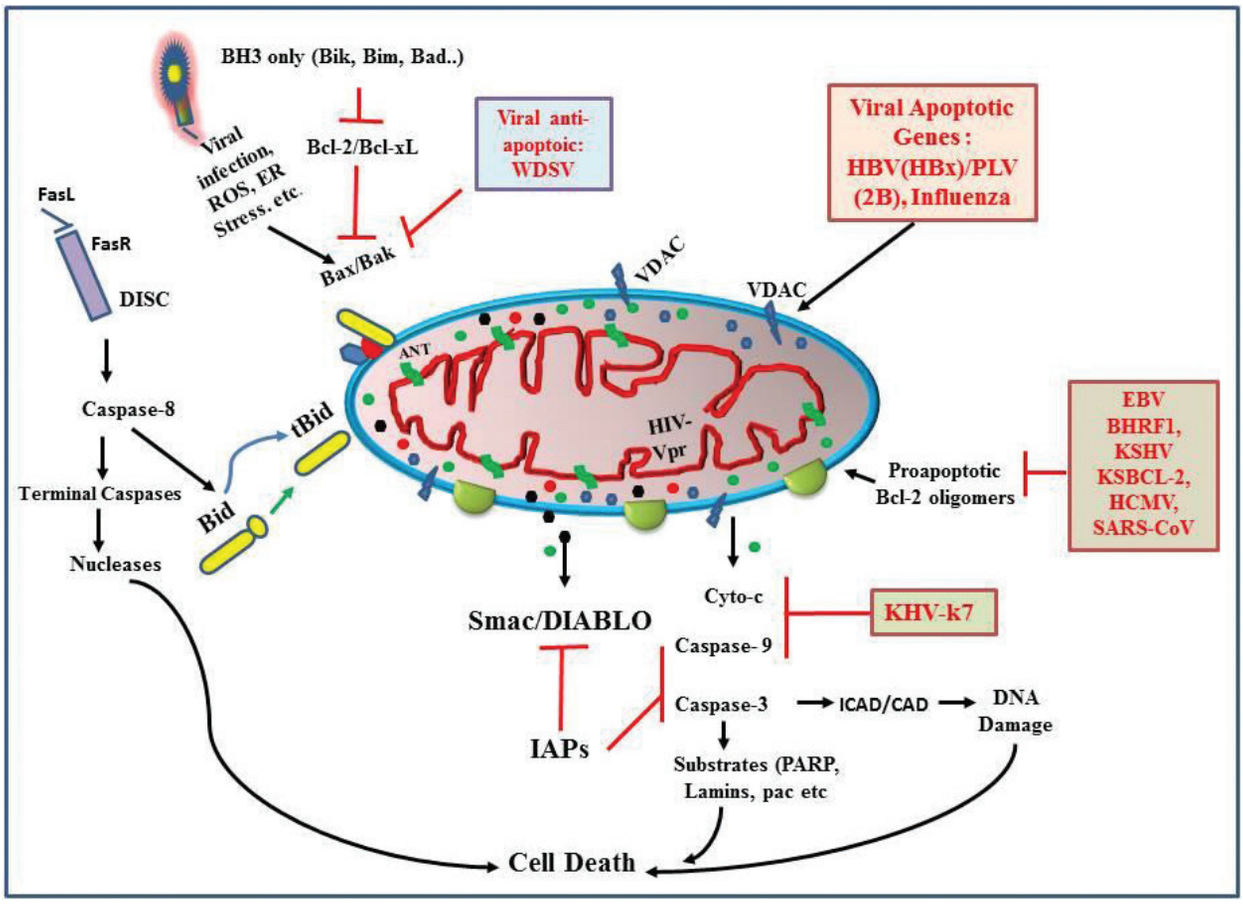


Figure 1. Modulation of cell death pathways in mitochondria by different viral infections or different viral proteins. In the extrinsic apoptosis pathway (middle left) [2], is activation of Fas death receptors at the cell surface by its ligand for activating the caspase-8 for either cleaved Bid to tBid for targeting into mitochondria [24] or activates the ROS/RIP3-mediated necroptosis via a nonmitochondria-mediated cell death process [2, 85]. In the intrinsic apoptosis pathway (top left), some death factors trigger death signals on disrupting mitochondrial function via loss of MMP and release the cytochrome c and activate the downstream caspase-3 for further triggering apoptotic cell death, but these mitochondria-mediated death signaling also regulated by anti-apoptotic family members such as Bcl-2 and Bcl-xL for rescuing host cells [8, 10, 11, 87]. On the other hand, IAP can inhibit the caspase-3 activation [88] but it is suppressed by the Smac/DIABLO molecule, which is released from mitochondria [24]. Finally, if viruses entering or expressing, they can also trigger proapoptotic signaling (indicated by black lines) or block anti-apoptotic signaling (indicated by red lines) via whole virus or viral gene productions in mammalian viruses, which is associated with activation of caspase-dependent [9] and caspase-independent executioner mechanisms [2], leads to cell death by viral genes from RNA and DNA viruses, respectively for inducing some damaged or human diseases [4, 27].

cellular targets. In HIV and hepatitis C virus infections, oxidative stress (OS) always plays a dominant pathogenic role. Peterhen and other researchers showed that almost all viruses (DNA/RNA viruses) cause cell death by generating oxidative stress in infected cells [12–14]. The OS generated during chronic hepatitis is associated with hepatic damage, a decrease in reduced glutathione (GSH) and decrease in plasma and hepatic zinc concentration [15, 16]. In case of influenza virus infection, the activated phagocytes release not only produces ROS but also cytokine and TNF. The pro-antioxidant effect of TNF may be relevant to influenza virus as shown by children with Rey's syndrome [17]. OS ultimately results in decrease in the functioning of the immune system.

2. Mitochondrial functions

Mitochondria are multifunctional organelles that are covered by an outer membrane (OM), within which lie the intermembrane space (IMS) and the inner membrane (IM). The IM is folded into special structures called cristae, so its surface area is much greater than that of the OM. The cristae function as matrices for protein complexes required for the electron transport chain (ETC), and they contain many integral membrane proteins, including adenine nucleotide translocator (ANT) and ATP synthase. The IM remains almost entirely impermeable under normal physiological conditions, thereby allowing the respiratory chain to create an electrochemical gradient. This electric potential is important for maintaining the mitochondrial membrane potential (MMP, $\Delta\psi m$) of the IM. The pumping of protons by the ETC out of the IM activates ATP synthase, which phosphorylates ADP to ATP. The ATP generated on the matrix side of the IM is then exported by ANT in exchange for ADP. The OM has many voltage-dependent anion channels (VDACs), which maintains permeability of solutes up to 5000 Da in size under normal physiological conditions. The IMS is chemically equivalent to the cytosol in terms of low molecular weight solutes and has its own special set of proteins. The human mitochondrial genome (about 16,500 bp), which is in the matrix (within the IM), only codes for 13 subunits of the respiratory chain. More than 99% of mitochondrial proteins are encoded by the nuclear genome and then selectively imported into one of the mitochondrial compartments. Thus, the mitochondrial OM, IM, IMS, and matrix have highly unique protein compositions.

Mitochondria act "powerhouse" of the cell and have several other important functions. The numerous functions of mitochondria make them indispensable to the cell, so when a virus "hijacks" mitochondrial function, it allows it to control the whole cell. Mitochondria have important roles in several signal transduction pathways [18, 19], the process of aging [20], regulation of different biochemical pathways related to cell metabolism [21, 22], PCD [23, 24], development [25, 26], the pathogenesis of numerous diseases immune responses [19], and cell cycle control [19, 27]. The circular mitochondrial genome encodes 13 polypeptides, 2 rRNAs, and 22 tRNAs. All of these mtDNA products are essential for function of the ETC and the generation of ATP by oxidative phosphorylation [9, 27], although many proteins from the nuclear genome are also required. Thus, any injury to mtDNA can affect the whole cell. The mtDNA is more susceptible to damage from ROS because it lacks protective histones, the mitochondrion has more limited DNA repair enzymes, and it is close to ETC, the main center of ATP and ROS production. The matrix of IMS, which contains cytochrome c oxidase (Cyt C, encoded by mtDNA), SMAC/DIABLO (encoded by nuclear DNA), and endonuclease G (encoded by nuclear DNA), acts as a buffer zone between the IM and OM. This matrix region contains many of the enzymes needed for aerobic respiration, dissolved oxygen, water, carbon dioxide, and recyclable intermediates that serve as energy shuttles and have other functions.

2.1. Loss of mitochondrial membrane potential

A loss of the MMP ($\Delta\psi m$) leads to imbalances in the membrane potentials of the IM and OM, and then to arrest of normal cellular biosynthetic function and bioenergetics, and finally to a "crisis" within the cell. A loss of the MMP ($\Delta\psi m$) also leads to release of several proapoptotic

proteins from the IMS, such as Cyt C and Smac/DIABLO, as well as caspase independent death effectors, such as apoptosis-inducing factor (AIF) and endonuclease G (EndoG) [9], which have important roles in caspase-independent and caspase-dependent cell death [9]. The MMP ($\Delta\psi m$) transition occurs during the pathogenesis of exogenous factors (e.g., viral proteins, toxins, and prooxidants [9, 10]). A prolonged loss of the MMP ($\Delta\psi m$) leads to serious cell damage, from which the cell cannot recover. Therefore, in the intrinsic pathway of apoptosis, any viral factor that influences the MMP ($\Delta\psi m$) has a major impact on cell fate, either by inducing or by blocking cell death [9].

In recent years, there has been an increasing focus on the role of the MMP ($\Delta\psi m$) in disease and health. Thus, several recent models based on *in vivo* and *in vitro* studies explain the mechanisms underlying the maintenance and loss of the MMP. A loss of the MMP by any mechanism leads to functional and structural collapse of the mitochondria and cell death [27]. A recent study for first time has shown that dengue virus (DV) infection of human hepatoma cell line (HepG2) leads alteration in the bioenergetic function of mitochondrial morphology leading to MMP loss [28]. The alteration in respiratory properties of HepG2 cells in DV infection results due to decrease in respiratory control ratio (PCR) and ADP/O ratio, which suggest significant alteration in mitochondrial morphology. Another additional feature observed by an increase in proton leak termed mitochondrial uncoupling which occurs by leaking of protons through F_oF_1 ATP synthase from inner membrane into matrix resulting in decrease in MMP loss. Thus, creating an imbalance in ATP synthesis ultimately affects the bioenergetic functions of cell. The biochemical mitochondrial damage induced in cell infected with HCV showed that E1 Protein together with core and NS3 are responsible for ROS production. Core and NS3 induce NO production which causes MMP loss by opening of transition pore [29]. NO could also interact with another free radical superoxide (O_2^-) to form strong peroxynitrite anion (ONOO–), which irreversibly inhibits multiple respiratory complexes (complexes I, II and IV) and aconitase, and activate proton leak and permeability transition pore [30, 31]. Therefore, interfering with energy metabolism by disrupting the ATP synthesis of cell results in modulation of mitochondrial function.

2.2. Effects of viral infections on mitochondrial processes

Mitochondria undergo a number of processes, such as fusion and fission, in normally functioning healthy cells. However, when mitochondria develop abnormalities, the cell can destroy it by the process of mitophagy [32]. Cells typically eliminate unhealthy mitochondria by mitochondrial fission; they typically use mitochondrial fusion to recycle matrix metabolites, including mtDNA and mitochondrial membranes, for the assembly of new and healthy mitochondria. Therefore, these three processes—mitophagy, fission, and fusion—are interlinked, and they all play prominent roles in maintaining healthy cells [33]. Mitophagy plays an important role in maintaining mitochondrial homeostasis, but can also eliminate healthy mitochondria in cases such as cell starvation, viral invasion, and erythroid cell differentiation [34, 35]. The mitochondrial fusion and fission are highly dynamic. Viruses interfere with these processes to distort mitochondrial dynamic to facilitate their proliferation. Thus, interfering with these processes promotes the interference of different cellular signaling pathways [36–38]. New castal virus

(NDV) uses strategy that interferes with P62-mediated mitophagy to promote viral propagation [39]. The severe acute respiratory syndrome coronovirus (SARS-CoV) escapes the innate immune response by translocating its ORF-9b to mitochondria and promotes proteosomal degradation of dynamin-like protein (Drp1) leading to mitochondrial fission [40]. However, still more studies are needed to explain the exact role of mitophagy in the viral disease pathogenesis, which regulates the cell death process [41].

2.3. Role of mitochondria in host immune response

During the coevolution of viruses and hosts, some viruses have evolved proteins that mimic the activity of host proteins, thereby allowing the virus to complete its life cycle without inducing an immune response in the host. For example, Mimivirus, a genus with a single species in the newly created Mimiviridae, has genes for many proteins, including a viral mitochondrial carrier protein (VMC-I) [42], which mimics the host cell's mitochondrial carrier protein, allowing it to control mitochondrial transport in infected cells. Therefore, this virus takes control of the host cell's transportation of ADP, dADP, TTP, dTTP, and UTP in exchange for dATP, which the virus uses as an energy source for genome replication and production of progeny [27].

2.4. Viruses target mitochondrial DNA and disable host cells

Numerous viruses appear to have adopted a "strategy" of damaging the host cell mitochondrial DNA to control the whole cell. For example, the herpes simplex virus (HSV) causes productive and latent infections in human hosts by disruption of mitochondrial function. The HSV-1UL12 gene encodes two distinct yet similar proteins, UL12 and UL12.5. UL12 is an alkaline nuclease, and UL12.5 is an N terminally truncated 500-aa polypeptide that lacks the first 126 residues of UL12. UL12 plays a crucial role in viral genome replication and processing; UL12.5 also has nuclease and strand-exchange activities but does not accumulate in the host cell nucleus. Instead, UL12.5 localizes predominantly to the mitochondria, where it triggers massive degradation of mitochondrial DNA during early HSV replication. In particular, UL12.5 occurs directly within the mitochondrial matrix, and its nuclease activity degrades mtDNA [43]. HIV and hepatitis C virus infections cause metabolic stress due to mtDNA depletion in coinfected patients [44]. The Zta protein encoded by Ebola virus (EBV) genome translocates into mitochondria and interacts with mitochondrial single-strand protein, which ultimately affects mtDNA replication [45]. The OS generated during HCV infection also interferes with mtDNA [31].

3. Human viruses in mitochondria-mediated diseases

3.1. Epstein: Barr virus

The Epstein–Barr virus (EBV) is an oncovirus that is associated with breast cancer, gastric cancer, and numerous other cancers. Recent studies showed that EBV-encoded latent membrane protein 2A (LMP2A) leads to increased mitochondrial fission [46]. Further, molecular studies showed that LMP2A activates the NOTCH pathway, which alters the expression of Drp1 and then increases mitochondrial fission. Although increased Drp expression does not directly

increase mitochondrial fission, the recruitment of Drp by mitochondria and activation of GTPase leads to mitochondrial fission. Therefore, the EBV-induced changes in mitochondrial function, due to the LMP2A protein, may play a major role in the pathogenesis of several cancers [47].

3.2. Herpes simplex virus (alphaherpesvirus)

Infections by the herpes simplex virus type 1 (HSV-1) and pseudorabies virus (PRV) lead to imbalances in the calcium homeostasis of host cells. A study on rodents indicated that this calcium imbalance leads to disruption of mitochondrial function in the cervical ganglion neurons [48]. An imbalance in the cellular calcium pool affects the Miro protein (a calcium-binding protein), altering its interaction with kinesin-1. Therefore, HSV-1 and PRV "hijack" host cell proteins, and this disrupts mitochondrial dynamics, thereby allowing the viruses to replicate and spread to neighboring cells.

3.3. Influenza A virus

3.3.1. Influenza A virus induces oxidative stress in mitochondria

Reactive oxygen species have important roles in the overall function of normal cells and play a vital role in the host adaptive immune response [49, 50]. For example, production of $O_2^{\cdot -}$ is an important defense against microbial infections. However, a large increase in the production of $O_2^{\cdot -}$during influenza A virus infection leads to damage of lung parenchyma cells [51]. Further studies that OS increased lung injuries caused by the influenza virus and viral replication, irrespective of the viral strain [52, 53]. Excessive and nonspecific knockdown of stress-related enzymes, such as superoxide dismutase 2 (SOD2), led to T-cell apoptosis and many developmental defects, resulting in overall weakening of the adaptive immune system and an increased susceptibility to influenza A virus subtype H1N1 [54, 55].

3.3.2. Influenza A virus-encoded protein PB1-F2 targets mitochondria

Influenza A viruses encode the proapoptotic protein PB1-F2, which localizes to the mitochondria due to a target sequence on its C terminal domain. PB1-F2 is conserved within the influenza family [56]. After PB1-F2 binds to mitochondria, it interacts with two important mitochondrial proteins, VDAC1 on the OM and ANT3 on the IM [57, 58]. This leads to alterations in mitochondria morphology, release of proapoptotic proteins, loss of MMP, and then cell death.

3.4. HCV virus

3.4.1. HCV induces oxidative stress that damages mitochondria

HCV infection typically leads to generation of ROS, which interferes with the calcium signaling pathways of the cell [9]. This disruption of calcium homeostasis alters the structure of the endoplasmic reticulum, and increased calcium is taken up by the mitochondria, leading to disruption of the MMP. Recent molecular studies have shown that many other HCV proteins, such as E2 [59], and NS4B [60], are important in generating oxidative stress. In addition, the nonstructural HCV protein NS5A is an integral membrane protein that is important for viral

replication, apoptosis, immune responses (such as interferon resistance), and changes in cellular calcium [61]. The proteins NS5Aand NS3 have roles in increasing calcium uptake and in the oxidation of glutathione (GSH) to glutathione disulfide (GSSG) in mitochondria, which ultimately leads to oxidative stress [61–63]. The imbalance of ROS created in the mitochondria leads to activation and translocation of NF-κB and STAT3 to the nucleus, as part of disease progression. Antioxidants block the NS5A-mediated activation of NF-κB and STAT3 [64]. NS4B also promotes translocation of NF-κB to the nucleus in a PTK-mediated pathway. The resulting production of ROS and nitric oxide (NO) causes oxidative damage and inhibits DNA repair [60] and leads to apoptosis. ROS-mediated disruption of mitochondria is believed to be the sole cause of liver inflammation in HCV infections [9].

3.4.2. HCV-encoded proteins target mitochondria

HCV remains persistent in its host because it lowers the host cell immune response. The HCV protein NS3/4A is a serine protease that inhibits interferon beta production by the retinoic acid-inducible gene I (RIG-I) pathway. Studies of the NS3/4A protein show that this protease cleaves MAVS at Cys-508, a few residues before its mitochondrial targeting domain. Cleavage of MAVS inactivates this protein because its soluble form is not functional. NS3/4A has a mitochondrial localizing signal, so it can directly cleave MAVS in the mitochondria [65, 66]. Substitution of Cys-508 with arginine prevents cleavage of MAVS. Cleavage of MAVS is thus an important mechanism by which HCV reduces host cell defenses [66].

3.5. Hepatitis B virus targets mitochondria

Hepatitis B virus x protein (HBx) is potentially essential for viral replication, and it has oncogenic properties in animal models [67]. HBx sensitizes hepatocytes to apoptosis induced by stimuli such TNF-α [68]. Studies of the overexpression of HBx showed that this protein causes apoptosis by causing a perinuclear clustering of mitochondria and a loss of the MMP [69]. Studies of HBx mutants identified that certain hydrophobic residues (a mitochondrial targeting sequence, MTS) are important for its induction of mitochondrial localization, loss of MMP, and cell death [70]. The HBx protein usually interacts with at least two mitochondrial proteins, heat shock protein 60 (HSP60) [71] and HVDAC3 [72]. The interaction of HBx with these two proteins (which are important in maintaining mitochondrial integrity) ultimately disrupts mitochondrial function in infected cells. These two mitochondrial proteins play major roles in chronic liver disease and carcinogenesis. Therefore, HBx plays a major role in the pathogenesis of HBV infection due to its alteration of host cell mitochondria.

4. Control strategies

4.1. RNA interference treatment of viral diseases that target mitochondria

Despite the many advances in molecular biology and in treatment of viral diseases, the prevention and control of viral infections remains a challenge. Alteration of the interaction of the virus and host is one general strategy. Therefore, a complete understanding of the interactions

of the host and virus at the molecular level is needed to develop new antiviral drugs and vaccines. There is an urgent need to find more effective therapeutic agents for the treatment of viral infections. Researchers have recently started testing treatments based on RNA interference (RNAi), using either microRNA (miRNA) or small interfering RNA (siRNA). Although this approach is still in its infancy, there has been some success in silencing the viral genes responsible for virulence [73, 74].

RNAi is an endogenous defense that cells use as a defense against harmful nucleic acids, either generated by the cell itself or from external environment (such as a viral invasions) [75]. RNAi is successful against many virus infections, but the delivery and stability of RNAi molecules within the cell are major concerns. The stability of RNAi is affected by its charge and biochemical activity within a cell, so these two parameters must be considered when designing RNAi-based therapies. In addition, the effectiveness of RNAi-based therapies depends on the delivery route [76], target gene [77, 78], target pathogen [75, 78], and target tissue [75]. The adverse effects of using RNAi-based treatment on the environment and treatment costs must also be considered, and we must have a deeper understanding of RNAi at the molecular level. The growing interest of molecular virologists in the use of RNAi suggests that this is one of the most exciting new therapeutic approaches for treatment of viral diseases [75].

4.2. Host antioxidant defense system fights viral invasion

The increased generation of ROS and reactive nitrogen species (RNS) is a key part of the pathogenesis of many virus infections. OS induces loss of the MMP, so mitochondria are become more susceptible to ROS damage. However, cells also have defenses against ROS, such as reduced glutathione (GSH),which acts as an antioxidant during the oxidative production of ATP in healthy cells [9, 79–81]. An imbalance between the generation of ROS and ROS quenching by the cell's endogenous antioxidant defense system usually leads to a disease and is common during viral invasion. In recent years, due to the unavailability of antiviral drugs, researchers have proposed a number of new strategies to protect against free radical-induced OS. These strategies may be characterized as repair and protection. Protection is achieved by enzymes and by nonenzymatic compounds, such as carotenoids, vitamin C, vitamin E, GSH, and flavonoids [82]. Recent studies have shown the importance of both classes of these molecules in defense against oxidative stress [9, 83–86].

5. Concluding remarks

Identifying the main cause of a new epidemic is the most important factor in controlling disease outbreak. Many host responses appear to contribute to the pathogenesis of viral infections, and recent cellular and molecular studies have shown that many viruses specifically target mitochondria. Several different host responses and viral proteins directly or indirectly act on the mitochondria and lead to loss of the MMP. Mitochondria play important roles in cell survival and cell death, so a better understanding how different viruses use mitochondrial responses to control cells may provide a foundation for the development of new treatments for different viral diseases. More specifically, clarification of the roles of viruses

and viral proteins in host mitochondria may help to develop methods that protect against pathogenic viruses. Therefore, molecular examination of the exact roles of viruses and viral proteins on mitochondria may help to guide the discovery of novel therapeutic strategies and provide important insights into different mitochondrial viral diseases. However, there are major unanswered questions regarding the mechanism of virus- and protein-induced loss of the MMP. Answering these questions may lead to the discovery of key molecules or pathways involved in loss of MMP, a common feature in the pathogenesis of many viral diseases. The research summarized in this review clearly shows that mitochondria are the main target of invading viruses, and that disruption of mitochondrial function is a major part of the pathogenesis of viral diseases. Although the prevention and treatment of viral diseases is challenging, molecular pathogenesis studies examining virus-host interactions will help in the design of new drugs and therapeutic strategies against different viral diseases.

Acknowledgements

This work was supported by a grant (NSC 98-2313-B-006-004-MY3 and NSC 101-3011-P-006-006) awarded to Dr. Jainn-Ruey Hong from the National Science Council, Taiwan, Republic of China.

Conflict of interest

The authors declare no conflicts of interest in terms of funding or authorship.

Abbreviations

DISC	death-inducing signaling complex
ER	endoplasmic reticulum
HCV	hepatitis C virus
HBV	hepatitis B virus
PLV	poliovirus
KPSV	Kaposi sarcoma virus
Bid	BH3 interacting-domain death agonist
WDSV	walleye dermal saecoma virus
HCMV	human cytomegalovirus
EBV	Epstein–Barr virus
SARS-CoV	severe acute respiratory syndrome coronovirus

VDAC	voltage-dependent anion channel
HIV	human immunodeficiency virus
IAPs	inhibitor of apoptosis proteins.

Author details

Latif Reshi[1,2], Hao-Ven Wang[2] and Jiann-Ruey Hong[1,3]*

*Address all correspondence to: jrhong@mail.ncku.edu.tw

1 Lab of Molecular Virology and Biotechnology, Institute of Biotechnology, College of Bioscience and Biotechnology, National Cheng Kung University, Tainan City, Taiwan, ROC

2 Department of Life Sciences, College of Bioscience and Biotechnology, National Cheng Kung University, Tainan City, Taiwan, ROC

3 Department of Biotechnology and Bioindustry Sciences, National Cheng Kung University, Tainan City, Taiwan, ROC

References

[1] Liu J, Chen I, Kwang J. Characterization of a previously unidentified viral protein in porcine circovirus type 2-infected cells and its role in virus-induced apoptosis. Journal of Virology. 2005;**79**:8262-8274

[2] Ashkenazi A, Dixit VM. Death receptors: Signaling and modulation. Science. 1998;**281**: 1305-1308

[3] Münz C. Viral evasion of autophagy. Cell Host & Microbe. 2007;**1**:9-11

[4] Benedict CA, Norris PS, Ware CF. To kill or be killed: Viral evasion of apoptosis. Nature Immunology. 2002;**3**:1013-1018

[5] Wong J, Zhang J, Si X, Gao G, Mao I, et al. Autophagosome supports coxsackie virus B3 replication in host cells. Journal of Virology. 2008;**82**:9143-9153

[6] Lee YR, Lei HY, Liu MT, Wang JR, Chen SH, et al. Autophagic machinery activated by dengue virus enhances virus replication. Virology. 2008;**374**:240-248

[7] Levine AJ. The cellular gatekeeper for growth and division. Cell. 1997;**1997**(88):323-331

[8] Rao L, White E. Bcl-2 and the ICE family of apoptotic regulators: Making a connection. Current Opinion in Genetics & Development. 1997;**7**:52-58

[9] Reshi L, Su YC, Hong JR. RNA viruses: ROS-mediated cell death. International Journal of Cell Biology. 2014;**2014**:467-452

[10] Reshi L, Wu JL, Wang HV, Hong JR. Aquatic viruses induce host cell death pathways and its application. Virus Research. 2016;**211**:133-144

[11] Reshi L, Wang HV, Hui CF, Su YC, Hong JR. Anti-apoptotic genes Bcl-2 and Bcl-xL overexpression can block iridovirus serine/threonine kinase-induced Bax/mitochondria-mediated cell death in GF-1 cells. Fish & Shellfish Immunology. 2017;**61**:120-129

[12] Peterhans E, Grob M, Urge TB, Zanoni R. Virus-induced formation of reactive oxygen intermediates in phagocytic cells. Free Radical Research Communications. 1987;**3**(1-5):39-46

[13] Vierucci A, DeMartino M, Graziani E. A mechanism for liver cell injury in viral hepatitis: Effects of hepatitis B virus on neutrophil function in vitro and in children with chronic active hepatitis. Pediatric Research. 1983;**17**(10):814-820

[14] Muller F. Reactive oxygen intermediates and human immunodeficiency virus (HIV) infection. Free Radical Biology and Medicine. 1992;**13**(6):651-657

[15] Boya P, Peña AD, Beloquietal O. Antioxidant status and glutathione metabolism in peripheral blood mononuclear cells from patients with chronic hepatitis C. Journal of Hepatology. 1999;**31**(5):808-814

[16] Bianchi GP, Marchesini G, Brizietal M. Nutritional effects of oral zinc supplementation in cirrhosis. Nutrition Research. 2000;**20**(8):1079-1089

[17] Cooperstock MS, Tucker RP, Baublis JV. Possible pathogenic role of endotoxin in Reye's syndrome. The Lancet. 1975;**1**(7919):1272-1274

[18] Bossy-Wetzel E, Barsoum MJ, Godzik A, Schwarzenbacher R, Lipton SA. Mitochondrial fission in apoptosis, neurodegeneration and aging. Current Opinion in Cell Biology. 2003;**15**: 706-716

[19] Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging and cancer: A dawn for evolutionary medicine. Annual Review of Genetics. 2005;**39**:359-407

[20] Chan DC. Mitochondria: Dynamic organelles in disease, aging and development. Cell. 2006;**125**:1241-1252

[21] Hackenbrock CR. Ultrastructural bases for metabolically linked mechanical activity in mitochondria. I. Reversible ultrastructural changes with change in metabolic steady state in isolated liver mitochondria. Journal of Cell Biology. 1966;**30**:269-297

[22] Mannella CA, Pfeiffer DR, Bradshaw PC, Moraru II, Slepchenko B, et al. Topology of the mitochondrial inner membrane: Dynamics and bioenergetics implications. IUBMB Life. 2001;**52**:93-100

[23] McBride HM, Neuspiel M, Wasiak S. Mitochondria: More than just a powerhouse. Current Biology. 2006;**16**:R551-R560

[24] Kroemer G, Galluzzi L, Brenner C. Mitochondrial membrane permeabilization in cell death. Physiological Reviews. 2007;**87**:99-163

[25] Mandal S, Guptan P, Owusu-Ansah E, Banerjee U. Mitochondrial regulation of cell cycle progression during development as revealed by the tenured mutation in drosophila. Developmental Cell. 2005;**9**:843-854

[26] Honda S, Hirose S. Stage-specific enhanced expression of mitochondrial fusion and fission factors during spermatogenesis in rat testis. Biochemical and Biophysical Research Communications. 2003;**311**:424-432

[27] Reshi L, Hong JR. Mitochondria as a favourite organelle for invading viruses. Molecular Biology. 2017;**6**:181

[28] El-Bacha T et al. Mitochondrial and bioenergetic dysfunction in human hepatic cells infected with dengue 2 virus. Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease. 2007;**1772**(10):1158-1166

[29] Machida K et al. Hepatitis C virus infection activates the immunologic (type II) isoform of nitric oxide synthase and thereby enhances DNA damage and mutations of cellular genes. Journal of Virology. 2004;**78**(16):8835-8843

[30] Hortelano S et al. Nitric oxide induces apoptosis via triggering mitochondrial permeability transition. FEBS Letters. 1997;**410**(2-3):373-377

[31] Machida K et al. Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation. Journal of Virology. 2006;**80**(14):7199-7207

[32] Twig G, Shirihai OS. The interplay between mitochondrial dynamics and mitophagy. Antioxidants & Redox Signaling. 2011;**14**:1939-1951

[33] Chen H, Chan DC. Mitochondrial dynamics—Fusion, fission, movement, and mitophagy—in neurodegenerative diseases. Human Molecular Genetics. 2009;**18**:R169-R176

[34] Shitara H, Kaneda H, Sato A, Inoue K, Ogura A, Yonekawa H, Hayashi JL. Selective and continuous elimination of mitochondria microinjected into mouse eggs from spermatids, but not from liver cells, occurs throughout embryogenesis. Genetics. 2000;**156**:1277-1284

[35] Ebato C, Uchida T, Arakawa M, Komatsu M, Ueno T, Komiya K, et al. Autophagy is important in islet homeostasis and compensatory increase of beta cell mass in response to high-fat diet. Cell Metabolism. 2008;**8**:325-332

[36] Seth RB et al. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-κB and IRF3. Cell. 2005;**122**(5):669-682

[37] Castanier C et al. Mitochondrial dynamics regulate the RIG-I-like receptor antiviral pathway. EMBO Reports. 2010;**11**(2):133-138

[38] West AP, Shadel GS, Ghosh S. Mitochondria in innate immune responses. Nature Reviews Immunology. 2011;**11**(6):389

[39] Meng G, Xia M, Wang D, Chen A, Wang Y, Wang H, Yu D, Wei J. Mitophagy promotes replication of oncolytic Newcastle disease virus by blocking intrinsic apoptosis in lung cancer cells. Oncotarget. 2014;**5**(15):6365-6374

[40] Shi C-S et al. SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome. The Journal of Immunology. 2014;**193**(6):3080-3089

[41] Xia M, Meng G, Jiang A, et al. Mitophagy switches cell death from apoptosis to necrosis in NSCLC cells treated with oncolytic measles virus. Oncotarget. 2014;**5**(11):3907

[42] Monn'e M, Robinson AJ, Boes C, Harbour ME, Fearnley IM, et al. The mimivirus genome encodes a mitochondrial carrier that transports dATP and dTTP. Journal of Virology. 2007;**81**:3181-3186

[43] Martinez R, Shao L, Bronstein JC, Weber PC, Weller SK. The product of a 1.9-kb mRNA which overlaps the HSV-1 alkaline nuclease gene (UL12) cannot relieve the growth defects of a null mutant. Virology. 1996;**215**:152-164

[44] de Mendoza C, Sánchez-Conde M, Timmermans E, et al. Mitochondrial DNA depletion in HIV-infected patients with chronic hepatitis C and effect of pegylated interferon plus ribavirin therapy. AIDS .2007;**21**(5): 583-588

[45] Wiedmer A, Wang P, Zhou J, et al. Epstein-Barr virus immediate-early protein Zta co-opts mitochondrial single-stranded DNA binding protein to promote viral and inhibit mitochondrial DNA replication. Journal of Virology. 2008;**82**(9):4647-4655

[46] Young LS, Rickinson AB. Epstein–Barr virus: 40 years on. Nature Reviews. Cancer. 2004;**4**: 757-768

[47] Pal AD, Basak NP, Banerjee AS, Banerjee S. Epstein–Barr virus latent membrane protein-2A alters mitochondrial dynamics promoting cellular migration mediated by Notch signaling pathway. Carcinogenesis. 2014;**35**:1592-1601

[48] Kramer T, Enquist LW. Alphaherpesvirus infection disrupts mitochondrial transport in neurons. Cell Host & Microbe. 2012;**11**:504-514

[49] Rott R, Klenk HD, Nagai Y, Tashiro M. Influenza viruses, cell enzymes, and pathogenicity. American Journal of Respiratory and Critical Care Medicine. 1995;**152**(4):S16-S19

[50] Kido H, Sakai K, Kishino Y, Tashiro M. Pulmonary surfactant is a potential endogenous inhibitor of proteolytic activation of Sendai virus and influenza A virus. FEBS Letters. 1993;**322**(2):115-119

[51] Hennet T, Peterhans E, Stocker R. Alterations in antioxidant defences in lung and liver of mice infected with influenza A virus. Journal of General Virology. 1992;**3**:39-46

[52] Geiler J, Michaelis M, Naczk P, et al. N-acetyl-l-cysteine (NAC) inhibits virus replication and expression of proinflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus. Biochemical Pharmacology. 2010;**79**(3):413-420

[53] Vlahos R, Selemidis S. NADPH oxidases as novel pharmacologic targets against influenza A virus infection. Molecular Pharmacology. 2014;**86**(6):747-759

[54] Case AJ, McGill JL, Tygrett LT, Shirasawa T, Spitz DR, Waldschmidt TJ, Legge KL, Domann FE. Elevated mitochondrial superoxide disrupts normal T cell development, impairing adaptive immune responses to an influenza challenge. Free Radical Biology & Medicine. 2011;**50**(3):448-458

[55] Allen RG, Balin AK. Oxidative influence on development and differentiation: An overview of a free radical theory of development. Free Radical Biology and Medicine. 1989;**6**(6): 631-661

[56] Bruns K, Studtrucker N, Sharma A, Fossen T, Mitzner D, et al. Structural characterization and oligomerization of PB1-F2, a proapoptotic influenza A virus protein. The Journal of Biological Chemistry. 2007;**282**:353-363

[57] Gibbs JS, Malide D, Hornung F, Bennink JR, Yewdell JW. The influenza A virus PB1-F2 protein targets the inner mitochondrial membrane via a predicted basic amphipathic helix that disrupts mitochondrial function. Journal of Virology. 2003;**77**:7214-7224

[58] Zamarin D, Garcia-Sastre A, Xiao X, Wang R, Palese P. Influenza virus PB1-F2 protein induces cell death through mitochondrial ANT3 and VDAC1. PLoS Pathogens. 2005;**1**:4

[59] Hsieh MJ, Hsieh YS, Chen TY, Chiou HL. Hepatitis C virus E2 protein induce reactive oxygen species (ROS)-related fibrogenesis in the HSC-T6 hepatic stellate cell line. Journal of Cellular Biochemistry. 2011;**112**(1):233-243

[60] Li S, Ye Y, Yu X, et al. Hepatitis C virus NS4B induces unfolded protein response and endoplasmic reticulum overload response-dependent NF-κB activation. Virology. 2009;**391**:257-264

[61] Liang Y, Ye H, Cong BK, HoS Y. Domain 2 of nonstructural protein 5A (NS5A) of hepatitis C virus is natively unfolded. Biochemistry. 2007;**46**:11550-11558

[62] Thoren F, Romero A, Lindh M, Dahlgren C, Hellstrand K. A hepatitis C virus-encoded, nonstructural protein (NS3) triggers dysfunction and apoptosis in lymphocytes: Role of NADPH oxidase-derived oxygen radicals. Journal of Leukocyte Biology. 2004;**76**(6):1180-1186

[63] García-Monzón C, Majano PL, Zubia I, Sanz P, Apolinario A, Moreno-Otero R. Intrahepatic accumulation of nitrotyrosine in chronic viral hepatitis is associated with histological severity of liver disease. Journal of Hepatology. 2000;**32**(2):331-338

[64] Gong G, Waris G, Tanveer R, Siddiqui A. Human hepatitis C virus NS5A protein alters intracellular calcium levels, induces oxidative stress, and activates STAT-3 and NF-κB. Proceedings of the National Academy of Sciences of the United States of America. 2001;**98**(17):9599-9604

[65] Meylan E, Curran J, Hofmann K, Moradpour D, Binder M, et al. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature. 2005;**437**: 1167-1172

[66] Li XD, Sun L, Seth RB, Pineda G, Chen ZJ. Hepatitis C virus protease NS3/4A cleaves mitochondrial antiviral signaling protein off the mitochondria to evade innate immunity. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**:17717-17722

[67] Wang Y, Lau SH, Sham JST, Wu MC, Wang T, et al. Characterization of HBV integrants in 14 hepatocellular carcinomas: Association of truncated X gene and hepatocellular carcinogenesis. Oncogene. 2004;**23**:142-148

[68] Su F, Schneider RJ. Hepatitis B virus HBx protein sensitizes cells to apoptotic killing by tumor necrosis factor alpha. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**:8744-8749

[69] Takada S, Shirakata Y, Kaneniwa N, Koike K. Association of hepatitis B virus X protein with mitochondria causes mitochondrial aggregation at the nuclear periphery, leading to cell death. Oncogene. 1999;**18**:6965-6973

[70] Henkler F, Hoare J, Waseem N, Goldin RD, McGarvey MJ, et al. Intracellular localization of the hepatitis B virus HBx protein. The Journal of General Virology. 2001;**82**:871-882

[71] Rahmani Z, Huh KW, Lasher R, Siddiqui A. Hepatitis B virus X protein colocalizes to mitochondria with a human voltage-dependent anion channel, HVDAC3, and alters its transmembrane potential. Journal of Virology. 2000;**74**:2840-2846

[72] Tanaka Y, Kanai F, Kawakami T, Tateishi K, Ijichi H, et al. Interaction of the hepatitis B virus X protein (HBx) with heat shock protein 60 enhances HBx-mediated apoptosis. Biochemical and Biophysical Research Communications. 2004;**318**:461-469

[73] Buchon N, Vaury C. RNAi: A defensive RNA-silencing against viruses and transposable elements. Heredity. 2006;**96**:195-202

[74] Rijiravanich E, Berezikov E. Small RNAs and the control of transposons and viruses in Drosophila. Trends in Microbiology. 2009;**17**:163-171

[75] Reshi ML, Wu JL, Wang HV, Hong JR. RNA interference technology used for the study of aquatic virus infections. Fish & Shellfish Immunology. 2014;**40**(1):14-23

[76] Attasart P, Kaewkhaw R, Chimwai C, Kongphom U, Namramoon O, Panyim S. Inhibition of white spot syndrome virus replication in *Penaeus monodon* by combined silencing of viral rr2 and shrimp PmRab7. Virus Research. 2009;**145**:127-133

[77] Shockey JE, O'Leary NA, de la Vega E, Browdy CL, Baatz JE, Gross PS. The role of crustins in *Litopenaeus vannamei* in response to infection with shrimp pathogens: An in vivo approach. Developmental and Comparative Immunology. 2009;**33**:668-673

[78] Han-Ching Wang K, Tseng CW, Lin HY, Chen IT, Chen YH, Chen YM, et al. RNAi knock-down of the *Litopenaeus vannamei* Toll gene (LvToll) significantly increases mortality and reduces bacterial clearance after challenge with Vibrioharveyi. Developmental and Comparative Immunology. 2010;**34**:49-58

[79] Stout AK, Raphael HM, Kanterewicz BI, Klann E, Reynolds IJ. Glutamate-induced neuron death requires mitochondrial calcium uptake. Nature Neuroscience. 1998;**1**(5):366-373

[80] White E, Shannon JS, Patterson RE. Relationship between vitamin and calcium supplement use and colon cancer. Cancer Epidemiology Biomarkers and Prevention. 1997;**6**(10):769-774

[81] Smith AR, Shenvi SV, Widlansky M, Suh JH, Hagen TM. Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress. Current Medicinal Chemistry. 2004;**11**(9):1135-1146

[82] Sharoni Y, Danilenko M, Dubi N, Ben-Dor A, Levy J. Carotenoids and transcription. Archives of Biochemistry and Biophysics. 2004;**430**(1):89-96

[83] Schrauzer GN. Interactive effects of selenium and chromium on mammary tumor development and growth in MMTV infected female mice and their relevance to human cancer. Biological Trace Element Research. 2006;**109**(3):281-292

[84] Packer L, Suzuki YJ. Vitamin E and alpha-lipoate: Role in antioxidant recycling and activation of the NF-κB transcription factor. Molecular Aspects of Medicine. 1993;**4**(3):229-239

[85] Reshi ML, Hong JR. Role of oxidative stress in RNA virus–induced cell death. In: Shamimi A, editor. Reactive Oxygen Species in Biology and Human Health. New York: Taylor & Francis group; 2016. pp. 471-485

[86] Pryor WA. Vitamin E and heart disease: Basic science to clinical intervention trials. Free Radical Biology and Medicine. 2000;**28**(1):141-164

[87] Ferri KF, Kroemer G. Organelle-specific initiation of cell death pathways. Nature Cell Biology. 2001;**3**:E255-E263

[88] Clem RJ, Duckett CS. The IAP genes: Unique arbitrators of cell death. Trends in Cell Biology. 1997;**7**:337-339

IntechOpen

IntechOpen

IntechOpen