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Review Article

Viral Infection and Mitochondria in Eukaryotic Mammalian, Insect and Plant Cells

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Abstract

Background and Aims: Viruses manipulate intracellular organelles such as mitochondria, endoplasmic reticulum, cytoskeleton, and lipid droplets to facilitate their own replication. In response, host cells initiate antiviral defenses and reorganize these organelles to combat infection. Mitochondria are a primary target in this process, as viral proteins exploit them to inhibit the host's antiviral mechanisms. In plants, viral manipulation of mitochondria can disrupt energy production, impacting overall plant health. Similarly, in insects, which serve as crucial vectors for many plant viruses, viral interactions can alter mitochondrial function, affecting both vector competence and the dynamics of disease transmission. The intricate relationship between viruses and mitochondrial dynamics highlights the complexity of host-virus interactions across various biological systems. This paper explores mitochondrial communication with viral infections in mammals, insects, and plants.

Keywords: Eukaryotic cells, Mitochondria, Viral infection

Introduction

Mitochondria are complex organelles involved in numerous cellular signaling and metabolic pathways, playing a critical role in calcium homeostasis and triggering antiviral responses, including innate immunity and apoptosis. Viruses as intracellular parasites hinge strongly on host metabolic functions and, to varying extents, manipulate these functions to facilitate their replication (1). Although only a few viruses with large coding capacities encode their own metabolic enzymes, all viruses utilize host resources such as lipids, amino acids, and energy to support processes like viral assembly and release. Recent research has increasingly focused on the metabolomics of viral infections and the impacts of viral manipulation on mitochondrial metabolism (2). Viral- induced mitochondrial redistribution within host cells can often be inhibited through disruption of the microtubule network (3).

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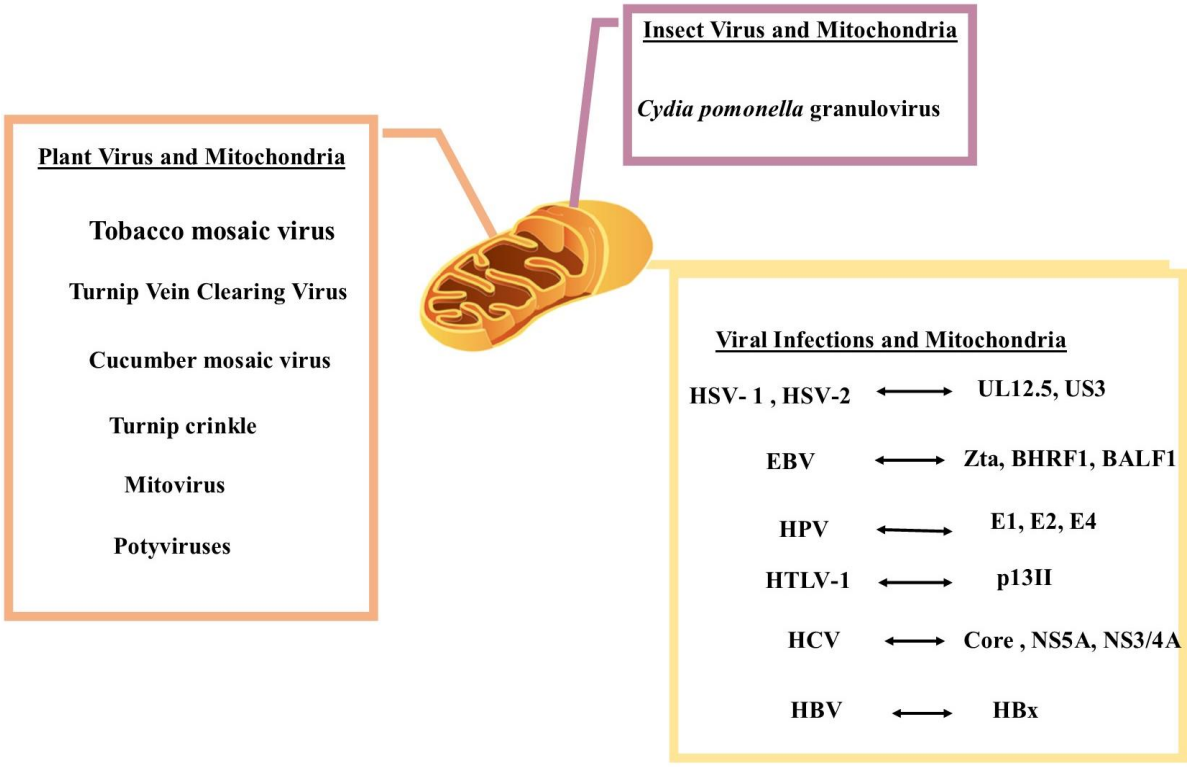

Fig. 1. Graphical Abstract

Mitochondria are specifically targeted by viruses and their proteins to suppress the host's antiviral response (4). During viral infection, pattern recognition receptors such as PRRs roust the production of interferons (IFNs). Mitochondrial antiviral-signaling protein (MAVS) serves as a critical signaling hub for pathways activated by RIG-I-like receptors that detect viral RNA(5). Viruses also impact host cell metabolism, causing notable disruptions in cellular and physiological functions (6). Although the duty of mitochondrial activity patterns during viral infections is being explored, mitochondria are central to both innate and cellular immunity, positioning them as a valuable focus for further molecular studies in viral pathogenesis (7). This paper reviews current insights into factors affecting mitochondria during viral infections (Figure 1).

Viral Infections and Mitochondria

In addition to the essential role in cellular metabolism, mitochondria are key players in the function of innate immunity, especially during viral infections. Immune signaling can be triggered through interactions on the mitochondrial surface, as well as through the release of damage-associated molecular patterns (DAMPs) like mtDNA as mitochondrial DNA, that occurs alongside dynamic changes in mitochondrial morphology (8).

mtDNA is typically tightly bound by Transcription Factor A Mitochondrial (TFAM) within the mitochondrial matrix (9). Studies show that TFAM-coated mtDNA is more stable and less susceptible to oxidative damage from reactive oxygen species (ROS), while newly synthesized, uncoated mtDNA is more prone to leakage and oxidation into the cytosol (10). This release of mtDNA is linked to reduced TFAM binding, driven by an increase in PKA-mediated phosphorylation of TFAM (11).

During viral infections, RNA degradation pathways-especially those targeting defective or misprocessed RNAs can be hijacked or disrupted by viruses to evade immune detection and manipulate host cell functions. The PNPase–SUV3 complex, for instance, can modulate antiviral signaling pathways, including those mediated by mitochondrial antiviral signaling (MAVS) proteins (12). Many viruses encode

proteins that target mitochondria to regulate the apoptosis process of infected cells. Proapoptotic proteins of viruses translocate to the mitochondrial membranes, inducing mitochondrial membrane permeabilization (MMP), almost accompanied by mitochondrial fragmentation and swelling (13).

Mammalian Cells Mitochondria and Viral Infections

The genomes of HSV-1 and HSV-2 encode a conserved viral serine/threonine protein kinase, US3, found in all α-herpesviruses. While US3 is not important for viral growth in vitro, it demonstrate a significant role in various aspects of HSV replication and pathogenesis (14). US3 expression significantly influences several signal transduction pathways, including the JNK and PKB/Akt pathways, and inhibits mitochondrial electron transport in HSV-1-infected cells. Additionally, US3 phosphorylates numerous cellular and viral proteins in infected cells and exhibits potent anti-apoptotic activity in both transfected and infected cells (15).

The replication cycle of HSV-1 progresses rapidly, with viral genome replication beginning early in the infection. This dependence on cellular metabolites is reflected in NADH2 levels, a critical cofactor for various cellular metabolic processes. HSV-1 can tolerate a decrease in intracellular NADH2, often due to the activation of poly(ADP-ribose) polymerase (PARP) family members in response to replication-associated DNA damage (16). Emphasizing the importance of mtDNA in infection, certain viral factors specifically target this genome. One such factor is UL12.5, an N-terminally truncated isoform of the HSV-1 UL12 protein, which localizes to mitochondria and promotes mitochondrial DNA depletion (17).

HIV-1 (Human immunodeficiency virus type 1), is among the most prevalent viruses worldwide and carries a significant pathogenic impact. It is also one of the best-characterized viruses, with considerable research devoted to understanding the mitochondrial metabolic aspects of its life cycle. Notably, both HIV infection itself and antiretroviral therapy, especially HAART (highly active antiretroviral therapy), are associated with mitochondrial toxicity (18). Nucleoside analogue reverse transcriptase inhibitors, a component of HAART, are responsible for mtDNA depletion, leading to disruptions in cellular energy production. Since mtDNA encodes subunits essential for the respiratory chain complexes, mtDNA depletion inevitably affects mitochondrial respiration. However, studies suggest a different impact in asymptomatic HIV-infected pediatric patients (19).

In another context, the Epstein-Barr virus (EBV) Zeta protein, a DNA-binding protein, hijacks the mitochondrial single-stranded binding (mtSSB) protein by directly attaching to it and redirecting it to the nucleus, where the viral genome is located. This interaction is crucial for facilitating EBV lytic replication while simultaneously suppressing mtDNA replication (20). The Epstein-Barr virus (EBV) encodes two Bcl-2 homologs: BHRF1 and BALF1 (21). BHRF1 shares similar three-dimensional structures, localization profiles, and positive effects on cell survival with Bcl-2. It effectively suppresses apoptosis, and mitochondrial membrane permeabilization (MMP) enforced by various stimulants, including c-myc activation, heterologous viral infections, antitumor chemotherapeutic drugs, and gamma radiation. BHRF1 significantly inhibits TRAIL-mediated apoptosis, which involves caspase-8 function and loss of mitochondrial membrane potential.

However, unlike Bcl-2 and Bcl-xL, BHRF1 lacks an exposed, preformed BH-3 binding groove, preventing it from sequestering and inhibiting proapoptotic BH-3-only proteins (22). Although BHRF1 can bind the proapoptotic BH-3-only protein Bim, it does not interact with Bak, offering some protection.

Interestingly, the content of Bim bound with BHRF1 is relatively small compared to the levels of Bim expression induced during apoptosis, suggesting that BHRF1 may function through Bim to inhibit apoptosis (23). BALF1, another Bcl-2 homolog, also interacts with the proapoptotic proteins Bax and Bak and may counteract the effects of BHRF1, although its role in the viral life cycle remains controversial. Additionally, the nuclear antigens EBNA-3C

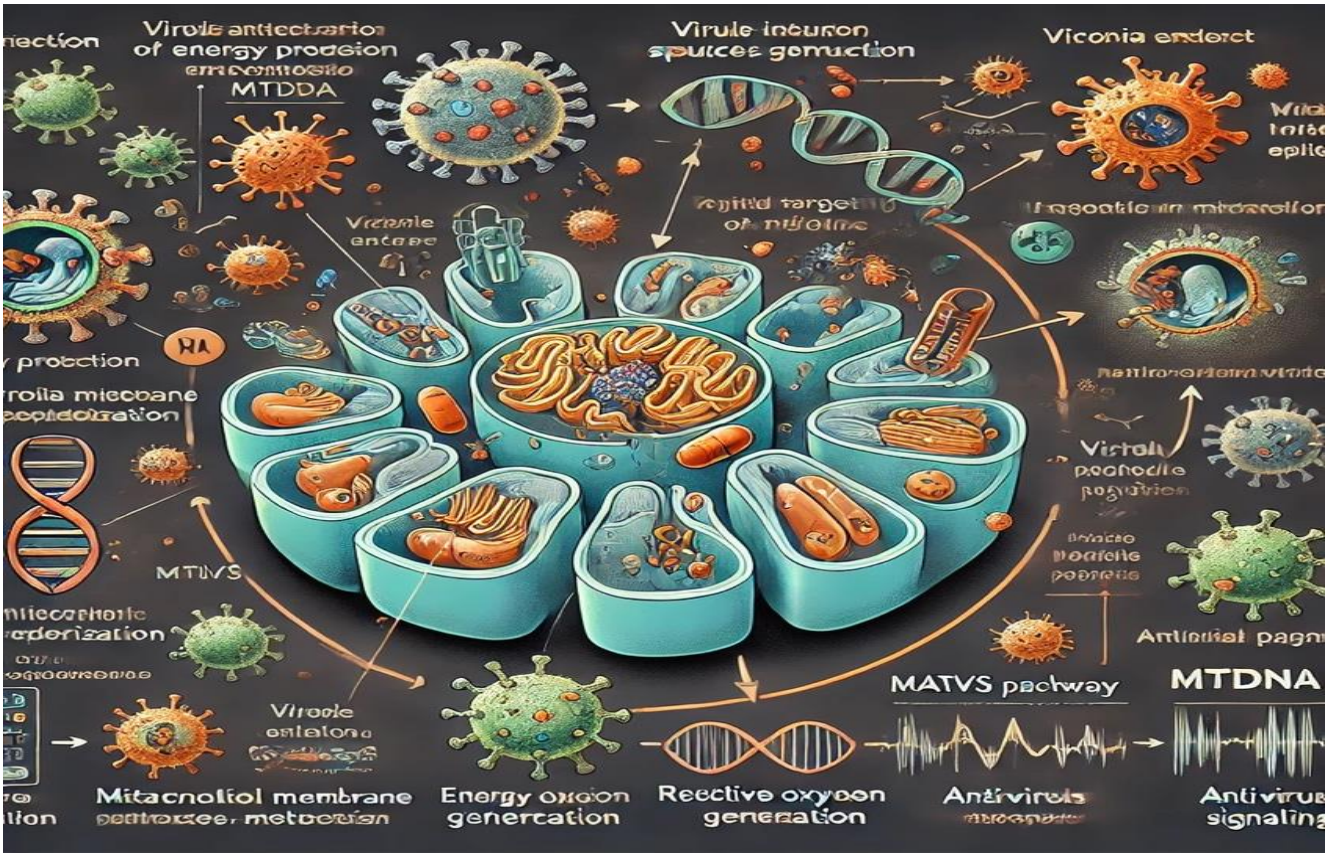

Fig. 2. This figure illustrates the complex interplay between mitochondria and human viral infection within mammalian cells, emphasizing how viral infections manipulate mitochondrial functions and host immune responses (This figure drawn by Chatgpt).

EBNA3A, are responsible for lymphoblastoid cell lines, exhibiting anti-apoptotic properties. They cooperate to down-regulate the expression of the BH-3-only protein Bim (24). Since Bim is an important regulator of B-cell survival and acts as a tumor suppressor in B cells, its depletion by the nuclear EBNA3 proteins may facilitate EBV-mediated lympho-magenesis. The EBNA-leader protein (LP) disrupts host transcription and the cytoplasmic apoptotic machinery, interacting with Bcl-2 via the cellular HS1-associated protein X-1 (HAX-1), a mitochondrial inhibitor of apoptosis regulated by Omi/HtrA2 (25). The E2 protein of human papillomavirus (HPV) indirectly affects mitochondrial function by inducing p32 (26), an RNA-binding protein that associates with TFAM, which is crucial for mitochondrial transcription and translation (27).

Additionally, the mitochondrial localization of the E1^E4 protein is ascribed to a leucine-rich area in its N-terminus (28). Through a mechanism that remains unclear, E1^E4 promotes the detachment of mitochondria from microtubules, leading to the formation of a single large cluster of mitochondria adjacent to the nucleus (13).

Human T-lymphotropic virus type 1 (HTLV-1), a causative agent of adult T-cell leukemia, encodes several unique regulatory and accessory proteins within the pX area of its provirus, including p13II, derived from open reading frame II. The p13II protein specifically localizes to the region of the inner mitochondrial membrane, where it influences mitochondrial function and morphology (29); Within the mitochondria, p13II induces internal potassium (K^+) current, resulting in mitochondrial swelling, membrane depolarization, enhanced respiratory chain function, and increased generation of ROS (reactive oxygen species) (30, 31). Additionally, p13II sensitizes cells to apoptosis induced by Fas ligand and ceramide, while suppressing cell proliferation and tumorigenesis in cells co-expressing Myc and Ras (32).

HCV (Hepatitis C virus) has been demonstrated to impact mitochondrial biogenesis and transcription. The virus disrupts mitochondrial trans-

cription through its two NS5A and core proteins, resulting in endoplasmic reticulum (ER) stress and increased calcium (Ca^{2+}) transmission from the ER to mitochondria. This dysregulation can cause to increased generation of ROS, increased susceptibility to mitochondrial permeability transition, impaired oxidative phosphorylation, and cell death, all of which contribute to viral pathogenesis (33). Additionally, the NS3/4A protein of HCV, functioning as a serine protease, specifically inhibits RIG-I-mediated signaling by cleaving MAVS (mitochondrial antiviral signaling) at Cys508 (34).

Beta-oxidation generates acetyl-CoA, which is a crucial substrate for mitochondrial function and is necessary for the replication cycle of some viruses. HCV serves as a well-characterized example of viral manipulation for this metabolic pathway. HCV replication depends on the act of the enzyme dodecanoyl coenzyme A delta isomerase (DCI), that is associated in the degradation of long-chain unsaturated fatty acids that have double bonds at odd-numbered carbon positions (35). The significance of beta-oxidation, particularly DCI in HCV replication, is supported by several lines of evidence: (I) Knockdown of DCI, (II) pharmacological inhibition of long-chain fatty acid transport into mitochondria using etomoxir, both result in reduced HCV replication in Huh7 hepatoma cells, and (III) mitochondrial fatty acid oxidetion and the availability of its associated enzymes are generally enhanced during HCV infection (3).The X protein from Hepatitis B virus (HBx) plays a significant role in the development of hepatocellular carcinomas by acting as a transcriptional activator for both viral and cellular genes. HBx is communicated with mitochondria, likely through an assumed transmembrane area (amino acids 54–70), and it transfects cells and sensitizes infected to apoptosis induced by TNF-α (36).

Recent studies have demonstrated that HBx induces cyclophilin D-mediated mitochondrial penetrance transmission, leading to calcium influx into the cytoplasm. Additionally, HBx communicates with the mitochondrial matrix chaperone Hsp60 and Hsp70. Further research is needed to clarify the mechanisms underlying HBx-related mitochondrial regulation (37). Interaction between mammalian cells and viral infection demonstrated in Figure 2.

Plant Cells Mitochondria and Viral Infections

Different studies have been managed to elucidate the functions of plant viruses due to replication and movement by using cell biological, biochemical, genetical, and molecular methods, Specially, studies related to cell biology contributed extremely to the description of the plasmodesmata structure, the intra/intercellular movement of viral proteins, and the interplay between viral factors and cells. Presumably, there are yet undetermined, complex relations between virus movement and virus replication (38). As plant cell systems are intricated, it is important to note that several plant viruses demonstrated various reactions to distinct host factors or hosts. For instance, actin filament affects the motions of Tobacco Mosaic Virus (TMV), but the motions of Turnip Vein Clearing Virus (TVCV) are not linked to the actin filaments (39). Despite significant efforts to understand virus infections, further research is still needed to find answers to many unresolved questions. Numerous host factors must be identified to fully understand the precise mechanisms employed by viruses for the replication of intracellular/intercellular movement. Although *Nicotiana benthamiana* is a commonly used plant model for studying plant viruses, its use has only recently expanded due to previously limited genomic resources (40). Since the *N. benthamiana* genome became available, more precise genetic studies can now be carried out to identify (41).

Plant viruses exhibit a high level of diversification and can induce significant alterations and deformations within a plant host cell. Their genomes can be composed of single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), double-stranded RNA (dsRNA), or single-stranded RNA (ssRNA), all encapsulated by a capsid made of coat protein molecules (42). Generally, the viral genome encodes proteins essential for the initiation and maintenance

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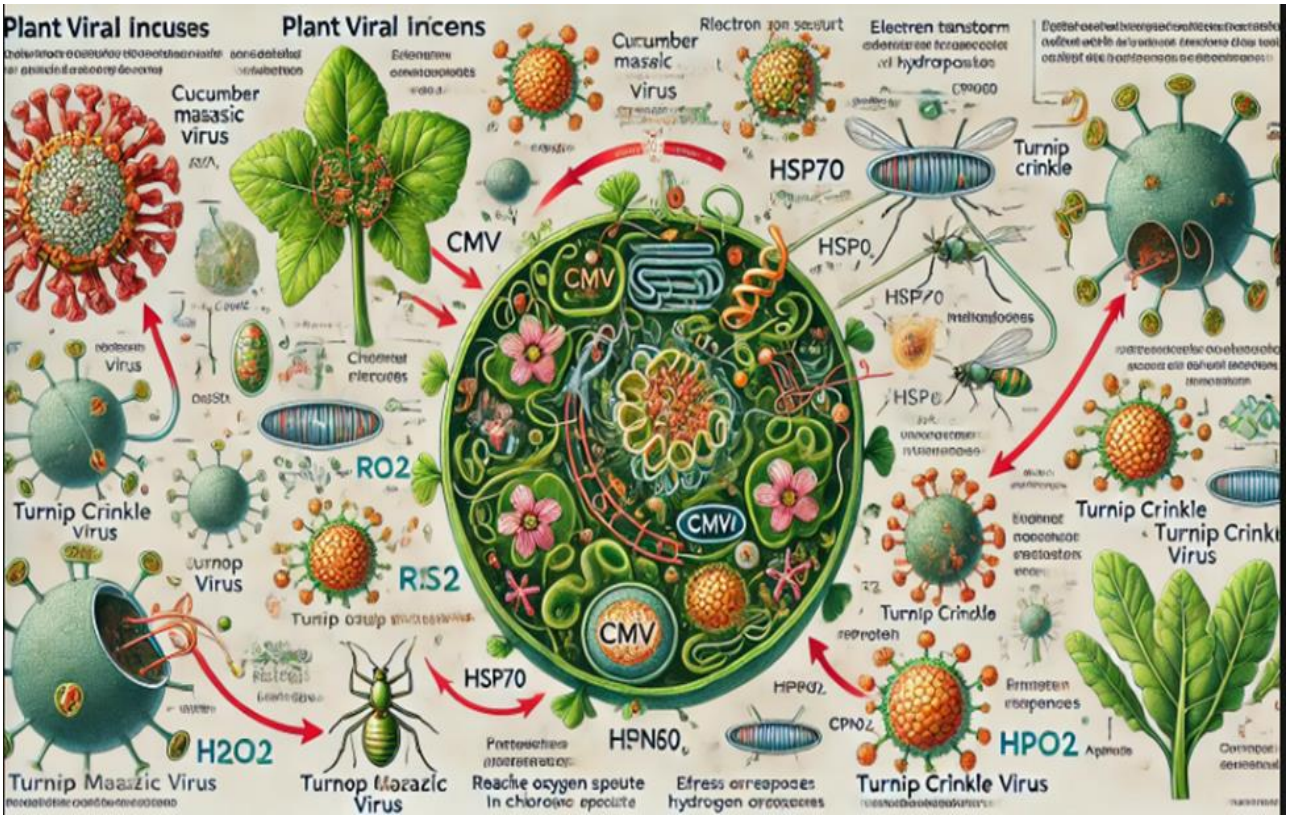

Fig. 3. Here's a scientific diagram depicting plant viral infections and their interactions with mitochondria in plant cells. It highlights key elements like CMV and Turnip crinkle virus effects on mitochondrial and chloroplast function, stress response proteins, and transmission via insect vectors (This figure drawn by Chatgpt).

of viral infection through local and systemic transport mechanisms. As a result, plant viruses operate exclusively within the host cell, triggering multilayered alterations in its internal systems during the infection process (43). Mitochondria play an important role in the electron transport chain. Infection by Cucumber mosaic virus (CMV) disrupts the electron transport chains in both chloroplasts and mitochondria, resulting in increased electron flow to oxygen (O2) and a heightened accumulation of hydrogen peroxide (H2O2) (44). Due to infection with TVCV, the expression of mitochondrial matrix proteins HSP70 and CPN60 elevates in infected plants as a stress response to mitochondrial injury caused by the virus (45).

In quinoa plants that were infected with a Mitovirus, mitochondria-rich fractions were separated through cell fractionation to examine the impact of viral infection on the mitochondrial proteome. The analysis indicated that infection leads to the upregulation of proteins communicated with stress responses to drought (46, 47). Mitovirus possess small positive-sense RNA genomes, replicate with mitochondria, and have been shown to infect just fungi to date (48). Potyviruses can replicate and express their own genomes in the cytoplasm, primarily within closely affiliated membranous structures including the endoplasmic reticulum (ER) or in its vicinity. Our findings provide the first evidence of Potato virus Y (PVY) capsid proteins and particles being present inside the mitochondria during compatible interactions, while in hypersensitive reflexes, these interplays were detected within chloroplasts (49).

Many plant viruses that pose significant agricultural challenges are transferred by insect vectors, such as thrips, aphids, leafhoppers, and planthoppers, persistently. Increasing evidence suggests that the persistent transmission of viruses results in only limited adverse effects, rather than full-blown pathogenesis, in their insect vectors (50). Interaction between plant cells and viral infection demonstrated in Figure 3.

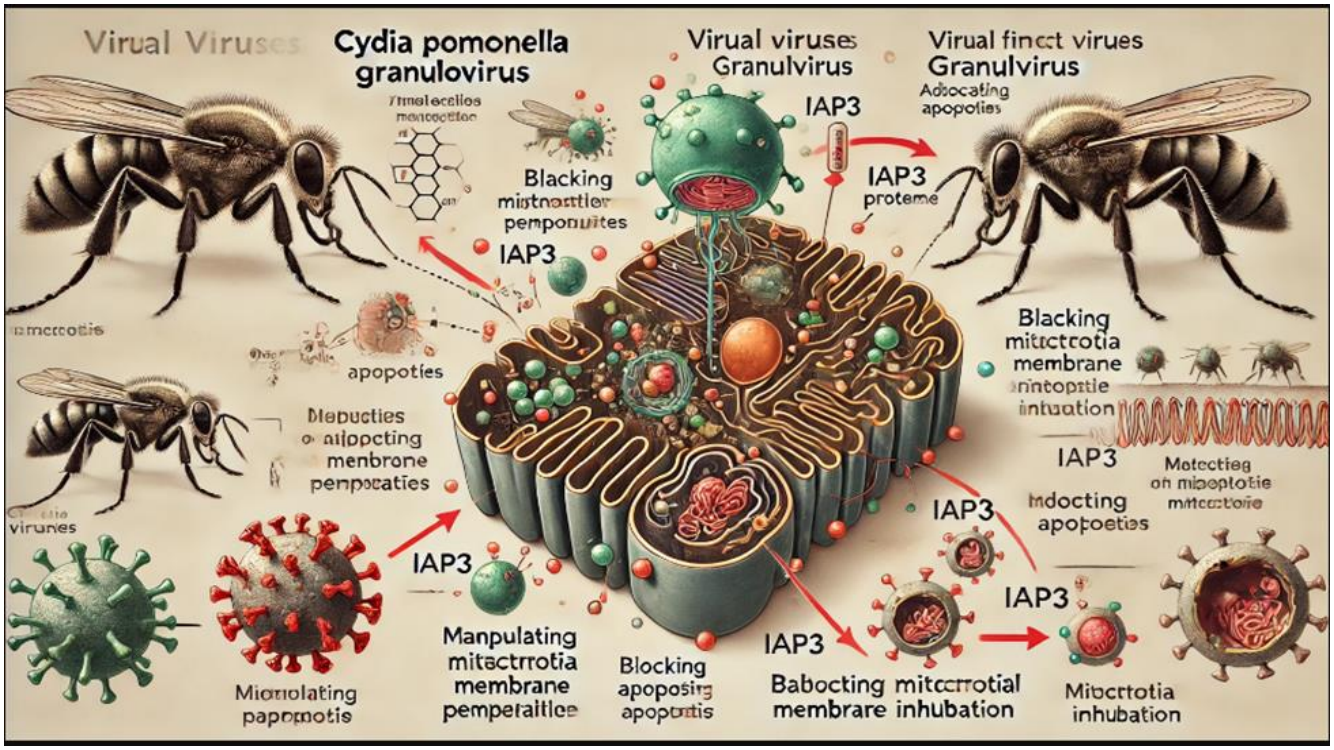

Fig. 4. Here's a scientific diagram illustrating the effects of viral infections on mitochondria in insect cells, with a focus on how viruses like *Cydia pomonella* granulovirus influence mitochondrial functions and inhibit apoptosis (This figure drawn by Chatgpt).

Insect Cells Mitochondria and Viral Infections

It is noteworthy that in insect viruses, replication occurs in various cellular compartments, including the host cell nucleus, cytoplasm, or even in between these regions, as seen with *Cydia pomonella* granulovirus (51, 52) in response to infection, the host activates its antiviral defenses and reorganizes its organelles to combat the viral threat (53). *Cydia pomonella* granulovirus is a natural pathogen of *Cydia pomonella* and is utilized as a biocontrol agent to manage insect populations (54).

The IAP3 protein of CpGV (*Cydia pomonella* granulovirus) was the earliest described member of the baculoviral IAP family, known for its ability to district apoptosis in various biological systems. IAP3 is exclusively localized in the cytoplasm. Subcellular fractionation experiments have shown that the protein exists in both membrane-bound cytosolic fractions and soluble, with the membrane-bound fraction containing IAP3 communicated with the mitochondria (55). Interaction between insects' cells and viral infection demonstrated in Figure 4.

Conclusion

In conclusion, the interaction between mitochondria and viruses across insects, plants, and eukaryotic cells reveals a complex interplay that is essential for understanding viral pathogennesis and host responses. Mitochondria not only function as critical energy producers but also play significant roles in cellular signaling and immune responses. Viruses exploit these mitochondrial functions to enhance their replication and evade host defenses, resulting in diverse outcomes across different organisms. In plants, manipulation of mitochondrial functions can disrupt energy balance and stress responses, while in insects, it impacts vector competency and viral transmission.

In eukaryotic pathogens, mitochondrial interacttions can influence virulence and lifestyle strategies. Future research should prioritize demonstrating the molecular functions underlying these interactions, as they present oppor-

tunities for developing innovative antiviral strategies.

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Conflict of Interest

No conflict of interest is declared.

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Ethics Approval and Consent to Participate

Not applicable.

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